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Theta phase synchronization between the human hippocampus and prefrontal cortex increases during encoding of unexpected information: A case study

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Abstract

Events that violate predictions are thought to not only modulate activity within the hippocampus and prefrontal cortex, but also to enhance communication between the two regions. Scalp and intracranial electroencephalography studies have shown that oscillations in the theta frequency band are enhanced during processing of contextually unexpected information. Some theories suggest that the hippocampus and prefrontal cortex interact during processing of unexpected events, and it is possible that theta oscillations may mediate these interactions. Here, we had the rare opportunity to conduct simultaneous electrophysiological recordings from the human hippocampus and prefrontal cortex from two patients undergoing presurgical evaluation for pharmaco-resistant epilepsy. Recordings were conducted during a task that involved encoding of contextually expected and unexpected visual stimuli. Across both patients, hippocampal-prefrontal theta phase synchronization was significantly higher during encoding of contextually unexpected study items, relative to contextually expected study items. Furthermore, the hippocampal-prefrontal theta phase synchronization was larger for contextually unexpected items that were later remembered compared to later forgotten items. Moreover, we did not find increased theta synchronization between the prefrontal cortex and rhinal cortex, suggesting that the observed effects were specific to prefrontal-hippocampal interactions. Our findings are consistent with the idea that theta oscillations orchestrate communication between the hippocampus and prefrontal cortex in support of enhanced encoding of contextually deviant information.

Introduction

Unexpected events that violate internal predictions are more likely to be successfully encoded to memory (e.g., Axmacher et al. 2010; Murty & Adcock, 2014; Schomaker et al., 2014; Elhalal et al, 2014). It has been proposed (Ranganath & Rainer, 2003; Lisman & Grace, 2005) that the hippocampus and the prefrontal cortex (PFC) play a critical role in the detection and formation of memories of *contextually* unexpected events (e.g., rare events of a specific category that are randomly encountered within the majority of events of a different category) (Von Restorff, 1933). Consistent with this idea, functional magnetic resonance imaging (fMRI) studies in humans have indicated that processing of contextually unexpected information is associated with increased activation in the hippocampus and PFC (and other cortical/ subcortical regions) (Strange & Dolan 2001; Bunzeck & Düzel, 2006; Yassa & Stark, 2008; Murty et al., 2013; Murty & Adcock, 2014). Interestingly, functional connectivity between the hippocampus and the PFC is enhanced during successful memory encoding and retrieval (e.g., Grady et al., 2003; Ranganath et al. 2005; Nee & Jonides, 2008). Therefore, a currently unresolved question is whether or how these regions interact during encoding or processing of contextually unexpected events.

Several EEG studies have suggested that neural oscillations in the theta band are enhanced following contextually unexpected events. Studies using intracranial EEG have shown that hippocampal theta power is increased during encoding of contextually unexpected information (Axmacher et al., 2010; Chen et al., 2013). Furthermore, contextually unexpected events elicit increases in scalp-recorded frontal theta power (e.g., Cavanagh et al., 2012; Walsh & Anderson, 2012; Cavanagh & Frank, 2014), and recent EEG studies have demonstrated increases in theta phase synchrony between frontal and temporal scalp sites during contextually unexpected stimuli (Lee et al., 2014;

Harper et al., 2017). In light of this evidence, it is possible that theta oscillations facilitate communication between the prefrontal cortex and hippocampus during encoding of contextually unexpected events.

Results from other paradigms have indicated that interactions between the prefrontal cortex and the hippocampus could be mediated by theta coupling. For instance, intracranial EEG studies in humans have reported increased theta phase synchronization between the PFC and medial temporal lobe cortical regions during virtual navigation and memory retrieval (Kahana et al., 1999; Anderson et al., 2010; Watrous et al., 2013; but see, Raghavachari et al., 2006), but these studies did not report changes in phase synchrony specifically with the hippocampus. Recent studies on memory retrieval in humans using source localization on magnetoencephalography data or combined EEG-fMRI data also suggest that theta oscillations correlate with hippocampal-PFC connectivity (Fuentemillla et al., 2014; Herweg, Apitz et al., 2016; Kaplan et al., 2017).

Consistent with the idea that theta oscillations might facilitate communication between the PFC and hippocampus, local field potential recordings in rodents have shown that salient events (e.g. those occurring at choice points in a maze learning task) increase oscillatory power in the theta band (4-8 Hz) within the hippocampus and the PFC (e.g., Winson, 1978; Hasselmo et al., 2002; O'Neill et al., 2013; Totah et al., 2013; Donnelly et al., 2014). Furthermore, recordings in rodents and non-human primates have also shown that theta oscillations synchronize between the two areas (Benchenane et al., 2010; Brincat & Miller, 2015; Fujisawa & Buzsáki, 2011; Hyman et al., 2005; Jones & Wilson, 2005). For example, enhanced theta phase synchrony between the hippocampus and the PFC has been shown during performance of a spatial T-maze task

(Benchenane et al., 2010) and during retrieval of object-context associations (Place et al., 2016). These findings in the rodent brain are consistent with the idea that phase synchronization in the theta frequency band is relevant for spike-timing-dependent plasticity (Fell & Axmacher, 2011). However, little is known about the extent to which the findings of frontal-hippocampal synchronization in rodents correspond to activity in the human brain.

