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Reduced hippocampal recruitment during response conflict resolution in mesial temporal lobe epilepsy

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ABSTRACT

Recent evidence suggests that the human hippocampus (HC) is not only involved in the processing of motivationally relevant approach-avoidance conflicts but is also engaged in the resolution of more general response conflicts as measured in the Stroop paradigm. Here we investigated whether neural activity in the HC is necessary for successful response conflict resolution. We compared hippocampal recruitment during an auditory Stroop paradigm in 20 patients with mesial temporal lobe epilepsy (MTLE) due to hippocampal sclerosis and 20 age-matched healthy controls using functional magnetic resonance imaging (fMRI). We analyzed hippocampal activation and behavioral performance in conflict trials relative to non-conflict trials. Moreover, functional connectivity (FC) analyses with left and right HCs as seeds were performed. Subjects' regional gray matter volumes were analyzed based on high-resolution T2-weighted MRI scans. The current study replicated previous results showing increased activation in left HC during the processing of conflict trials in healthy subjects. By contrast, MTLE patients showed higher behavioral costs of response conflict resolution and reduced conflict-related HC activation. In patients with left MTLE, left HC activation was predictive of faster conflict-related response times (RTs). By contrast, right HC activation was related to RT slowing, suggestive of a maladaptive compensation attempt in MTLE patients. Our results provide evidence that left hippocampal activation is required for the successful resolution of response conflicts.

1. Introduction

The role of the HC for processes beyond memory and spatial navigation has gained increasing interest by researchers from various fields (Bach et al., 2014; Chan et al., 2001; Davidson and Jarrard, 2004; Ito and Lee, 2016; Loh et al., 2017; Oehrn et al., 2015; Sakimoto et al., 2013; Schumacher et al., 2016). Converging evidence suggests that the HC helps guiding behavior in conditions of environmental instability, i.e. when goals or response options compete. It is well established that the HC supports extinction learning, in particular when contexts change (Isaacson and Wickelgren, 1962; Jarrard and Lewis, 1967). More recently, research conducted in rodents has shown that the HC is also involved in inhibitory response control during approach-avoidance conflicts (Abela et al., 2013; Chudasama et al., 2012; Schumacher et al., 2016, 2018). Similarly, neuroimaging evidence in humans suggests that the HC, and in particular its anterior part, is activated during processing of approach-avoidance conflicts (Bach et al., 2014; Loh et al., 2017; O'Neil et al., 2015). In a previous study, Bach et al. (2014) investigated patients with MTLE and provided first evidence that the human HC indeed plays a causal role in processing approach-avoidance conflicts. However, it is less well known whether the HC is generally involved in guiding behavior during response conflicts beyond motivational approach-avoidance conflicts.

A common way to investigate non-motivational response conflict processing is the Stroop paradigm (Stroop, 1935). In the classic version of this task, subjects name the ink colour of a colour word (e.g., they say

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"blue" to the word "red" when it is written in blue ink). A response conflict is elicited when the more automatic process (reading the word) interferes with the current goal (naming the ink color) and has to be inhibited. Resolving this response conflict leads to behavioral costs in terms of reaction time slowing and/or increased error rates. The "conflict monitoring and cognitive control theory" is arguably the most influential framework for conflict processing (Botvinick et al., 2001). In short, it proposes that the level of conflict in streams of information processing is continuously being evaluated by the anterior cingulate cortex (ACC), which signals the level of top-down cognitive control (implemented by the dorsolateral prefrontal cortex [dorsolateral PFC]) that is needed in order to maintain goal-directed behavior. Several fMRI and electroencephalography (EEG) studies confirmed the prominent roles of dorsomedial and dorsolateral PFC in response conflict processing (Bartoli et al., 2018; Botvinick et al., 2004; MacDonald et al., 2000; Oehrn et al., 2014; van Veen and Carter, 2005).

Recently, we investigated whether the HC is also involved in response conflict processing in a Stroop task combining two particularly sensitive methods: hypothesis-driven (i.e., region of interest [ROI]-based) fMRI analyses in healthy subjects and intracranial EEG recordings in presurgical epilepsy patients with hippocampal depth electrodes (Oehrn et al., 2015). Both methods provided converging evidence for a functional role of the left HC in the resolution of response conflicts in the Stroop task. However, is the HC also necessary for this task? Only few neuropsychological studies have investigated possible impairments of Stroop conflict resolution in patients with HC lesions (Pinto et al., 2017; Wang et al., 2007). We thus specifically tested MTLE patients for their response conflict resolution performance using the same auditory Stroop task as in our previous study (Oehrn et al., 2015). Indeed, we found increased response conflict resolution costs in MTLE patients compared to healthy controls, indicated by reduced response accuracies during incongruent relative to congruent trials (Ramm et al., 2019). The difference in response accuracy between incongruent and congruent condition was negatively related to HC volume, suggesting that the HC is indeed causally relevant for response conflict resolution in the Stroop paradigm.

While neuroimaging findings in healthy subjects (Oehrn et al., 2015) do not allow one to conclude whether the HC is indeed necessary for response conflict resolution, neuropsychological studies alone (Ramm et al., 2019) cannot unequivocally show whether the HC itself has caused the performance decline because this may also be due to secondary structural and/or functional alterations in other (e.g., prefrontal) brain regions whose contribution to response conflict resolution is well established. Indeed, previous studies have revealed prefrontal volume reductions in MTLE patients (Keller et al., 2009). Thus, the necessity of hippocampal recruitment for successful response conflict resolution still remains unclear. To the best of our knowledge, no study so far has performed fMRI during a Stroop task in subjects with mesial temporal lobe pathology. Our hypotheses were as follows: First, healthy controls show an increase of activation in incongruent relative to congruent trials in the HC as described previously (Oehrn et al., 2015). Second, the conflict-related increase of activation in the HC is reduced in MTLE patients compared to healthy controls, which might underlie the impairment of cognitive response conflict resolution observed at a behavioral level in these patients (Ramm et al., 2019). Third, participants showing more pronounced response conflict-related activation increases in the HC exhibit lower amounts of performance decline in incongruent relative to congruent trials. To test these hypotheses, we used the same first-level contrast (incongruent vs. congruent trials) on a bilateral hippocampal ROI as adopted before in healthy controls (Oehrn et al., 2015).

2. Methods

2.1. Subjects

Twenty-two patients with MTLE according to International League Against Epilepsy criteria (Scheffer et al., 2017) were initially enrolled in the study. Exclusion criteria were multifocal epilepsy, comorbid neurological disorders and severe psychiatric disorders. Two patients were excluded as they were not compliant to task instructions. In total, twenty patients (8 left TLE, 10 right TLE, 2 bilateral TLE) were included (Table 1). Ninety percent of these patients (18/20) were also included in our previous behavioral and structural neuroimaging study (Ramm et al., 2019). Nine patients received antiepileptic drug (AED) monotherapy and eleven patients were on polytherapy (AED doses are reported in Supplemental Table S1). Left and right MTLE patients did not significantly differ in terms of age at disease onset ($t_{(11.5)} = -0.6$; $p = 0.59$) and disease duration ($t_{(16)} = -0.93$; $p = 0.37$; Table 1).

