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Human Hippocampal Dynamics during Response Conflict

Highlights

- Hippocampal iEEG and BOLD activity increases during response conflicts in humans
- Hippocampal theta oscillations (3–8 Hz) predict behavioral performance
- Medial temporal conflict effects occur specifically in the hippocampus
- Our results suggest a role of the hippocampus beyond memory and spatial navigation

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In Brief

A new study by Oehrn, Baumann, et al. combining iEEG recordings from the hippocampus of epilepsy patients with fMRI from healthy participants provides converging evidence that the human hippocampus, in particular the magnitude of hippocampal theta power (3–8 Hz), plays a role for the resolution of response conflict.

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Human Hippocampal Dynamics during Response Conflict

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SUMMARY

Besides its relevance for declarative memory functions [1–5], hippocampal activation has been observed during disambiguation of uncertainty and conflict [6, 7]. Uncertainty and conflict may arise on various levels. On the perceptual level, the hippocampus has been associated with signaling of contextual deviance [8–10] and disambiguation of similar items (i.e., pattern separation) [11–13]. Furthermore, conflicts can occur on the response level. Animal experiments showed a role of the hippocampus for inhibition of prevailing response tendencies and suppression of automatic stimulus-response mappings [14–17], potentially related to increased theta oscillations (3–8 Hz) [18]. In humans, a recent fMRI study demonstrated hippocampal involvement in approach-avoidance conflicts [19]. However, the more general significance of hippocampal activity for dealing with response conflicts also on a cognitive level is still unknown. Here, we investigated the role of the hippocampus for response conflict in the Stroop task by combining intracranial electroencephalography (iEEG) recordings from the hippocampus of epilepsy patients with region of interest-based fMRI in healthy participants. Both methods revealed converging evidence that the hippocampus is recruited in a regionally specific manner during response conflict. Moreover, our iEEG data show that this activation depends on theta oscillations and is relevant for successful response conflict resolution.

RESULTS

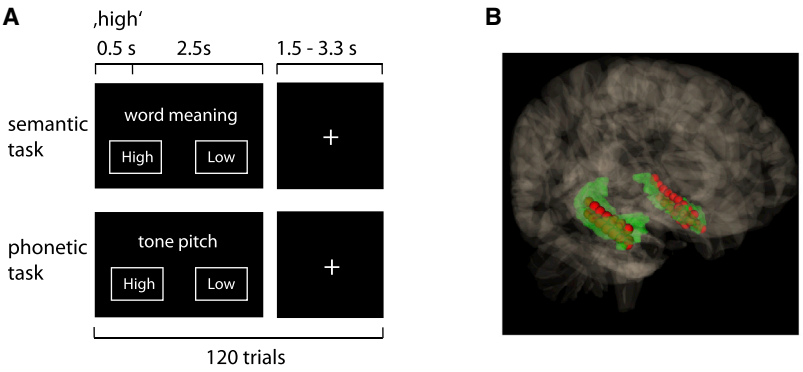
Inconsistency of Stimulus Characteristics during the Phonetic Task Leads to Behavioral Response Conflict in Patients and Healthy Subjects