In the present study, we used intracranial EEG to determine whether human hippocampal-PFC theta phase synchrony is enhanced during (i) processing of contextually unexpected events and (ii) whether hippocampal-PFC theta phase synchrony predicts later memory performance. We used a "Von Restorff" paradigm (Von Restorff, 1933) in which patients encoded trial-unique images from two different categories (for exemplary trials, see Fig. 2A). Importantly, one type of stimuli comprised of the majority of encoding stimuli in a given encoding-test block (i.e. "contextually expected items"; e.g. grayscale faces on a red background), and the other type of stimuli only comprised a small percentage (i.e. 14%) of the encoding stimuli in a given encoding-test block (i.e. "contextually unexpected items"; e.g. grayscale houses on a green background). During the encoding phase, we recorded intracranial EEG simultaneously from the hippocampus and PFC in two pharmaco-resistant epilepsy patients. The locations of the implanted prefrontal electrodes also allowed us to explore whether theta phase synchronization with the hippocampus might be evident with specific subregions of the PFC. In addition, we also investigated phase synchronization between the PFC and sites in the rhinal cortex.

Methods

We recorded intracranial EEG from two pharmaco-refractory epileptic patients at the Department of Epileptology at the University of Bonn, Germany. Both patients (one female; 46 and 48 of age) were implanted with bilateral depth electrodes in the hippocampus and the adjacent rhinal cortex, as well as with bilateral subdural electrodes covering parts of the PFC (i.e. one fronto-polar and one fronto-lateral electrode strip bilaterally covering rostral/ anterior and lateral PFC regions, respectively; see Fig. 1). From the larger sample of patients reported in Axmacher et al. (2010), the two patients were the only patients who had both implanted hippocampal and PFC electrodes. Details about the patients and analyses of event-related potentials and oscillatory power from hippocampal sites in these two patients are presented in Axmacher et al. (2010). Because epileptic seizures were focused on left hippocampal and surrounding medial temporal lobe areas in one patient and left medial temporal lobe areas and left temporo-lateral areas in the other patient, we only considered data from the hippocampal, rhinal and PFC electrodes on the right hemisphere. The local ethics committee approved the study, and both patients gave written informed consent.

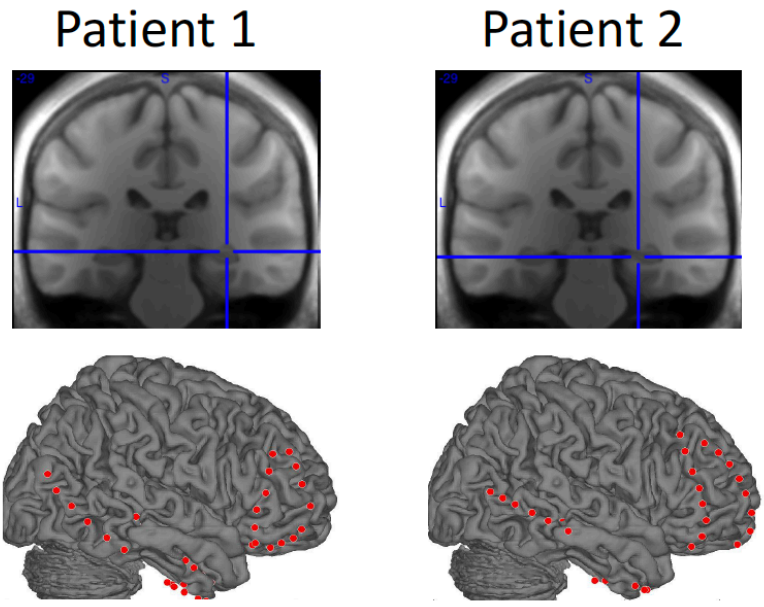

Figure 1. Locations of hippocampal and prefrontal electrodes. On the top, the location of the selected hippocampal electrode is depicted for each patient (Patient 1: MNI 32 -29 -7; Patient 2: MNI 26 -29 -10). On the bottom, all implanted subdural strip electrodes covering the right hemisphere are depicted for each patient. Only the frontopolar and frontolateral strips were analyzed for each patient.

Both patients took part in a variant of a "Von Restorff" paradigm (Von Restorff, 1933; for details of the experimental procedure, see Axmacher et al., 2010). During the encoding phase for which iEEG results are reported here, patients encoded trial-unique images from two different categories (for exemplary trials, see Fig. 2A). Importantly, one type of stimuli comprised of the majority of encoding stimuli in a given encoding-test block (i.e. "contextually expected items"; e.g. grayscale faces on a red background as shown in Fig. 2A), and the other type of stimuli only comprised a small percentage (i.e. 14%) of the encoding stimuli in a given encoding-test block (i.e. "contextually unexpected items"; e.g. grayscale houses on a green background as shown in Fig. 2A). Categories and colors of contextually expected and unexpected stimuli were counterbalanced across blocks in each patient. Following the encoding phase, patients completed a recognition memory test for these images (Fig. 2B). Memory accuracy (i.e. Hits – False Alarms collapsed across 'confident old' and 'unconfident old' responses) was higher for contextually unexpected compared to expected events in Patient 1 (40% vs. 35%) but not in Patient 2 (44% vs. 53%).