In addition to patients, twenty age-matched healthy controls participated in the study (Table 1). Subjects with a neurological or psychiatric disorder, a CNS medication or cerebral lesions were excluded. The study was approved by the local ethics committee, and all participants provided written informed consent.

The structural MRI scans received concordant evaluations by two radiologists following a standardized protocol to assess typical findings for hippocampal sclerosis (Dekeyzer et al., 2017), and all findings were consensual among them. No temporal lobe/hippocampal lesion was found in any of the healthy controls. In most patients ($n = 17$), persuasive signs of hippocampal sclerosis were found (Supplemental Table S1). One patient with right MTLE had undergone right selective amygdalohippocampectomy. Excluding this patient from the analysis did not change the conclusions.

2.2. MRI data acquisition

Structural and functional images were collected using a 3T Achieva Philips MR scanner (Philips Medical Systems, Best, NL) equipped with a six-channel head coil. MRI scanning included an anatomical 3D T1-weighted (T1w) turbo field echo (TFE) sequence (repetition time [TR] = 7.4 ms; echo time [TE] = 3.4 ms; inversion time [TI] = 900 ms; flip angle = 9°; 176 slices; matrix = 256 × 224; field of view [FOV] = 256 × 224 mm^2; slice thickness = 1 mm).

Moreover, an MRI protocol specifically developed for the analysis of mesial temporal lobe structures was applied. Paracoronal T2-weighted (T2w) images perpendicular to the long axis of the hippocampi were

Table 1
Demographic and clinical data.

	MTLE (n = 20)	Healthy controls (n = 20)	Statistics	*p*
Demographics				
Age (years)	45.6 ± 14.4	44.9 ± 13.8	t (37.9) = −0.17	0.87
Gender (female/male)	8/12	12/8	X2 (1) = 1.6	0.21
Educational level[a]	1/14/5	0/10/10	X2 (1) = 3.3	0.19
Clinical data				
Epilepsy lateralization (left/right/bilateral)	8/10/2			
Age at seizure onset (years)	30.6 ± 13.5 (LH: 27 ± 19) (RH: 32 ± 13)			
Duration of disease (years)	15.2 ± 13.6 (LH: 20 ± 20) (RH: 13 ± 11)			
Depression (yes/no)	2/18			
Medication (GABAergic/non-GABAergic)	4/16			
Antiepileptic Drugs (Mono-/Polytherapy)	9/11			

[a] Education: middle mature/training/A level or academic degree; LH, left MTLE, RH, right MTLE.

acquired using a turbo spin echo (TSE) sequence (TR = 5196 ms; TE = 118 ms; parallel imaging factor [SENSE] = 1.5; turbo factor = 26; 38 slices; FOV = 200 × 200 mm^2; acquisition matrix = 372 × 312; slice thickness = 2 mm; slice gap = 0.2 mm).

During the auditory Stroop task, in total 215 T2*-weighted gradient echo echo-planar images (EPI) were acquired (TR = 2630 ms; TE = 35 ms; 36 axial slices; interleaved acquisition in ascending direction; FOV = 230 × 230 mm^2; matrix = 64 × 63; slice-thickness = 3.6 mm; no inter-slice gap; flip angle = 90°). The first 9 volumes acquired during instructions were discarded. The imaging volumes were tilted upwards by 15° from the AC-PC-plane in order to reduce distortions and signal dropouts in the anterior temporal lobes.

2.3. Experimental paradigm

We used an auditory Stroop paradigm (Fig. 1A) identical to the phonetic block of the paradigm used in previous fMRI studies (Haupt et al., 2009; Oehrn et al., 2015). Participants listened to the German equivalents of the English words "high" and "low", spoken in either a high or a low pitch. This resulted in congruent trials in which semantic and phonetic information match and incongruent trials with conflicting stimulus characteristics. Outside the scanner, the subjects had at least 10 practice trials to familiarize themselves with the Stroop task. During this period, the experimenter verified that the participants understood the instructions correctly and had intact auditory perception. The participants were asked to respond to the pitch of the word by pressing the left or the right button on a response box and to ignore the word meaning. In the incongruent condition, the subjects were required to inhibit the more automatic response to the word meaning, inducing behavioral effects of response conflict. Each auditory stimulus was presented for 0.5s followed by a 2s interval during which instructions remained on the screen, giving additional time to respond. Trials were interleaved with a 0.5s fixation crosshair. Congruent and incongruent trials were presented in a randomized order making sure that the same stimulus type was not presented more than three times in a row. The paradigm was employed in a mixed block/event-related design with 12 task blocks (12 trials each, 144 trials in total) that alternated with 8s resting periods (fixation). To increase the sampling rate of the trial-related blood oxygen level dependent (BOLD) response, we ensured that onsets of trials were not multiples of the TR.

Statistical analysis of the behavioral data was carried out with IBM SPSS® Statistics Software (Version 25.0, IBM, Armonk, NY, USA) and R Software (version 3.5.0, R Core Team, 2017). Mean RTs (including only correct responses) were analyzed with two-way mixed analyses of variances (ANOVA) with "congruency" (incongruent vs. congruent) as a within-subject factor and "group" (MTLE vs. healthy controls) as a between-subjects factor. In the analysis of accuracy, we performed a robust mixed ANOVA using 10% trimmed mean accuracy based on the Wilcox' WSR2 "bwtrim" function (Mair and Wilcox, 2018). Furthermore, post-hoc t-tests or Wilcoxon-tests (when general linear model assumptions were not met) were conducted on the RT difference (incongruent minus congruent trials) and the accuracy difference (congruent minus incongruent trials). Behavioral data analysis revealed that in a subgroup of participants (3 controls, 2 patients) one of the two congruent stimuli (the word "high" presented in high pitch) was consistently misidentified (as low pitch). This was the case for significantly more than 50% of these trials in three control subjects (58%, 64%, 94%), one patient with left MTLE (100%) and one patient with bilateral MTLE (80.5%). We therefore excluded this stimulus from the analysis in these subjects.