In an auditory version of the Stroop task [20, 21], participants responded to either the meaning or the pitch of the words "high" and "low," resulting in consistent and inconsistent trials (Figure 1A). Figure 1C summarizes the mean (across subjects' means) and SE for accuracy and reaction time (RT) for the following conditions: (1) inconsistent, consistent, and control (i.e., the word "good") conditions in the phonetic and the semantic task in the intracranial electroencephalography (iEEG) study and (2) inconsistent and consistent conditions in the phonetic task in the fMRI study. We investigated conflict effects and behavioral differences between the two study groups (iEEG versus fMRI) using a repeated-measures ANOVA with the within-subject factor "consistency" (inconsistent versus consistent trials in the phonetic task) and the between-subject factor "group." For RTs, this analysis revealed a main effect of consistency ($F_{1,34} = 32.7$, $p < 0.001$), but no interaction ($F_{1,34} = 3.1$, $p = 0.09$) and no main effect of group ($F_{1,34} = 2.6$, $p = 0.12$). For accuracy, we found main effects of consistency ($F_{1,34} = 15.7$, $p < 0.001$) and group ($F_{1,34} = 12.8$, $p = 0.001$), as well as a significant interaction ($F_{1,34} = 5.6$, $p = 0.02$). Accuracy values of fMRI participants were generally higher than accuracy values of iEEG patients. Furthermore, post hoc paired-sample t tests showed that conflict effects on accuracy reached significance in the fMRI group ($t_{26} = -2.7$, $p = 0.01$), while there was only a trend toward an effect in the iEEG group ($t_8 = -2.1$, $p = 0.073$).

In the iEEG study, effects of consistency on behavior were specific to the phonetic task. Stimulus consistency exerted an effect neither on reaction times nor on accuracy during the semantic task (both $t < 0.8$, both $p > 0.4$). An ANOVA including performance from both tasks revealed a significant task × consistency interaction for RTs ($F_{1,8} = 5.7$, $p = 0.04$) and a trend for such an interaction on accuracy ($F_{1,8} = 4.2$, $p = 0.076$).

Response Conflict Is Associated with Increased Hippocampal Pre-response and Decreased Post-response Theta Power

First, we analyzed the power of hippocampal (Figure 1B) theta oscillations related to the onset of consistent and inconsistent trials during the phonetic task, where stimuli caused behavioral conflict (stimulus-locked analysis; Figure 1D). Processing of inconsistent trials relative to consistent trials was associated with a theta power decrease during a late time window



C

		phonetic task			semantic task	
		incons	cons	control	incons	cons
i) iEEG	RTs (ms)	1035±179	906±155	981±189	801±59	798±72
	accuracy (%)	76±10	93±3	84±6	98±1	95±4
ii) fMRI	RTs (ms)	825±37	757±33	x	x	x
	accuracy (%)	95±2	99±0	x	x	x

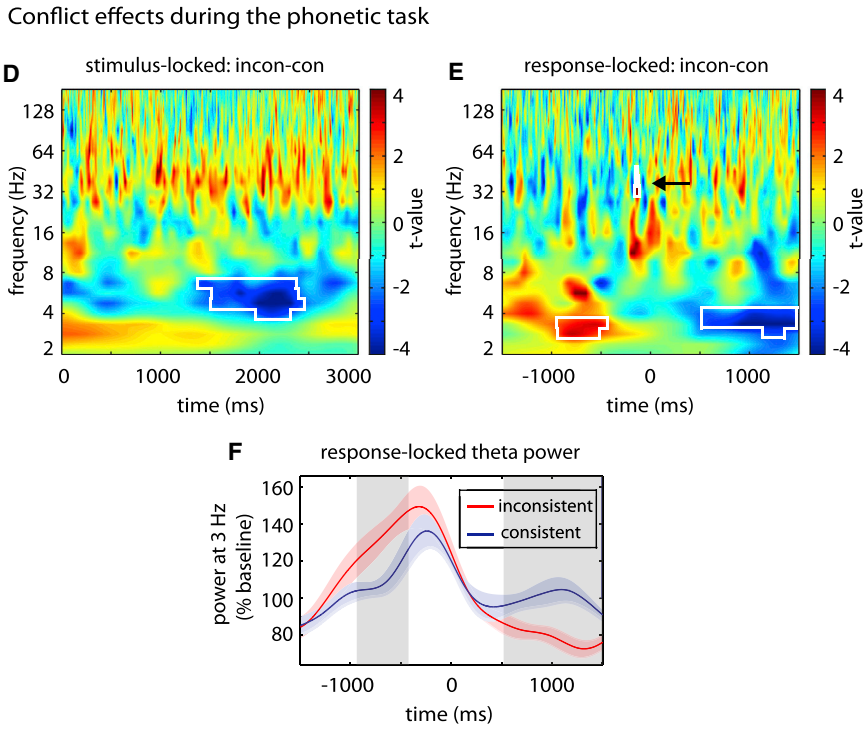


Figure 1. Experimental Design, Electrode Location, Behavioral Results, and Hippocampal Power Effects