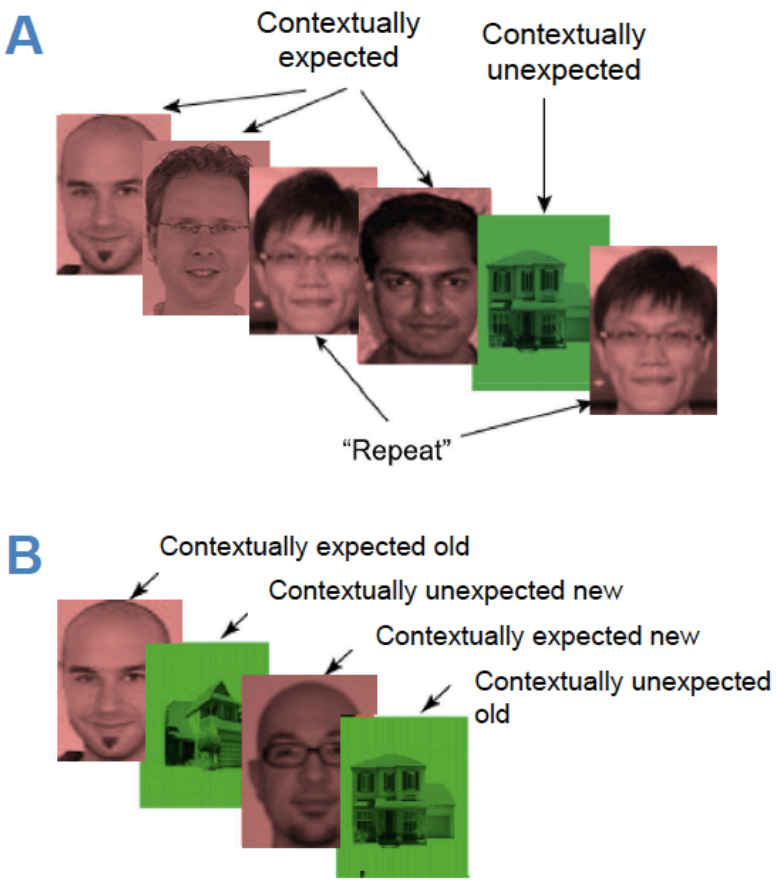

Figure 2. Experimental Procedure. (A) During the encoding phase for which iEEG results are reported here, patients encoded images of stimuli that comprised of the majority of encoding stimuli ("contextually expected items") and the other type of stimuli only comprised a small percentage ("contextually unexpected items"). Categories (i.e., faces, houses) and colors (i.e., red, green) of contextually expected and unexpected stimuli were counterbalanced across blocks in each patient. (B) Following an encoding block, patients completed a recognition memory test.

First, we restricted our iEEG analyses to 'contextually unexpected' (Patient 1: 32 trials; Patient 2: 15 trials) and 'contextually expected' items (Patient 1: 68 trials; Patient 2: 45 trials) that were later correctly recognized in the recognition memory test (i.e.,

collapsed across correct ‘confident old’ and ‘unconfident old’ responses), in order to examine effects of contextual unexpectedness. This approach gave us sufficient number of trials and did not confound effects driven by contextual unexpectedness with memory encoding. Second, we asked whether any potential theta phase synchronization effects further predict later memory. To this end, we compared the later remembered items (from the previous analysis) to later forgotten items separately in the ‘contextually unexpected’ condition (forgotten items for Patient 1: 17 trials; Patient 2: 25 trials) and the ‘contextually expected’ condition (forgotten items for Patient 1: 18 trials; Patient 2: 29 trials). Forgotten trials included items with incorrect ‘confident new’ and ‘unconfident new’ responses, as well as items for which the patients did not give any response during the recognition test.

Because electrode placement varied across patients due to clinical needs of each patient, we focused our analyses on hippocampal contacts that were most consistently localized across the two patients. That is, we first selected one hippocampal electrode per patient that had maximal anatomical overlap between the two patients. The selected hippocampal electrode pair (one electrode from each patient) had the smallest Euclidean distance between the two patients (7 mm distance; Patient 1: MNI 32 -29 -7; Patient 2: MNI 26 -29 -10; see Fig. 1). We then used the EEGLAB toolbox (Delorme & Makeig, 2004) to segment the iEEG data into epochs from -2s to +3s relative to the onset of all items. To preprocess these data, first, we used an automated artifact detection procedure implemented in EEGLAB, in which EEG activity that exceeded more than three standard deviations from the mean on that electrode or five standard deviations across all electrodes were excluded from the analyses (Gruber et al., 2013). Second, in line with our original dataset (Axmacher et al., 2010) we then visually inspected the hippocampal and prefrontal raw data and further manually discarded trials

containing EEG artifacts and epileptiform activity from any further analyses (i.e., trials discarded because of artifacts or epileptic signals detected in a given channel were also excluded from the analysis for all other electrodes).

We also excluded data from the first electrode of each PFC electrode strip (i.e. most-inferior electrode) for both patients due to a very low signal-to-noise ratio as compared to all other remaining PFC electrodes (i.e., no visible event-related evoked responses across contextually unexpected and expected trials). Artifact-free iEEG data were then imported into the Fieldtrip toolbox (Oostenveld et al., 2011) for further analysis. First, standard time-frequency decomposition was performed on artifact-free raw EEG data to obtain power and phase information. We used a Morlet wavelet decomposition method with a width of 5 cycles in individual frequencies. Decomposition was conducted within the epoch time period of -0.2s to 1.2s (t1=onset of event) in steps of 0.02s and in the frequency range of 2-20 Hz.