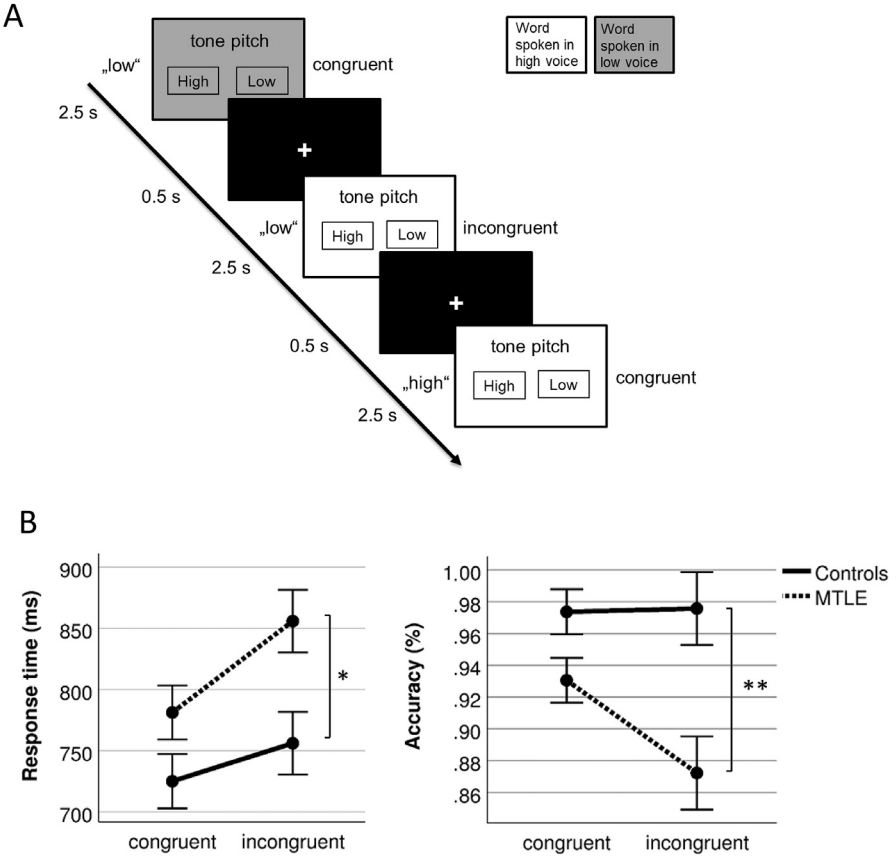

Fig. 1. Experimental procedure and behavioral results. (A) Auditory Stroop paradigm. Subjects responded to the words "high" and "low" spoken in either a high or a low pitch. They were instructed to respond to the pitch, not the word meaning. Response conflict was expected to occur in case of incongruent semantic information. **(B)** Behavioral results in MTLE patients and controls. Left: Response times; right: accuracy. Error bars represent standard error of the mean. MTLE, mesial temporal lobe epilepsy. * significant ($p < 0.05$), ** significant ($p < 0.01$).

2.4. fMRI data analysis

The fMRI data were preprocessed and analyzed with Statistical Parametric Mapping (SPM12; University College, London, UK). The functional images were inspected for movement artefacts. The analysis of the realignment parameters revealed maximum translations of about 2.6 mm (controls) and 3.1 mm (patients), in z-direction, suggesting only minor to moderate movements. Means of individual maximum translations did not differ between patients and controls ($t_{(38)} = -1.65$; $p = 0.11$). Functional EPIs were realigned to the first analyzed EPI volume, co-registered to the bias-corrected, skull-stripped T1w image, spatially normalized into MNI space using the T1-derived normalization parameters, resliced to a voxel-size of $2 \times 2 \times 2$ mm^3 and smoothed with a full-width half maximum Gaussian kernel of 8 mm. We randomly verified the accuracy of normalization in all participants.

A standard 2-stage procedure was used for statistical analysis. On the first level, a general linear model was employed for each participant. BOLD responses were modeled by delta functions at stimulus onset, convolved with a standard canonical hemodynamic response function. The first level model included two regressors for the experimental conditions (congruent and incongruent), one regressor for incorrect trials (in participants with at least one incorrect trial) and six movement regressors derived from the realignment procedure. First level individual t-contrast (incongruent > congruent) images were then entered into a random-effects second level analysis. Mean brain activity of this contrast for healthy controls and MTLE patients, each, was obtained by using separate one-sample t-tests. Differences between MTLE patients and controls were investigated via two-sample t-tests.

Activations were first identified at an uncorrected threshold of $p < 0.001$ and then corrected for multiple comparisons using family-wise error (FWE) correction at a threshold of $p < 0.05$. FWE correction was applied at the voxel-level within a small volume (for ROI-based analyses) and at a cluster level for whole-brain analyses.

In view of our a-priori hypotheses, we performed small volume correction for the ROI containing left and right HC as defined in the Automatic Anatomic Labeling (AAL) atlas (Brett, 2002). Unless otherwise stated, in the ROI analysis, cluster sizes correspond to the number of voxels which survived voxel-based FWE-correction ($p < 0.05$) within the bilateral HC ROI. According to the recommendations for a long axis segmentation of the HC in human neuroimaging (Poppenk et al., 2013) we subdivided the HC into an anterior ($Y \leq 21$ mm MNI) and posterior ($Y \geq 22$ mm MNI) part.

2.5. Correlational analyses

We tested for correlations between fMRI activations and behavioral measures of response conflict resolution (i.e., RT and accuracy differences between incongruent and congruent trials). Using MarsBaR for SPM, we defined a spherical ROI of 6 mm diameter centered on the coordinates of the peak activation for the "incongruent > congruent" contrast in the ROI (bilateral HC). First, we tested for a correlation between extracted activations within this ROI and response conflict resolution performance. Second, we added RT difference as a behavioral regressor and age as a covariate to the second-level model to test for correlations within the search volume of bilateral HC. Correlations were reported if they survived a threshold of $p < 0.05$ (FWE-corrected at the voxel level within the small volume).

We also tested for correlations between fMRI activations and regional brain volumes of HC, ACC and dorsolateral PFC. More precise definitions of the regional brain volumes and the analysis can be found in the Supplement.

We used non-parametric Kendall's tau correlations for all correlation analyses between extracted activations, behavior and regional volumes, as this parameter is unaffected by outliers and particularly suitable for the analysis of small groups. To compare the correlations between groups, we first transformed Kendall's tau into Pearson's r as described by Walker (2003) and then computed Fisher's Z statistic.

2.6. Functional connectivity analysis

FC analyses were conducted using CONN toolbox 18.b (www.nitrc.porg/projects/conn, RRID:SCR_009550). The default denoising pipeline (Whitfield-Gabrieli and Nieto-Castanon, 2012) was implemented on the preprocessed images which includes a temporal band-pass filtering (0.008–0.09 Hz) and linear regression of confounding effects in the BOLD signal. Signal noise from white matter, cerebrospinal fluid, subject movements and task effects were included as confounding variables.

Task-specific seed-based connectivity measures (seed-to-voxel) were computed using bivariate correlational analyses. We restricted the analyses to the incongruent trials. Individual beta values represent the z-transformed correlation coefficients describing the temporal correlation between the BOLD signal from the mean of a ROI and any other voxel in the brain. We selected the left and right HC as defined in the AAL atlas as the seed regions. First-level connectivity maps were then entered into a second-level ANOVA to explore FC differences between MTLE patients and healthy controls, and between left and right MTLE patients, during incongruent trials. Due to the low sample sizes within each MLTE subgroup, we report non-parametric statistics representing a permutation test with 10,000 simulations with cluster-size FWE-correction (two-sided) after an initial voxel threshold of $p < 0.001$.

2.7. Data and code availability

Due to ethical and privacy reasons the data that supports the findings of this study can be made available only via data sharing agreement. Software used in this study is openly available.