(A) Experimental procedure. Patients responded to the words "high" and "low" spoken in a high or low pitch, resulting in consistent and inconsistent stimuli. Two tasks were performed: response to word meaning (semantic task) or response to tone pitch (phonetic task). Conflict was only expected to occur during the phonetic task.

(B) Electrode location of hippocampal electrodes of all patients in Montreal Neurological Institute (MNI) space (red), mapped onto the MNI template and a hippocampal mask (green).

(C) Table summarizing behavioral data (across subjects' means ± SE for reaction times [RTs] and accuracy) for: (i) inconsistent (incons), consistent (cons), and control conditions in the phonetic and the semantic task in the iEEG study and (ii) inconsistent and consistent conditions in the phonetic task in the fMRI study.

(D–F) Results from analysis of hippocampal power data during the phonetic task.

(D and E) Graphs depict color-coded time-frequency resolved test statistics comparing power values during correct inconsistent (incon) and consistent (con) stimulus processing (i.e., t values; paired-sample t test). Stimulus-locked analysis (D): zero indicates stimulus onset. Response-locked analysis (E): zero indicates response onset. These effects were specific to the hippocampus and did not occur in adjacent brain regions (see also Figures S2A–S2F).

(F) Time course of mean ± SEM response-locked theta power fluctuations at 3 Hz during correct inconsistent (red) and correct consistent (blue) trials. Significant time periods are shaded in gray.

(4–7 Hz, 1,376–2,453 ms, $p = 0.02$; cluster-based correction for multiple comparisons; see Supplemental Experimental Procedures). There were no conflict effects (i.e., inconsistent > consistent) on high-frequency power (largest cluster: $p > 0.16$). Due to the rapid power fluctuations in the high-frequency range, cluster-based permutation statistics are not the most sensitive measure to reveal sustained high-frequency power changes. To assure that we were not missing any effects due to our choice of statistics, we conducted an additional analysis. To this end, we averaged high-frequency power in two frequency bands (low gamma: 30–60 Hz; high gamma: 61–181 Hz) within 100-ms intervals and assessed effects of the factors consistency, time window, and frequency band on power values. This analysis did not reveal a main effect of consistency ($F_{1,8} = 2.9$, $p = 0.13$) or interactions between factors (consistency × frequency band: $F_{1,8} = 0.06$, $p = 0.82$; consistency × time window: $F_{3.1,24.7} = 0.77$, $p = 0.53$; consistency × frequency band × time window: $F_{3.3,26} = 0.94$, $p = 0.44$).

Next, we conducted response-locked analyses of the same trials (see Supplemental Experimental Procedures; Figure 1E). These analyses revealed that oscillations at around 3 Hz for inconsistent relative to consistent trials were more pronounced before the response (−938 ms to −424 ms, $p = 0.046$) and reduced after the response (520–1,499 ms, $p < 0.01$). In addition, we found increased pre-response low-gamma power (32–45 Hz, −151 ms to −106 ms, $p = 0.049$). As reaction times are on average around 1,000 ms (see Figure 1C), the response-related reductions of theta oscillations occur at around 1,500–2,500 ms after stimulus presentation and thus probably reflect the same