Second, in order to address the role of theta phase synchrony between the hippocampus and the PFC, we calculated phase synchrony indices between the previously selected hippocampal electrode and each of the artifact-free frontal electrodes, resulting in 14 hippocampal-PFC electrode pairs for each patient. Phase synchrony was separately quantified for all four conditions (contextually unexpected remembered, contextually unexpected forgotten, contextually expected remembered, and contextually expected forgotten) using the debiased estimator of the squared weighted phase lag index (d-WPLI) implemented in Fieldtrip. The d-WPLI has the advantage that it alleviates problems related to volume conduction and other noise-related issues (Vinck et al., 2011).

To statistically determine whether contextually unexpected compared to expected items show a significant theta phase synchrony increase, we used a non-parametric statistical approach that randomly permutes condition labels to correct for multiple comparisons across electrode pairs. Analyses were conducted separately in each patient for all data points within a selected time-frequency range (time range: -0.2s to 1.2s; frequency range: 2 to 20 Hz). This analysis approach had the strength to reveal significant time-frequency clusters without prior selection of a specific time-frequency bin of interest. The steps are as follows: (1) We computed the d-WPLI values within the selected time-frequency range for each condition (in order to use an identical approach as for the surrogate data, we randomly selected equal trial numbers from two conditions of interest based on the minimum number of trials in one condition). We then computed the *difference* of the d-WPLI values between the conditions of interest (i.e., first analysis: contextually unexpected vs. expected items; second and third analyses: remembered vs. forgotten items in the contextually unexpected and contextually expected conditions, separately). Thereby, we obtained the empirical difference in theta phase synchrony (i.e., d-WPLI) between two conditions. (2) We shuffled trial labels by randomly selecting equal trial numbers from the two conditions based on the minimum number of trials in one condition, calculated surrogate phase synchrony values for all 14 electrode pairs, took the difference between the surrogate conditions for all 14 electrode pairs, and saved the maximum surrogate phase synchrony difference across all 14 electrode pairs (i.e. electrode-pair$_{max}$). (3) Step 2 was repeated 500 times. Based on the 500 permutations, we created a null distribution of all electrode-pair$_{max}$ difference values and determined the alpha cut-off point ($p < 0.05$; one-sided; i.e. 475th data point in surrogate difference distribution) in order to test the statistical significance of the empirical theta phase synchrony values for all electrode pairs. This stringent approach allowed us to correct for multiple comparisons across electrodes.

Results

As shown in Appendix Fig. 1, in both patients, permutation tests that corrected for multiple comparisons revealed that frontopolar (within Brodmann area 10) and dorsolateral prefrontal electrode sites (within Brodmann area 46) showed significantly increased theta phase synchrony with the hippocampus during encoding of contextually unexpected compared to expected items. Fig. 3 depicts one selected hippocampal-frontopolar electrode pair per patient showing phase synchronization increases for contextually unexpected compared to expected items in the theta frequency range (~3-8 Hz) (black contours show the permutation-based significant difference clusters in Fig. 3A). We found that the theta phase synchronization increase is specific to contextually unexpected items (Fig. 3B) and absent in contextually expected items (Fig. 3C).