3. Results

3.1. Behavioral results

Fig. 1B shows response conflict resolution performance in the two groups. We first investigated effects of conflict on RT using a two-way mixed ANOVA with "congruency" (incongruent vs. congruent trials) as within-subject factor and "group" (MTLE patients vs. controls) as between-subjects factor. We found main effects of congruency ($F_{(1,38)} = 27.1$; $p < 0.001$) and group ($F_{(1,38)} = 5.9$; $p = 0.02$) as well as a significant interaction ($F_{(1,38)} = 4.6$; $p = 0.038$). Post-hoc paired t-tests showed that RT slowing was highly significant in the patients group ($t_{(19)} = -5.7$; $p < 0.001$) while there was only a trend for control subjects ($t_{(19)} = -2.0$; $p = 0.06$).

For response accuracy, a robust mixed ANOVA revealed a main effect of group ($F_{(1,16)} = 5.7$; $p = 0.03$) and trends for an effect of congruency ($F_{(1,16.7)} = 3.4$; $p = 0.08$) and for an interaction ($F_{(1,16.7)} = 3.9$; $p = 0.066$). Non-parametric Wilcoxon tests showed that congruency effects were significant in MTLE patients ($W = 22.5$; $p = 0.01$) but not in healthy controls ($W = 78$; $p = 0.6$). Behavioral effects of congruency did not differ between left and right MTLE patients (all $p > 0.5$). In sum, these results provide clear evidence for impaired response conflict resolution in MTLE patients, in line with our previous findings (Ramm et al., 2019).

3.2. FMRI results

3.2.1. ROI analysis (hippocampus)

We first tested whether we could replicate our previous findings of conflict-related activation in the HC of control subjects (Oehrn et al., 2015). Indeed, controls showed an increased activation for incongruent relative to congruent trials within left HC (MNI coordinates −34/-20/-12; $Z = 4.47$; $p_{(FWE)} = 0.004$; cluster size = 11; Fig. 2A). The peak activation was located in the anterior HC but activation spread into the posterior HC (max/min Y(mm): -18/-24). No activation was found for the reverse contrast within the bilateral HC search volume.

In MTLE patients, the same analysis did not reveal any significant activation in the HC. A direct comparison between controls and patients revealed that MTLE patients showed significantly less conflict-related activation within the left HC than controls (MNI coordinates −34/-20/-12; Z = 3.96; $p_{(FWE)} = 0.017$; cluster size = 6; Fig. 2B). The peak activation resided within the anterior HC but again it spread into the posterior part (max/min Y(mm): -18/-22). Post-hoc analyses showed that these effects were due to decreased activation in the incongruent condition in patients as compared to controls ($t_{(38)} = 2.2$; p = 0.035) rather than increased activation in the congruent condition ($t_{(38)} = -0.04$; p = 0.97; Fig. 2C). No region within the search volume showed higher conflict-related activation in MTLE patients than in controls.

In a control analysis, we performed a second-level mixed ANOVA with the within-subject factor "congruency" (incongruent vs. congruent) and the between-subjects factor "group" (MTLE patients vs. healthy controls). No voxels in the HC ROI showed a main effect of group or congruency. However, the analysis revealed a trend interaction that almost reached significance (MNI coordinates −34/-18/-12; $F_{(1,76)} = 15.88$; Z = 3.61; $p_{(FWE)} = 0.051$; cluster size = 1), largely replicating our previous results.

3.2.2. Whole-brain analysis

How specific are these effects? Table S2 shows the results of a whole-brain BOLD analysis. In controls, incongruent compared to congruent trials elicited significantly higher activation in bilateral dorsomedial and dorsolateral PFC, bilateral middle frontal gyrus, right frontal operculum, right anterior insula and right angular gyrus (Fig. S2), i.e. in brain regions that have previously been found to be activated in other versions of the Stroop task (Botvinick et al., 2004; Chechko et al., 2014; Egner and Hirsch, 2005). The reverse contrast did not reveal any significant activation.

Using the same contrast, MTLE patients only showed increased activation in the left superior occipital cortex (Table S2). Importantly, however, directly comparing MTLE patients to controls revealed no significant activation differences (FWE-corrected at the cluster-level). Activations did not significantly differ between left and right MTLE patients.

To rule out that patients recruit a different neural network than controls, we intentionally applied a very liberal threshold (p < 0.001, uncorrected). These results are reported in the Supplement. In sum, the findings of the whole-brain analysis suggest that patients did not recruit a different neural network than controls that could plausibly serve a compensatory function for response conflict resolution.

3.3. Correlations between behavioral measures of response conflict and fMRI activations

We analyzed the relationship between brain activity and performance of the Stroop task (i.e., RT and accuracy differences between incongruent and congruent trials). We did not observe a significant correlation between brain activity and RT differences in either controls or MTLE patients (all Kendall's tau < .15, all p > 0.36; Fig. 3A). However, when we restricted the analysis to the group of patients with left MTLE, we indeed found a significant negative correlation (Kendall's tau = −.57; p = 0.048): Patients with greater remaining conflict-related HC activation showed better response conflict resolution performance (i.e., reduced RT slowing in incongruent as compared to congruent trials). Notably, this effect was not related to the age of left MTLE patients (Kendall's tau = 0.07; p = 0.8). A similar relationship was not found in right MTLE patients (Kendall's tau = −.02; p = 0.9). However, excluding the patient with right amygdalohippocampectomy changed it to an at least small to moderate (but still non-significant) correlation (Kendall's tau = −0.22; p = 0.4). Moreover, the transformed correlation was significantly greater in left MTLE patients compared to controls (Fisher's Z = −2.09; p = 0.044) but not when compared to right MTLE patients (Fisher's Z = −1.73; p = 0.083), in particular after excluding the patient with amygdalohippocampectomy (Fisher's Z = −1.14; p = 0.25). We did not observe a correlation between conflict-related left HC activation and accuracy differences in either patients or healthy controls (all Kendall's tau < 0.18; all p > 0.29). In sum, these findings suggest that remaining left HC activation in left MTLE patients is functionally relevant for response conflict resolution.

In order to further investigate the functional relevance of HC activation, we conducted a regression analysis in SPM. We added a behavioral regressor to the second-level model, testing for possible further correlations between RT differences and BOLD activity within our search volume of bilateral HC. In controls, we found a trend for a positive correlation (Z = 3.68; p = 0.058, FWE-corrected; Fig. 3B) between RT differences and right (not left) HC activation (MNI coordinates 34/-8/-22). The activation cluster comprised 23 voxels (p < 0.001, uncorrected) of which 22 voxels were located within the right anterior HC (y ≤ 12 mm MNI). This suggests that in contrast to the beneficial role of the left HC in