phenomenon as the stimulus-locked theta power decrease. By contrast, the pre-response increases of theta and gamma band activity were only observed in the response-locked and not in the stimulus-locked analyses, suggesting that they were more directly related to response execution. Furthermore, this increase in pre-response theta power was not simply attributable to enhanced declarative memory processes (i.e., task instruction recall). Task instructions need to be remembered for both inconsistent and control trials. A paired-sample one-tailed t test between average power values during inconsistent and control words in the significant time-frequency window (3 Hz; −938 ms to −424 ms) showed increased theta power during inconsistent compared to control words (t_8 = 1.9, p = 0.048; spectrogram in Figure S1Gi). On the other hand, theta power during control words was not different from consistent words (t_8 = 1.5, p = 0.09; spectrogram in Figure S1Gii). In the semantic task, no effect of consistency was observed at all (Figures S1Hi and S1Hii, all p > 0.21). To ensure that our response-locked results were not biased by condition-dependent baseline changes, we performed two additional analyses: first, we analyzed non-baseline-corrected power data, which, however, exhibit large fluctuations across trials. Second, we corrected each individual trial by the mean power over all conditions in each subject (within the same baseline period). We performed non-parametric cluster analyses in the time-frequency windows, where significant effects were observed in the original analysis (3 Hz: −1,000 to −400 ms, 500 to 1,500 ms; 32–45 Hz: −200 ms to response onset). We observed significant clusters both at low frequencies (3 Hz, not baseline corrected: −766 to −597 ms, p = 0.025 [inconsistent > consistent]; 524 to 923 ms, p = 0.022 [consistent > inconsistent]; baseline over all conditions: −908 to −442 ms, p < 0.01 [inconsistent > consistent]; 721 to 1,499 ms, p < 0.001 [consistent > inconsistent]) and at high frequencies (not baseline corrected: 32–38 Hz, −127 to −105 ms, p = 0.02 [inconsistent > consistent]; baseline over all conditions: 32–45 Hz, −147 to −106 ms, p < 0.001 [inconsistent > consistent]). These results are shown in Figures S1A–S1F and described in detail in the Supplemental Information.

Conflict-Related Changes in Pre-response Theta Oscillations Are Specific to the Hippocampus

Both stimulus- and response-locked pre-response effects were specific to the hippocampus (Figures S2A–S2F): no significant stimulus-locked or response-locked conflict-related effects were observed in the rhinal cortex (largest cluster: p = 0.3) or in the temporobasal cortex (largest cluster: p = 0.17) during the phonetic task. However, we did observe a response-locked pre-response gamma power decrease (but no increases as in the hippocampus) for inconsistent relative to consistent trials in temporolateral cortex (38–64 Hz, −656 ms to −569 ms, p = 0.02). By contrast, post-response power fluctuations seemed to be less specific: after the response, we observed conflict-related decreases in theta/alpha power in the temporobasal cortex (5–11 Hz, 813–1,152 ms, p = 0.041) and increases of gamma power in the temporolateral cortex (32–90 Hz, 1,173–1,232 ms, p = 0.034). No extra-hippocampal region showed an effect of consistency during the semantic task.

Enhanced Magnitude of Pre-response Hippocampal Theta Oscillations Is Associated with Increased Response Speed and Accuracy

Further analyses showed that the hippocampal response-locked effects during the phonetic task were functionally relevant. For inconsistent trials, we found that correct (as compared to incorrect) trials were associated with enhanced magnitudes of (1) pre-response theta oscillations (3–7 Hz, −866 ms to −105 ms, p < 0.01), (2) pre-response broadband gamma power (76–152 Hz, −287 ms to −248 ms, p = 0.03; 32–108 Hz, −252 ms to −117 ms, p < 0.001), and (3) post-response broadband gamma power (45–181 Hz, 361–431 ms, p < 0.001). These results are presented in Figure 2A. Due to the high overall accuracy of patients and a rigorous artifact correction, a relatively low number of incorrect inconsistent (on average seven) trials were available for this analysis. However, iEEG data provide a comparably high signal-to-noise ratio. Nevertheless, we corroborated these findings by testing the robustness of power estimates as a function of trial quantity. Our analyses indicated that a sufficient number of trials were available. For a detailed description, please refer to the Supplemental Information. For consistent trials, correct (as compared to incorrect) trials were again accompanied by increases in pre-response gamma power (32–45 Hz, −393 ms to −338 ms, p < 0.001; Figure 2C). However, no differences between correct and incorrect consistent trials occurred in the low-frequency range (all clusters p > 0.1; Figure 2C), indicating that these effects were specific to inconsistent trials.