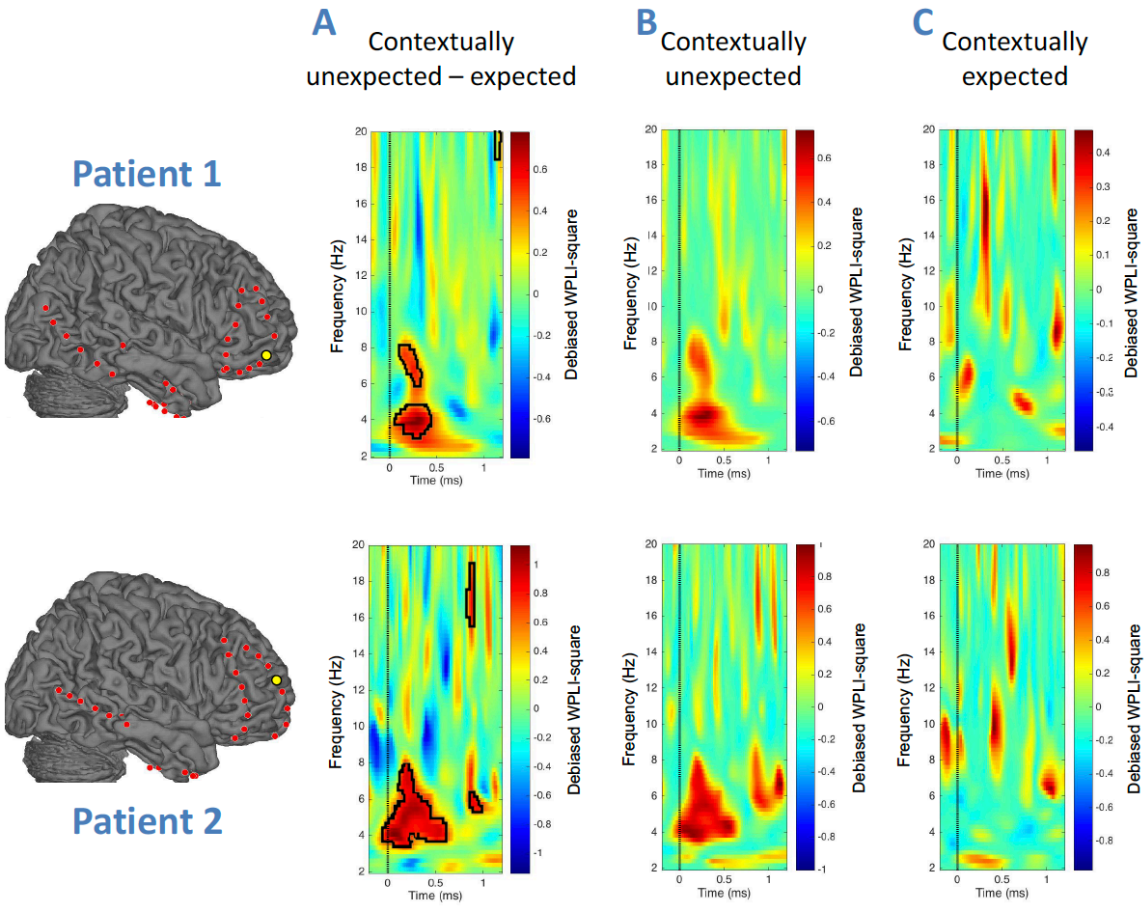

Figure 3. Increases in hippocampal-prefrontal theta phase synchrony for contextually unexpected compared to expected information for one selected frontopolar electrode per patient (highlighted in yellow). In both patients, frontopolar and dorsolateral prefrontal electrode sites showed significantly increased theta phase synchrony with the hippocampus during encoding of contextually unexpected compared to expected items (see Appendix Figure 1 for all 14 hippocampal-PFC electrode pairs). Phase synchrony was measured via the debiased WPLI-square estimator (d-WPLI) (Vinck et al., 2011). Top row depicts findings for Patient 1 and bottom row depicts findings for Patient 2. (A) Significant clusters revealed via permutation tests are depicted with black contours ($p<0.05$ family-wise error corrected). (B) Theta phase synchronization was evident for contextually unexpected events and (C) absent in contextually expected events.

In a second set of analyses, we investigated whether the increased theta phase synchronization related to contextual unexpectedness predicted later memory performance. Importantly, in the ‘contextually unexpected’ condition, across both patients, permutations tests revealed a significant increase in hippocampal-frontopolar theta phase synchronization for later remembered compared to later forgotten unexpected information (Fig. 4A). As such, the significant cluster of the contextually unexpected subsequent memory effect overlapped with the significant time-frequency cluster of the ‘contextually unexpected - expected’ contrast (see Fig. 4 for the same hippocampal-frontopolar electrode pairs as shown in Fig. 3). In contrast, the subsequent memory analysis for the ‘contextually expected’ condition only showed smaller significant clusters that did not overlap in the time-frequency domain with the original clusters from the ‘contextually unexpected - expected’ contrast (Fig. 4B). For completeness, Appendix Fig. 2 shows all 14 electrode pairs for the encoding-related phase synchronization in the contextually unexpected condition.