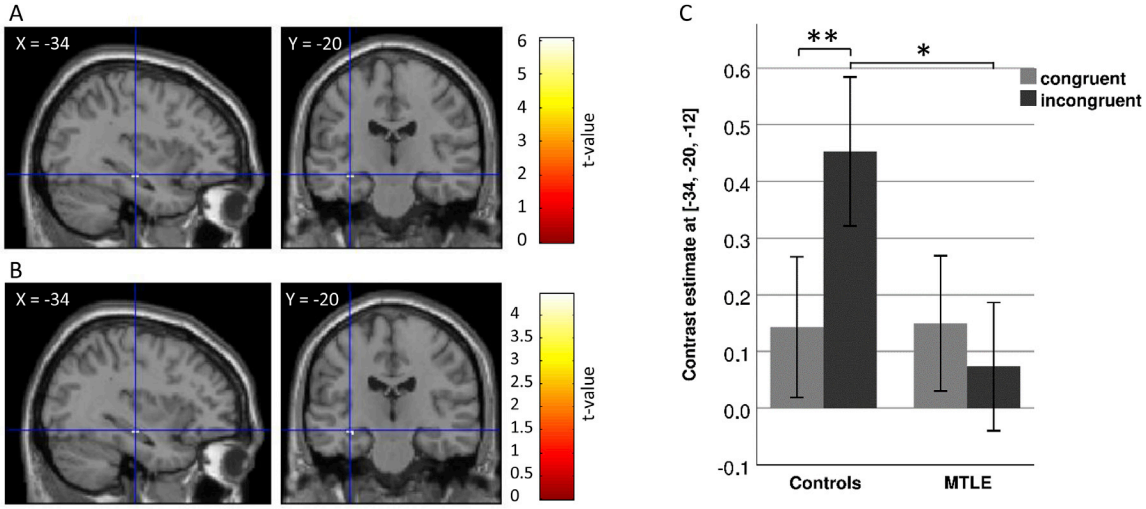

Fig. 2. Activations related to response conflict in the hippocampus. (A) Results in healthy controls for the contrast between incongruent vs. congruent trials within a search mask consisting of bilateral hippocampus. **(B)** Results for the group difference (controls > MTLE patients) within the same search mask. **(C)** Corresponding contrast estimates, separately for congruent and incongruent trials. Activations within the search mask are presented at a threshold of p < 0.05 (FWE-corrected). Error bars indicate standard error of the mean. MTLE, mesial temporal lobe epilepsy. * significant (p < 0.05), ** significant (p < 0.01).

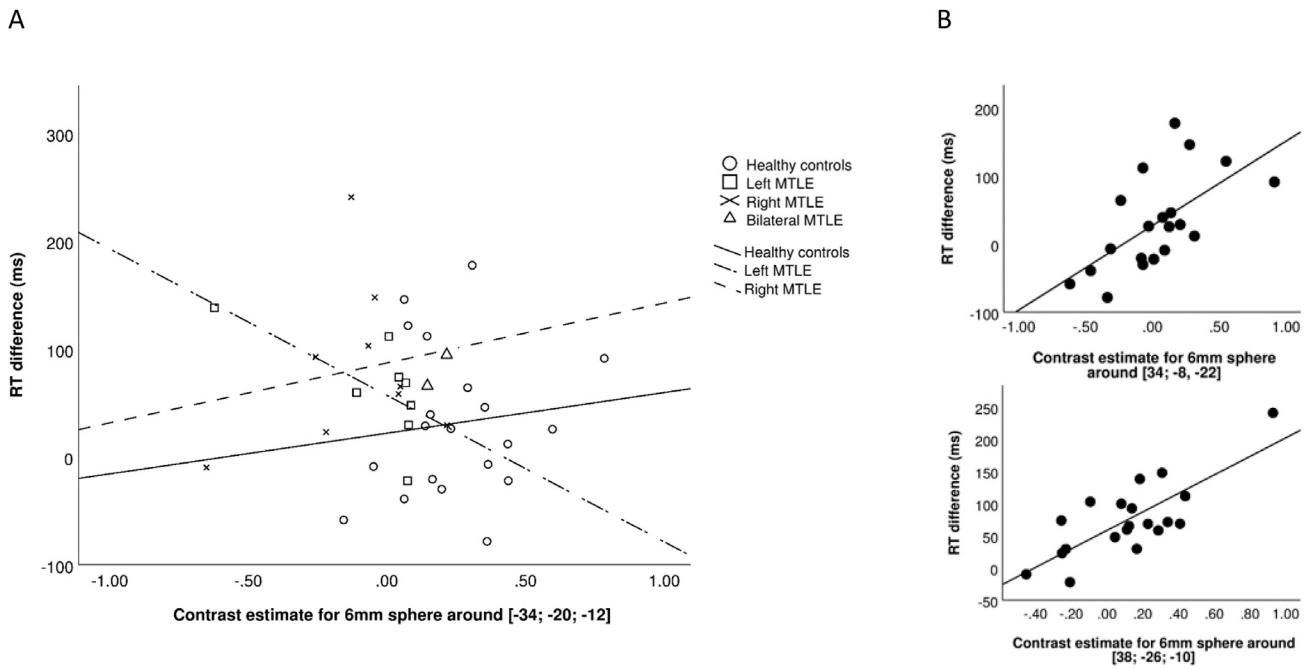

Fig. 3. Correlations between conflict-related hippocampal activation and response conflict resolution performance. (A) Scatterplot of the correlation between response time difference (incongrent - congruent trials) and left hippocampal activation. **(B)** Scatterplots of the multiple regression analysis results for healthy controls (top) and MTLE patients (bottom). MTLE, mesial temporal lobe epilepsy.

left MTLE patients described above, recruitment of the right HC is associated with more pronounced conflict-induced RT slowing. In MTLE patients, we even observed a highly significant positive correlation ($Z = 4.72$; $p = 0.001$, FWE-corrected; cluster size = 12; Fig. 3B) between conflict-induced RT slowing and BOLD responses of the right HC (MNI coordinates 38/-26/-10). In MTLE patients, the activation cluster clearly resided in the posterior HC ($y > 22$ mm MNI). No relationship was observed between accuracy differences and activations. These results suggest that recruitment of the right HC is actually dysfunctional.

We tested for correlations between Stroop task performance and activations in four regions with decreased activation in MTLE patients compared to controls (at a low threshold of $p = 0.001$, uncorrected; see Supplement). After correcting the p-values for multiple testing (p-value x 4), we found a trend for a positive correlation between more pronounced conflict-induced RT slowing and right dorsomedial PFC activation (MNI coordinates 16/34/26; cluster size = 1) in MTLE patients (Kendall's tau = 0.37; $p = 0.09$). The correlation did not differ between left and right MTLE patients. Since the result was restricted to a single voxel, we refrain from further interpretations. In controls, we did not observe a correlation of response conflict resolution performance (reflected by RT or accuracy) with BOLD activity in any of these regions (all corrected $p > 0.47$).

3.4. Relation of hippocampal fMRI activation to brain volumes and clinical variables

Hippocampal volumes are reported in the Supplement (see also Fig. S1). Left HC activation was neither correlated with left nor with right HC volume in either controls or MTLE patients (all Kendall's tau < 0.16, all $p > 0.3$). Also, in left MTLE patients, left HC activation was not related to left HC volume (Kendall's tau = 0.36; $p = 0.22$). Moreover, we found no significant correlations between left HC activation and volumes of ACC and dorsolateral PFC (all $p > 0.1$). These results showed that left HC activation differences cannot be directly explained by volume differences.