Next, we compared neural activity during processing of the faster 50% of trials as compared to the slower 50% of trials (Figure 2B). For this analysis, only correct trials were considered. For inconsistent trials, faster responses were associated with early reductions (3–5 Hz, −1,499 ms to −1,022 ms, p < 0.01) and later increases (3–5 Hz, −514 ms to 0 ms, p = 0.027) of pre-response theta oscillations. Similarly, pre-response low-gamma power increased for fast relative to slow inconsistent trials (32–45 Hz, −299 ms to −241 ms, p = 0.03). For consistent trials, no differences were observed between fast and slow trials (Figure 2D), again demonstrating specificity of behavioral effects for inconsistent trials.

Interestingly, the association between increased pre-response theta and gamma power and faster reaction times was also found on the level of individual trials (Figure 2E). For this analysis, we correlated pre-response theta and gamma power and RT across correct trials (for each subject). As functionally relevant power increases primarily occurred in pre-response intervals of around 500 ms (theta) or 300 ms (gamma), we correlated the single-trial power in these time-frequency windows (−500/−300 ms up to response onset for theta/gamma band activity, respectively) with reaction times. For inconsistent trials, both correlations were consistently negative, indicating increased power in faster trials (one-sample t tests of Fisher-z-transformed correlation values against zero; theta: t_8 = −2.6, p = 0.03; gamma: t_8 = −2.4, p = 0.041). In contrast, pre-response theta and gamma power did not play a functional role for the processing of consistent trials in the phonetic task (theta: t_8 = −1.1, p = 0.28; gamma: t_8 = −2, p = 0.08). Furthermore, the behavioral relevance of power fluctuations during inconsistent trials, in terms of correlations with reactions times, was specific to the phonetic task and absent during the semantic task (semantic