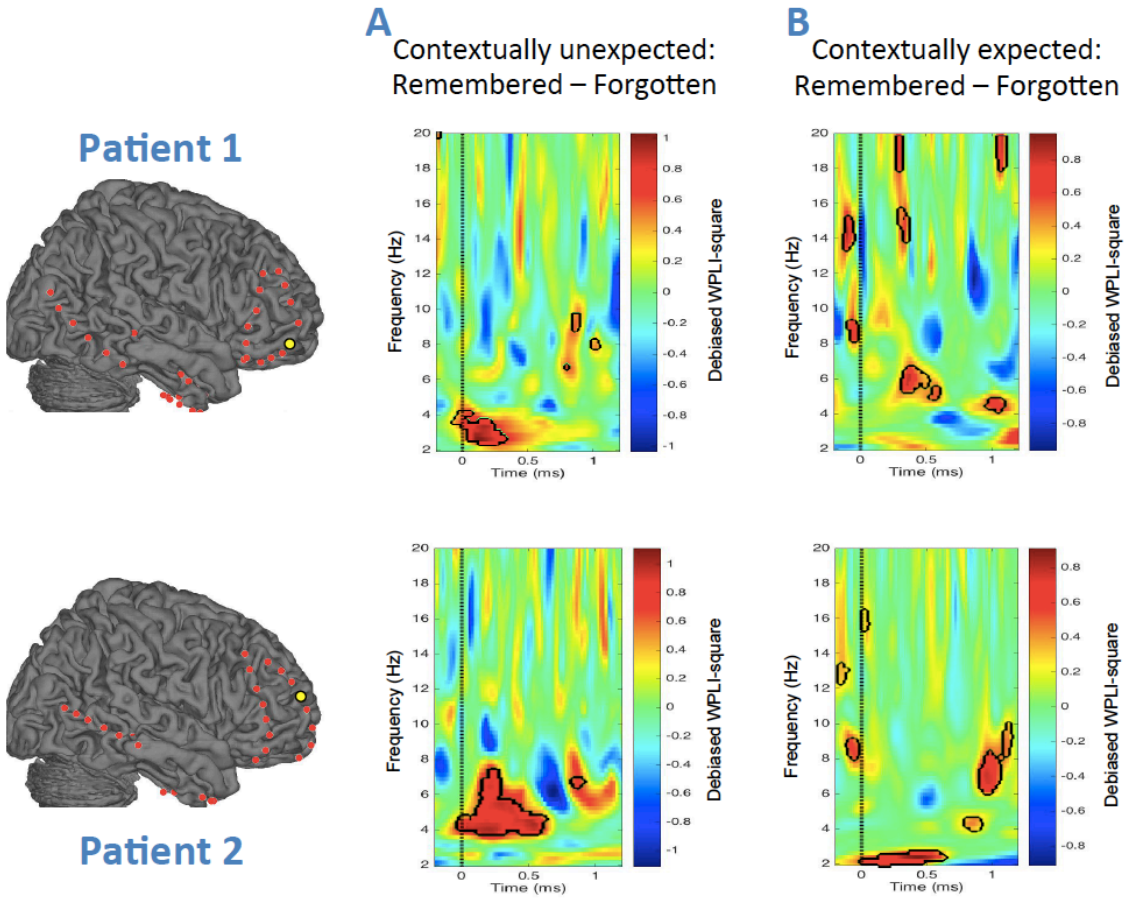

Figure 4. Subsequent memory analyses for the 'contextually unexpected' and 'contextually expected' condition. Across both patients, permutation tests revealed strong encoding-related hippocampal-frontopolar theta phase synchronization (same hippocampal-PFC electrode pairs as shown in Fig. 3) in the 'contextually unexpected' condition that overlapped with the time-frequency cluster of the previously observed theta phase synchronization increase for contextually unexpected events (see Appendix Figure 2 for all 14 hippocampal-PFC electrode pairs). In contrast, encoding-related theta phase synchronization in the 'contextually expected' condition was limited to small clusters that did not overlap with the previously reported phase synchronization for unexpected events.

To examine whether the theta phase synchrony effects were specific to hippocampal-PFC interactions, we performed control analyses in which we quantified theta phase synchrony between rhinal and PFC electrodes. We selected an electrode contact for each patient from the rhinal cortex (perirhinal/ entorhinal cortex) based on the smallest Euclidean distance between rhinal contacts in both patients resulting in 9 mm distance between both patients (distance between rhinal and hippocampal contact: 41 and 36 mm for Patient 1 and 2, respectively). Importantly, permutation tests that corrected for multiple comparisons across electrode pairs revealed that the frontal electrodes that showed increases in theta phase synchrony with the hippocampus did not show enhanced theta phase synchrony with the rhinal cortex for contextually unexpected compared to contextually expected trials.

Discussion

Our study demonstrates that theta phase synchrony between the hippocampus and PFC is enhanced during unexpected, contextually deviant events. Moreover, particularly at sites in the frontopolar cortex, results from both participants converged in revealing that hippocampal-frontopolar synchronization predicted later memory performance. These findings are consistent with the idea that theta oscillations facilitate communication between the PFC and hippocampus in support of successful memory encoding.

Although electrophysiological recording studies in rodents and non-human primates have provided evidence for task-evoked changes in theta synchronization between the hippocampus and PFC (Hyman et al., 2005; Benchenane et al., 2010; Fujisawa & Buzsáki, 2011; Brincat & Miller, 2015; Place et al., 2016), it is worth noting that non-human and human electrophysiological studies typically assess synchrony in

different ways. Studies in rodents often measure synchrony via single-unit spiking activity that is phase-locked to theta oscillations or via amplitude-based coherence of local field potentials between two regions (e.g., Jones & Wilson, 2005; Benchenane et al., 2010). Human studies, in contrast, commonly measure synchrony via phase alignment of theta oscillations between distant brain regions (e.g., Backus et al., 2016; Kaplan et al., 2017; Watrous et al., 2013). Despite these methodological differences in the measurement of synchrony, our findings in humans converge with findings in rodents in that they support the idea that theta synchrony facilitates interactions between the hippocampus and PFC and thereby facilitates memory formation.

Our findings are consistent with recent findings in rodents (Place et al., 2016) that have shown that hippocampal-PFC phase synchronization represents long-range communication. Based on the findings by Place et al. (2016) that the mnemonic operation determines the direction of information flow between the two regions, we speculate that information flow from the hippocampus to the PFC might underlie the encoding of unexpected events into memory. However, our analyses do not allow making any claim about the directionality and more advanced analyses would need to address this question.

It could be argued that theta synchronization might be a ubiquitous phenomenon during encoding, but at least two aspects of our findings are not consistent with this idea. First, theta synchrony between the two regions was larger for contextually unexpected compared to expected events and, second, this synchrony increase was specific between the PFC and the hippocampus, but did not extend to a cortical MTL region (i.e., no evidence for rhinal-PFC theta synchrony). Therefore, our findings suggest that increased theta synchrony might be specific to a brain network (involving the PFC and

hippocampus) that detects the salience of information rather than being a ubiquitous property during encoding.