In controls, activation in the right anterior HC was significantly related to increased right ACC volume (Kendall's tau = 0.39; $p = 0.016$) and also showed a trend correlation with right HC volume (Kendall's tau = 0.31; $p = 0.06$). In the entire group of MTLE patients, no significant correlations were found (all $p > 0.3$). Interestingly, specifically in left MTLE patients, activation in the right posterior HC correlated with volume decreases in the right HC (Kendall's tau = −0.76; $p = 0.03$), right ACC (Kendall's tau = 0.84; $p = 0.009$) and, on a trend level, in the right dorsolateral PFC (Kendall's tau = −0.70; $p = 0.051$). The correlation between right HC activation and left HC volume did not reach statistical significance (Kendall's tau = −0.46; $p = 0.26$). These findings support the notion that right HC activation increases when volumes of right HC, ACC and PFC are relatively low.

We tested whether antiepileptic treatment with GABAergic drugs had an impact on response conflict resolution performance and HC activation. RT differences did not differ between the four patients with and the sixteen patients without GABAergic AEDs ($t_{(18)} = -0.19$; $p = 0.9$), while accuracy differences were marginally higher in the small group of patients with GABAergic drugs ($U = 53$; $p = 0.050$). However, these patients were also significantly older than patients without GABAergic drugs ($t_{(17.8)} = 3.0$; $p = 0.007$). Extracted HC activations (6 mm sphere around local maximum) from the "incongruent > congruent" contrast did not differ between patients with as compared to without GABAergic drugs ($t_{(18)} = 1.4$; $p = 0.2$).

Finally, we explored possible effects of the age at seizure onset and of disease duration on performance and HC activation. However, patients' age at seizure onset and their disease duration did neither correlate with conflict effects on RT or accuracy nor with extracted HC activations.

3.5. Functional connectivity results

If hippocampal recruitment during response conflict resolution is reduced in case of HC dysfunction, there might be changes in the interaction between the HC and established conflict-control brain regions. Indeed, FC between the left HC and the PFC (including voxels of the left and right paracingulate cortex, left frontal pole, left ACC and left superior frontal gyrus) was reduced in MTLE patients relative to healthy controls (Fig. 4). For the right HC seed, FC was reduced with the posterior

cingulate cortex (PCC), ACC, and right frontal pole (Fig. 5).

As epilepsy lateralization has been shown to have an impact on hippocampal FC (Pereira et al., 2010), we compared FC in healthy controls relative to left MTLE and right MTLE, respectively. In left MTLE, we found reduced FC between the left HC and posterior regions including precuneus and PCC as well as anterior regions including ACC, bilateral paracingulate cortex, bilateral superior frontal gyrus and bilateral frontal pole. FC was increased with the left caudate nucleus. Importantly, the right HC did not show any changes in FC.

In right MTLE, the left HC seed showed reduced intrahippocampal and right HC FC. Moreover, similar to left MTLE patients, FC was reduced between left HC and the PFC (including bilateral paracingulate cortex, left frontal pole, ACC and left superior frontal gyrus). Notably, for the right HC seed, a decrease in FC was observed with voxels in right HC and left HC, in addition to bilateral amygdalae, parahippocampal gyri and various areas of the lateral temporal lobe. Moreover, FC was reduced in the ACC and parietal regions including PCC and precuneus.

In sum, FC between HC and PFC was reduced in all MTLE patients. More specifically, in left MTLE patients, the affected left HC showed reduced FC with both hemispheres while FC of the spared right HC was preserved. In right MTLE, widespread FC changes were observed for both the right and the left HC.

Finally, we tested whether hippocampal FC was modulated by task. The mixed ANOVA with the between-subjects factor "group" (controls, MTLE patients) and the within-subject factor "congruency (incongruent, congruent) did not reveal a significant interaction, though.

4. Discussion

The present study was conducted to further scrutinize the role of the HC in response conflict resolution. Using fMRI in MTLE patients and healthy controls, we investigated whether the impairment of response conflict processing in patients with hippocampal lesions that we had

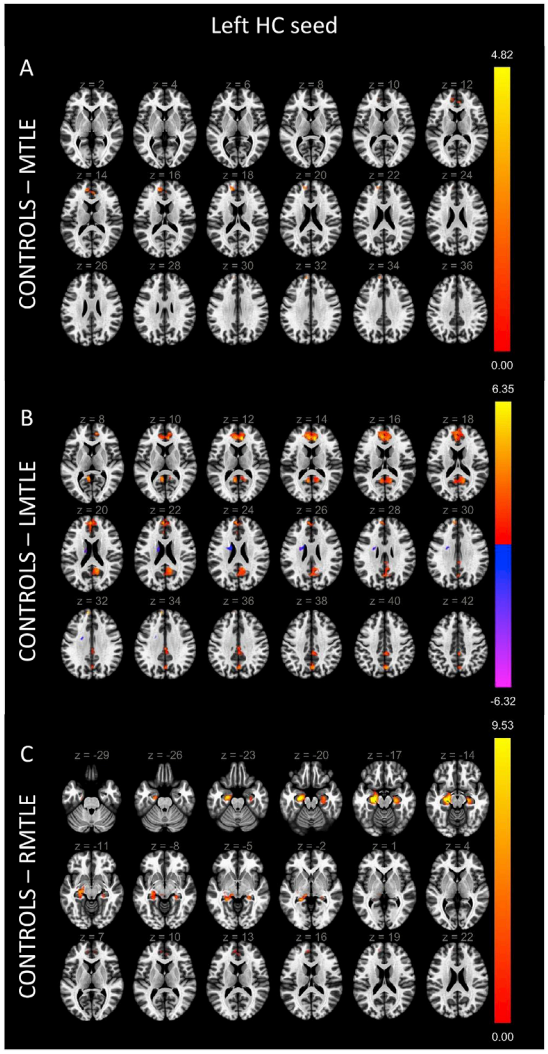

Fig. 4. Results from functional connectivity (FC) analysis for left HC seed. Differences in the left HC FC between healthy controls and **(A)** all MTLE patients, **(B)** left MTLE patients and **(C)** right MTLE patients. Yellow areas indicate significantly lower FC with the left HC seed as compared to controls. Clusters are presented when surviving a family-wise-error corrected cluster threshold of $p < 0.05$. Initial threshold was $p < 0.001$. The left side of the images corresponds to the left side of the brain. LMTLE, left mesial temporal lobe epilepsy; RMTLE, right mesial temporal lobe epilepsy; HC, hippocampus.