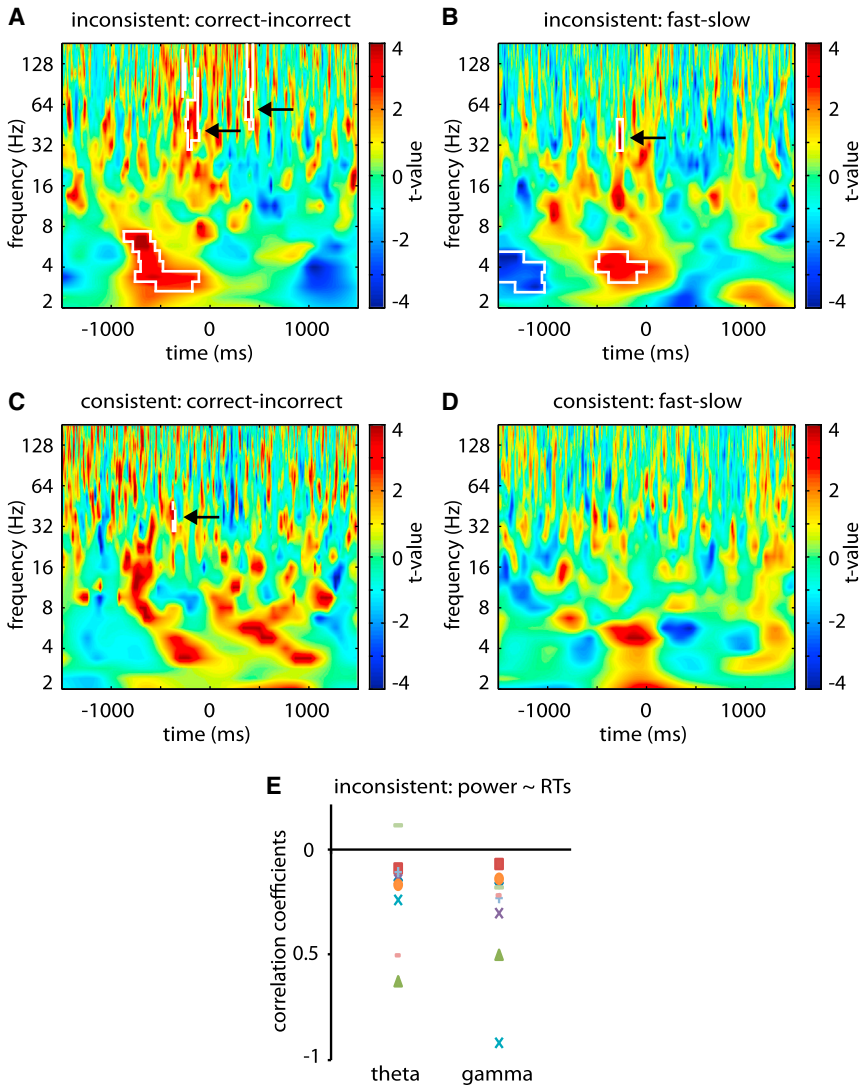


Figure 2. Hippocampal Power Enhancement Correlates with Successful Response Conflict Resolution

(A and C) Hippocampal power in relation to response accuracy for inconsistent (A) and consistent (C) trials: time-frequency resolved test statistic comparing power values during correct and incorrect inconsistent (A) and consistent (C) trials (i.e., t values; paired-sample t test).

(B and D) Relationship between hippocampal power and reaction times for inconsistent (B) and consistent (D) trials: time-frequency resolved test statistic comparing power values during correct fast and slow inconsistent (B) and consistent (D) trials (i.e., t values; paired-sample t test).

(E) Correlation coefficients resulting from within-patient correlations between single-trial power values in the significant time-frequency range and reaction times.

inconsistent theta: $t_8 = 0.6$, $p = 0.56$; semantic inconsistent gamma: $t_8 = -0.33$, $p = 0.75$).

Response Conflict Is Associated with an Increased BOLD Signal in the Hippocampus

In the fMRI experiment, we first tested whether we could replicate the findings of Haupt et al. [20] using a very similar paradigm. Indeed, we observed an increased activation for inconsistent relative to consistent trials in the left inferior frontal gyrus ($x = -52$, $y = +20$, $z = +6$, Z score = 3.24, $p = 0.033$ corrected for multiple comparisons) using search mask 2 (see search volume constraints; Table 1). Next, we investigated whether there was conflict-related activation within the hippocampus, similar to our iEEG data. We observed increased activation for inconsistent relative to consistent trials in two clusters within the left hippocampus (Figure 3; Table 1). Again, this effect did not occur in adjacent areas. Interestingly, we even observed more positive blood oxygenation level dependent (BOLD) responses (reduced deactivation) for consistent relative to inconsistent trials in the left and right parahippocampal gyrus (Figure S2G; Table 1).

DISCUSSION

Combining iEEG recordings in the hippocampus of epilepsy patients with fMRI in a restricted medial temporal search volume, we find converging evidence that the hippocampus is more active during processing of conflict than non-conflict stimuli. This activation is spatially selective and task relevant. Even though we cannot exclude that it only reflects processes related to response conflict resolution instead of response conflict resolution itself, hippocampal activation is specific for the condition with the largest amount of conflict.