We found an increase in theta phase synchrony during an early time period during the presentation of a contextually unexpected event. Further control analyses of time-frequency power for the hippocampus and PFC contacts did not reveal consistent early theta power increases for contextually unexpected events in the two patients. It is therefore unlikely that theta power effects in the two regions drove the phase synchronization findings. However, the early theta hippocampal-PFC synchrony coincides with our previously shown early event-related potential (ERP) finding in the human hippocampus (Axmacher et al., 2010). Therefore, the increase in theta synchrony between the PFC and hippocampus together with this early hippocampal ERP might suggest an early detection process that is elicited when expectations are violated and the on-going encoding processes need to be flexibly adapted towards the contextually unexpected information (cf. Axmacher et al., 2010). As pointed out in our earlier study (Axmacher et al., 2010), we cannot rule out that a third source might have driven the observed effect between the hippocampus and PFC. For example, as unexpected information depends on activity within a cortico-mesolimbic circuit, it would be interesting to test how other regions within the circuit might affect hippocampal-PFC synchrony (e.g., Benchenane et al., 2010; Fujisawa & Buzsáki, 2011). Due to the sparse implantation scheme of intracranial EEG, this method is not ideally suited to investigate this question.

Although the understanding of the direct anatomical connections between the hippocampus and frontopolar cortex is complicated by the fact that frontopolar cortex may be differentially organized in humans, as compared with non-human primates or

rodents (Semendeferi et al., 2002), one possible route could be via the nucleus reuniens of the ventral midline thalamus (Herkenham et al., 1978; Bokor et al., 2002) which has been shown to support long-term memory formation (Barker & Warburton, 2018). Alternative routes could be via the entorhinal cortex and parahippocampal cortex/ retrosplenial cortex (Ranganath & Ritchey, 2012).

One limitation of this study is that only two patients had electrodes placed in both the hippocampus and PFC. It would be beneficial for future studies to investigate this question with a larger sample and sufficient numbers of trials to test the reproducibility of the data. In addition, future research would need to address how the observed theta phase synchronization for contextually unexpected information that predicts later memory generalizes to different forms of salient stimuli (e.g., novel or rewarded information).

In conclusion, we have shown that contextually unexpected information elicits increased theta phase synchrony between the hippocampus and frontopolar cortex, and this increase in theta phase synchrony is associated with successful memory formation. Consistent with the literature on the relationship between theta activity and memory (for reviews, see Düzel et al., 2010; Hsieh & Ranganath, 2014), we suggest that theta synchrony between the hippocampus and the PFC may be an important neural mechanism that helps to facilitate memory formation of novel, unexpected information.