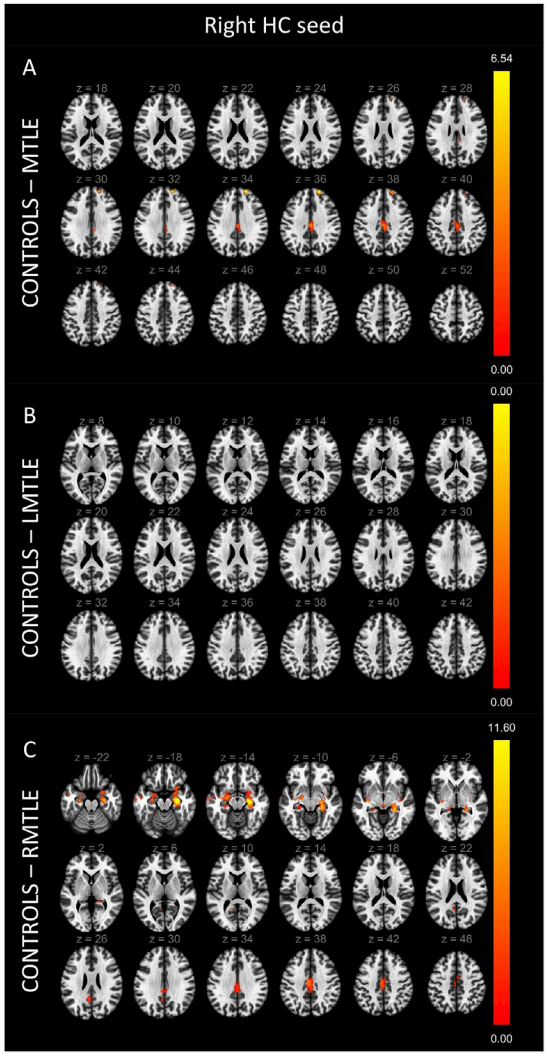

Fig. 5. Results from functional connectivity (FC) analysis for right HC seed. Differences in the right HC FC between healthy controls and **(A)** all MTLE patients, **(B)** left MTLE patients and **(C)** right MTLE patients. Yellow areas indicate significantly lower FC with the right HC seed as compared to controls. Clusters are presented when surviving a family-wise-error corrected cluster threshold of $p < 0.05$. Initial threshold was $p < 0.001$. The left side of the images corresponds to the left side of the brain. LMTLE, left mesial temporal lobe epilepsy; RMTLE, right mesial temporal lobe epilepsy; HC, hippocampus.

described before (Ramm et al., 2019) is indeed due to reduced recruitment of the HC and/or reduced activity of other (possibly connected) brain areas. We also tested whether other brain regions could compensate for impaired hippocampal functioning.

Using ROI-based fMRI analyses within bilateral HC, we indeed found evidence for a selectively reduced recruitment of the left HC in MTLE patients as compared to healthy controls. Remaining left hippocampal activation in patients with left MTLE was associated with better performance (i.e., reduced conflict-induced RT slowing). By contrast, conflict-associated activation of the right HC was correlated with lower performance, suggestive of a maladaptive compensatory attempt in MTLE patients. The results provide further support that the left anterior HC is indeed essential for successful response conflict resolution.

Most previous neuroimaging studies did not suggest a hippocampal involvement in cognitive control mechanisms (Niendam et al., 2012). This might be due to low sensitivity (i.e., high rate of type 2 errors) of standard whole-brain fMRI analyses. A previous study combining two more sensitive measures, i.e. intracranial EEG in the HC of epilepsy patients contralateral to their lesion and fMRI recordings in healthy controls, revealed evidence that the left HC is recruited during response conflicts, and the intracranial EEG results suggested that this recruitment is task-relevant (Oehrn et al., 2015). In the present study, we replicated the fMRI findings showing increased activation in left HC during response conflict resolution. Thus, our results support the notion that the role of the HC is not restricted to motivational approach-avoidance conflicts as established previously (Bach et al., 2014; Loh et al., 2017; O'Neil et al., 2015) but plays a more fundamental role in resolving conflicting response tendencies.

An important result of our study was a diminished left HC activation in MTLE patients, accompanied by an attenuated response conflict resolution performance. While an impaired Stroop task performance in MTLE patients has recently been demonstrated (Ramm et al., 2019), the reduced conflict-related HC activation is a completely novel finding in patients with hippocampal dysfunction. In the present study, we observed reduced HC activation in patients specifically for incongruent (but not for congruent) trials. This suggests that during response conflicts in the Stroop task the HC is not sufficiently recruited in MTLE patients, possibly contributing to their behavioral deficits.

Next, we tested whether the reduced HC activation in MTLE patients was specific or part of a decreased activation of large-scale brain networks. At a stringent threshold (using FWE correction for multiple comparisons), we did not observe any other area to show reduced activation across the brain. At a more liberal threshold, patients showed reduced activations in other areas previously associated with response conflict processing, in particular the right dorsolateral and dorsomedial PFC. Functional changes in the PFC are not surprising as HC and PFC are structurally and functionally connected (Li et al., 2015). Moreover, our result is in line with previous findings of prefrontal structural abnormalities in TLE patients (Keller et al., 2009). Thus, it is possible that not only HC dysfunction but also associated PFC functional changes or even an impaired HC-PFC circuitry contributed to impaired response conflict resolution performance in MTLE patients. The notion of an impaired HC–PFC circuitry might be supported by our FC analysis (Figs. 4 and 5) showing that left HC–PFC connectivity was reduced in both left and right MTLE patients which is in line with the existing literature (Kucukboyaci et al., 2013). Notably, we did not find FC to be modulated by congruency, so that we cannot infer that these FC changes are specific to response conflict resolution. Moreover, even at a low threshold, no up-regulation of the contralateral HC or other connected brain areas that are relevant for response conflict processing was observed, suggesting lack of any compensatory recruitment in MTLE patients. In sum, the fMRI results indicate that impaired response conflict resolution performance in MTLE patients is due to reduced left HC recruitment, possibly exacerbated by secondary changes in the HC–PFC circuitry.

So far, we are aware of only a single study that showed reduced HC activation during Stroop conflicts in a patient cohort, by investigating subjects with fibromyalgia (Martinsen et al., 2014). Since this is a rather non-specific pathology, however, the pathophysiology underlying this finding remains a bit unclear. By contrast, in our study, the reduced conflict-related activation in anterior (and to a lesser extent also posterior) portions of the left HC is congruent with our volumetric results of a reduced left HC volume – specifically in its body and head – that we observed in patients with left MTLE, but also by trend in right MTLE (see Supplement Fig. S1). In line with these findings, the FC analysis (Figs. 4 and 5) revealed that in right MTLE patients, also the left HC showed substantial connectivity changes, consistent with previous findings (Kucukboyaci et al., 2013). Notably, in left MTLE patients, FC of the right HC was preserved. Importantly, reductions of left HC volume and its FC in right MTLE does not seem to be clinically relevant as EEG, seizure semiology and radiological findings did not indicate bilateral MTLE in these patients. However, those functional changes in the intact left HC in right MTLE patients might explain why we found diminished activation in the whole MTLE group containing also right MTLE patients. The lack of significant correlations between left HC activation and left HC volumes suggests that functional changes in the HC cannot be directly explained by macroscopic structural impairments but possibly result from disease processes that also cause epileptogenesis. Importantly, volumes of ACC and dorsolateral PFC were not reduced in the MTLE patients (see Supplement), arguing against the possibility that reduced conflict-related HC activation in patients is due to prefrontal structural abnormalities.

The notion that the left HC is important for response conflict resolution is additionally supported by the finding that in left MTLE patients, remaining left HC activation during conflict trials correlates with better response conflict resolution performance. But why did we not observe such a correlation in right MTLE patients? First, we excluded the patient with right amygdalohippocampectomy to rule out that this patient may have biased our results. Indeed, the null correlation in right MTLE then changed to a small to moderate (but still not significant) correlation. Second, the results of volumetric and FC analyses suggest that left MTLE with hippocampal sclerosis did not affect the right HC, while in right MTLE, both right and left HC were affected (even though apparently without clinical consequence). We speculate that the significant correlation we observed in left MTLE may have been masked in right MTLE due to additional dysfunction in the right HC and connected areas that contribute to a decline in response conflict resolution performance. In other words, since the left HC is not the only affected area in right MTLE patients, remaining activation of left HC is less predictive for performance.