Conceptually, a role of the hippocampus for processing of response conflicts might appear surprising based on classic theories about hippocampal functioning, such as episodic memory formation [1–3] and spatial navigation [22, 23]. However, a significant body of evidence has indirectly been pointing toward a role of the hippocampus for conflict processing. Several studies in humans have shown that the hippocampus is activated during presentation of perceptual conflict, i.e., contextually deviant stimuli, which elicit a conflict between the expected and the actual experience [8–10]. Also, the hippocampal involvement in pattern separation might be conceptualized as reflecting a role for the processing of perceptually conflicting items: computational models [4, 5], knockout experiments in rodents [11], and human fMRI studies [12, 13] have shown that the hippocampus (and in particular the dentate gyrus) supports the disambiguation of perceptually similar items. This function may be related to oscillations at theta frequency [24], representing the most prominent oscillatory rhythm in the hippocampus [23].

Furthermore, conflicts can occur on the response level. Animal experiments indicate that the hippocampus plays a role in the inhibition of established response patterns [14–18].

Table 1. Overview of fMRI Results

Contrast and Brain Regions	MNI Coordinates x	y	z	p Value (*)	*Z* Score (Peak)	T Score
Search Mask 1: Medial Temporal Lobe						
Congruent > Incongruent						
Parahippocampal gyrus	−16	−34	−12	0.008	4.28	4.71
Parahippocampal gyrus	20	−32	−16	0.039	3.84	4.15
Incongruent > Congruent						
Hippocampus	−16	−4	−12	0.008	4.26	4.69
Hippocampus	−36	−16	−14	0.014	4.13	4.52
Search Mask 2: DLPFC/ACC/Pre-SMA						
Incongruent > Congruent						
Inferior frontal gyrus	−52	20	6	0.033	3.24	3.42

Top: results from an anatomically defined search mask in the medial temporal lobe (including hippocampus and parahippocampal gyrus). Bottom: results from an anatomically defined search mask based on findings from a previous study using a very similar paradigm [20]. p value (*) corrected for multiple comparisons using familywise error (FWE), p(FWE) < 0.05. Initial threshold at p < 0.001 uncorrected.

Human fMRI studies showed hippocampal involvement in the context of approach-avoidance conflict involving emotional manipulations [6, 7, 19] and reported conflict-induced correlations between activity in the anterior cingulate cortex (ACC) and the hippocampus [25]. Furthermore, human fMRI data suggest a role of the hippocampus in the inhibition of established responses to a more general gist of a stimulus [26]. However, previous fMRI studies (including our own [20]) investigating the neural bases of cognitive response conflict, as measured by the Stroop task, have yet failed to provide evidence for a significant role of the hippocampus. Several factors complicate the detection of hippocampal activity during conflict processing. First, hippocampal activity is generally difficult to establish, and whole-brain correction for multiple comparisons in previous fMRI studies may not have been sufficiently sensitive. Here, we used a region of interest (ROI)-based approach based on our a priori hypothesis and maximized sensitivity using an uncommon fMRI sequence with a variable echo time (TE) that is optimized for detecting activity in medial temporal regions [27]. Second, our iEEG