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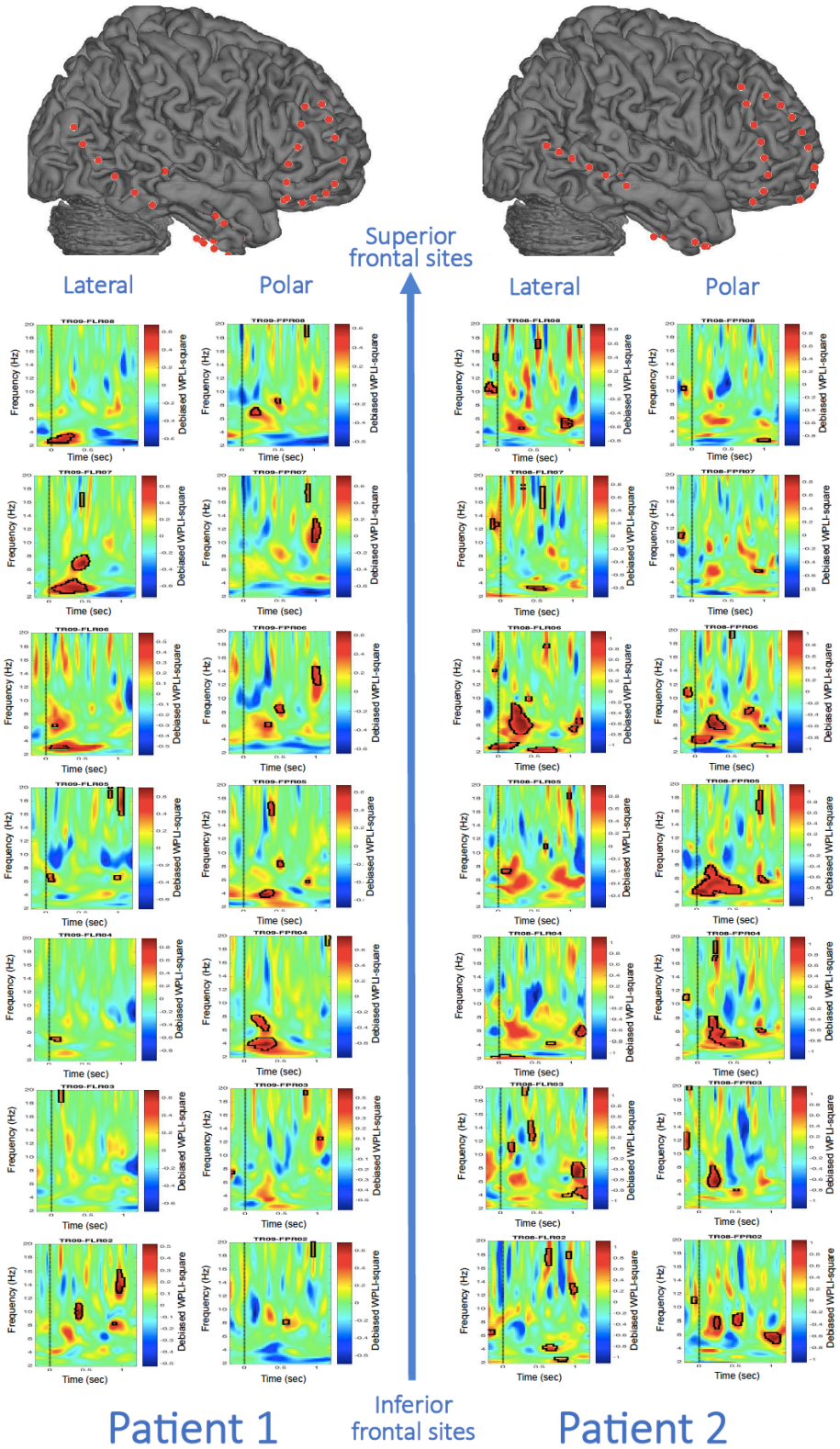
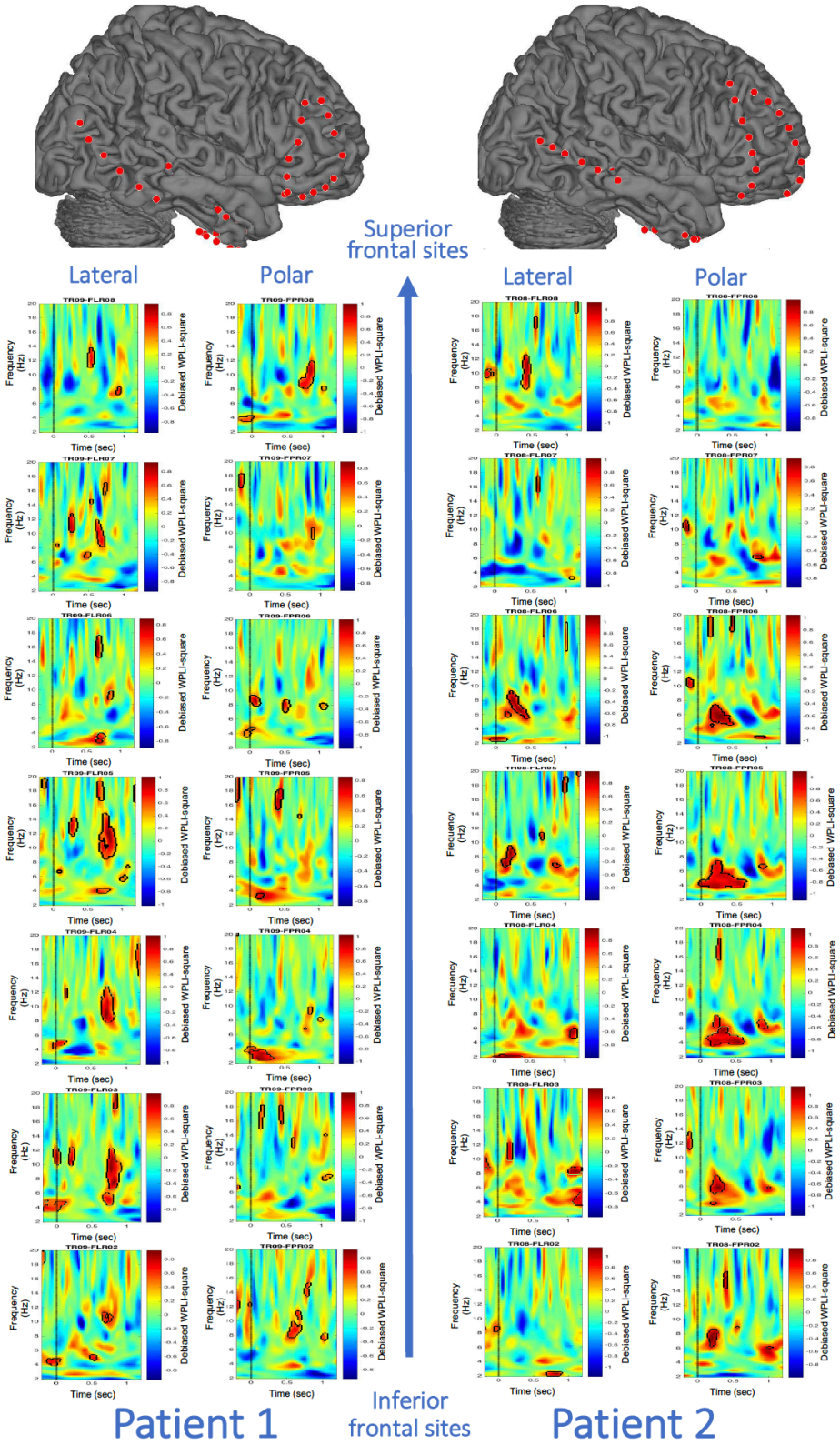


Appendix Figure 1. Increase in theta phase synchronization for contextually unexpected compared to contextually expected events between the hippocampus and frontopolar and dorsolateral prefrontal cortex electrode sites. All selected 14 hippocampal-PFC electrode pairs are shown. Significant clusters revealed via permutation tests are depicted with black contours.



Appendix Figure 2. Encoding-related increase in theta phase synchronization in the 'contextually unexpected' condition between the hippocampus and frontopolar electrode sites across both patients. All selected 14 hippocampal-PFC electrode pairs are shown. Significant clusters revealed via permutation tests are depicted with black contours.