Another unexpected finding was that left HC activation and response conflict resolution performance were unrelated in controls. Again, we do not have a conclusive explanation for this result – in particular because in our previous study, response conflict-related oscillatory responses in the hippocampus did correlate with response conflict resolution performance (Oehrn et al., 2015). Thus, it may be that fMRI BOLD responses are a less sensitive measure of response conflict resolution than brain oscillations measured via intracranial EEG are. Notably, however, the intracranial EEG responses in that previous study were also recorded in epilepsy patients (although we carefully excluded data from electrodes within the seizure onset zone). Alternatively, one may speculate that the lack of a direct relationship between hippocampal BOLD responses and response conflict resolution performance in healthy controls points to the hippocampal role within a larger cognitive control network. Considering that the left HC is less functionally connected to the PFC in MLTE patients, we suggest that HC dysfunction could not be compensated by the PFC. In contrast, in healthy controls, response conflict behavior relies less strongly on HC function but is rather controlled by communication between HC and a widespread conflict resolution network. This might explain that response conflict resolution performance is less closely related to left HC recruitment in healthy controls compared to left MTLE patients.

While we show evidence that response conflict resolution is partly sub-served by left HC, further regression analyses suggest that right HC

recruitment during this task is in fact dysfunctional. In left MTLE patients, this effect may represent a maladaptive attempt to compensate for left HC dysfunction. A similar interpretation may also be assumed for right MTLE patients who also showed a trend for a reduced volume of the left HC, possibly indicating pathology (see Fig. S1). This interpretation fits with previous findings in patients with TLE, where up-regulation of contralateral HC during a memory encoding task was related to worse rather than improved memory performance (Powell et al., 2007; Schwarze et al., 2009). Moreover, previous studies showed that post-operative episodic memory decline was predicted by preoperative activity in the affected HC rather than remaining activity in the contralateral HC (Bonelli et al., 2010; Powell et al., 2008), suggesting that compensatory increase of contralateral HC recruitment cannot maintain cognitive functionality. Accordingly, we suggest that also with regard to response conflict resolution, reorganization of left HC function to right HC is a futile compensatory attempt. Moreover, correlational analyses revealed that augmented right HC activation was related to relatively low right HC volume in left MTLE patients. Thus, lower right HC volumes in patients with left hippocampal sclerosis might further contribute to dysfunctional right HC activation. In healthy controls, the correlation between conflict-related right HC activation and lower response conflict resolution performance is less likely to suggest a dysfunctional compensatory attempt. Thus, other explanations should be taken into account. Increased right HC activation might reflect greater incidental memory encoding during incongruent compared to congruent trials. This explanation would be in line with previous findings of enhanced memory encoding of target stimuli that were displayed together with incongruent distracting information (Krebs et al., 2015). Thus, the trend correlation in healthy controls might reflect a competition between memory and response conflict resolution processes, leading to the finding of decreased performance accompanied by increased right HC activation.

Why exactly the left HC contributes to response conflict resolution remains unclear. In the auditory Stroop task, subjects need to suppress the automatic response tendency arising from the fast processing of semantic information in favor of the phonetic information. The hippocampal role might rely on its well described pattern separation function (Leutgeb et al., 2007) that could help to reduce overlap between automatic and goal-related response patterns. Alternatively, the relevance of the HC for context-dependent extinction learning (Kalisch et al., 2006; Lissek et al., 2018; Lissek et al., 2019) suggests that the Stroop paradigm requires representing current task contexts which prompt a different response than has been previously established. Finally, the HC might supply a general behavioral inhibition function (Gray and McNaughton, 2000), and efficient inhibition may promote faster PFC-mediated selection and execution of the correct, goal-directed response. As the irrelevant verbal/semantic information should be processed primarily by the left hemisphere in right-handed subjects, it seems plausible that the left HC would be particularly needed to suppress responses related to semantic information. This would explain why conflict-related HC activation was specifically observed on the left side in our current as well as our previous study (Oehrn et al., 2015).

Some alternative explanations that may explain patients' diminished HC activation during response conflict processing apart from their hippocampal dysfunction itself have to be considered. Antiepileptic drugs (AED), in particular those with a GABAergic action, were shown to affect motivational approach-avoidance conflict processing (Bach et al., 2018). However, our data do not suggest that patients on GABAergic drugs have substantially biased our findings regarding performance and hippocampal activation. On the other hand, some AEDs have even been shown to improve cognition (von Stulpnagel et al., 2010) and to normalize task-related fMRI activation patterns (Bakker et al., 2012; Wandschneider et al., 2014). Finally, it remains unclear how the reduced conflict-related activation of the left HC is related to the memory functions of the HC. The Stroop paradigm does not rely on memory, and thus the results cannot be explained by memory impairments. Still, the impact of conflict-related HC activation on memory formation should be tested in future fMRI studies combining a response conflict paradigm with a memory task.

The study has several limitations. First, the auditory Stroop task was employed in a mixed event-related/block design to resemble previous behavioral and EEG studies in which we implemented a randomized trial order. A disadvantage of the design is a short inter-trial-interval leading to an overlap between hemodynamic responses. This might also explain why we did not find significant task-modulation of FC in either controls or MTLE patients. Jittered and longer intervals might have increased sensitivity. In the present design, however, we ensured that each trial onset was not a multiple of the TR to increase the sampling rate of the BOLD response. Second, the inclusion of patients with left and right pathology probably caused greater variability in conflict-relation activations which might have attenuated activations in the patient group. Third, epileptiform EEG activity might have influenced the results. Even though previous studies suggested rather mild general effects of epileptic activity on cognitive performance (Aldenkamp and Arends, 2004), further studies with patients with a neocortical temporal lobe epilepsy are needed to rule out epileptic activity as a relevant factor. Last, brain development might have been affected by a chronic therapy-refractory epilepsy or medication use. We analyzed the effect of seizure onset and disease duration, showing that both measures had no impact on the main results.

5. Conclusion

Our findings show that activation of the left HC is required for the behavioral control of automatic response patterns. The left HC serves a unique role within a larger response conflict resolution network that apparently cannot be compensated in patients with MTLE.

Declaration of competing interest

The authors declare no conflict of interest.

CRediT authorship contribution statement

Markus Ramm: Data curation, Formal analysis, Writing - original draft. **Benedikt Sundermann:** Data curation, Formal analysis, Writing - original draft. **Carlos Alexandre Gomes:** Formal analysis. **Gabriel Möddel:** Resources. **Lisa Langenbruch:** Writing - original draft. **Nina Nagelmann:** Data curation. **Mahboobeh Dehghan Nayyeri:** Formal analysis, Writing - original draft. **Peter Young:** Funding acquisition. **Bettina Pfleiderer:** Formal analysis, Writing - original draft. **Nikolai Axmacher:** Formal analysis, Writing - original draft.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuroimage.2020.116723.

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