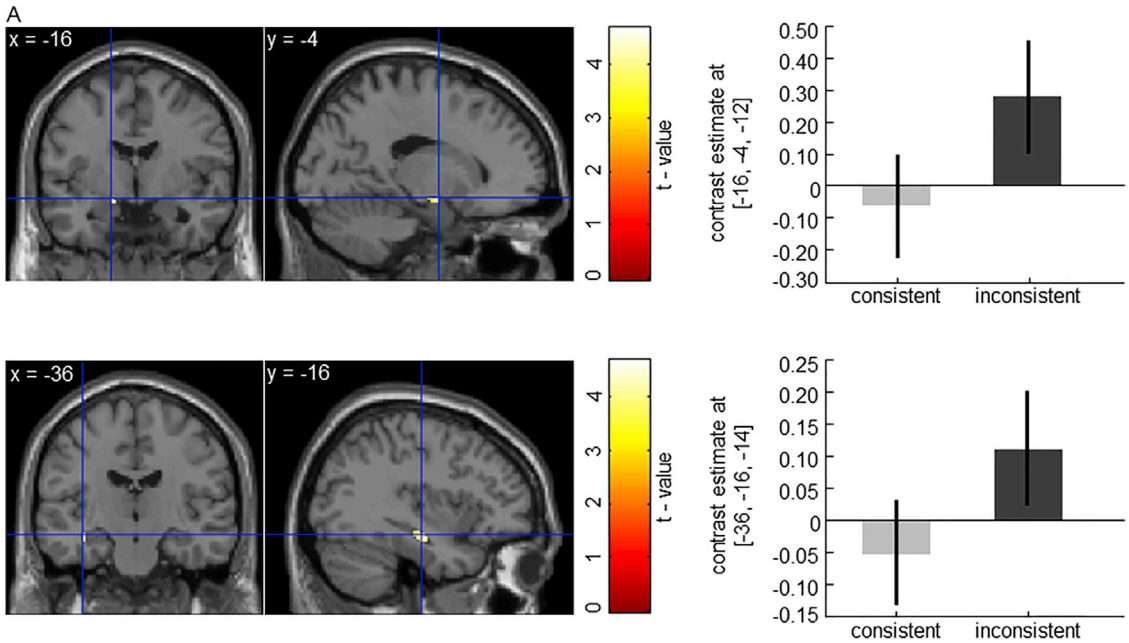


Figure 3. Response Conflict Is Associated with BOLD Signal Enhancement in the Hippocampus

(A) Results within a search mask consisting of hippocampus and parahippocampal gyrus. Left: brain activation within the left hippocampus for the contrast correct inconsistent > correct consistent trials. Right: corresponding contrast estimates. Statistical threshold p < 0.05 corrected for multiple comparisons using familywise error (FWE) within the search mask (small volume corrected). These effects were not present in adjacent brain regions (see also Figure S2G). Error bars indicate 90% confidence interval.

data reveal that the dynamics of conflict processing in the hippocampus are quite complex, involving both a pre-response increase and a post-response decrease of theta oscillations. Notably, such complex pattern would have been impossible to resolve with other methods lacking the high temporal and spatial resolution of iEEG.

Taken together, many hints in the previous literature have been indicating a possible role of the hippocampus in conflict processing. However, the unprecedented spatial and temporal resolution of our electrophysiological data and the adjusted analytic approach with regard to our hippocampal fMRI data allowed us to show for the first time that the hippocampus plays a behaviorally relevant role in the resolution of cognitive response conflicts.

To which extent the observed neural processes reflect similar mechanisms as engaged during perceptual conflicts, e.g., during mismatch detection and pattern separation, remains to be elucidated. Pattern separation as well as mismatch detection (see [28] for a review) involve comparisons to memory traces. However, there is no conventional association between the words "high" and "low" and a high or low voice pitch, as used in our study, indicating that our observed oscillatory changes reflect processes beyond comparisons between incoming and expected perceptual information. Notably, pre-response theta power enhancements and all behavioral correlations were specific to the stimulus type eliciting behavioral conflict (inconsistent words during the phonetic task) and absent for the identical stimuli shown during the semantic task, indicating that the observed changes are not attributable to mismatching stimulus properties per se but rather to processes related to behavioral response conflict.

In summary, this study provides evidence that the human hippocampus plays a role in the resolution of response conflict. Our findings suggest hippocampal functions far beyond its well-known engagement in memory and spatial navigation.

SUPPLEMENTAL INFORMATION

Supplemental Information includes Supplemental Results, Supplemental Discussion, Supplemental Experimental Procedures, and two figures and can be found with this article online at http://dx.doi.org/10.1016/j.cub.2015.07.032.

AUTHOR CONTRIBUTIONS

N.A. and J.F. designed the experiment. C.R.O. collected and analyzed iEEG data. C.B. acquired and analyzed fMRI data. H.L. contributed to the fMRI data analysis. C.R.O., C.B., J.F., H.L., H.K., U.H., S.H., and N.A. interpreted the data and wrote the manuscript.

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