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# Prediction of successful memory encoding based on single-trial rhinal and hippocampal phase information

Marlene Höhne [a], Amirhossein Jahanbekam [a], Christian Bauckhage [b,c], Nikolai Axmacher [d,e], Juergen Fell [a,*]

[a] Department of Epileptology, University of Bonn, D-53105 Bonn, Germany
[b] Bonn-Aachen International Center for Information Technology, University of Bonn, D-53113 Bonn, Germany
[c] Fraunhofer Institute for Intelligent Analysis and Information Systems IAIS, D-53757 Sankt Augustin, Germany
[d] Department of Neuropsychology, Institute of Cognitive Neuroscience, Faculty of Psychology, Ruhr University Bochum, D-44801 Bochum, Germany
[e] German Center for Neurodegenerative Diseases (DZNE), D-53175 Bonn, Germany

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ABSTRACT

Mediotemporal EEG characteristics are closely related to long-term memory formation. It has been reported that rhinal and hippocampal EEG measures reflecting the stability of phases across trials are better suited to distinguish subsequently remembered from forgotten trials than event-related potentials or amplitude-based measures. Theoretical models suggest that the phase of EEG oscillations reflects neural excitability and influences cellular plasticity. However, while previous studies have shown that the stability of phase values across trials is indeed a relevant predictor of subsequent memory performance, the effect of absolute single-trial phase values has been little explored. Here, we reanalyzed intracranial EEG recordings from the mediotemporal lobe of 27 epilepsy patients performing a continuous word recognition paradigm. Two-class classification using a support vector machine was performed to predict subsequently remembered vs. forgotten trials based on individually selected frequencies and time points. We demonstrate that it is possible to successfully predict single-trial memory formation in the majority of patients (23 out of 27) based on only three single-trial phase values given by a rhinal phase, a hippocampal phase, and a rhinal-hippocampal phase difference. Overall classification accuracy across all subjects was 69.2% choosing frequencies from the range between 0.5 and 50 Hz and time points from the interval between −0.5 s and 2 s. For 19 patients, above chance prediction of subsequent memory was possible even when choosing only time points from the prestimulus interval (overall accuracy: 65.2%). Furthermore, prediction accuracies based on single-trial phase surpassed those based on single-trial power. Our results confirm the functional relevance of mediotemporal EEG phase for long-term memory operations and suggest that phase information may be utilized for memory enhancement applications based on deep brain stimulation.

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## Introduction

During recent years a growing body of studies has provided evidence for the impact of oscillatory phases of local field potentials (LFPs) and electroencephalographic (EEG) signals on neural processing. LFP/EEG phases interact with neural membrane potentials and thereby modulate the degree of excitability of neurons and influence their discharge times (Elbert and Rockstroh, 1987; Fröhlich and McCormick, 2010; Anastassiou et al., 2010). In this sense, LFP/EEG phases can be thought of as facilitating or impeding the occurrence of neural activity within a required time window or processing stage (e.g. Fell and Axmacher, 2011).

Indeed, several investigations have shown that LFP/EEG phases affect perceptual and cognitive operations. For instance, the phases of alpha oscillations of scalp EEG were reported to be predictive for visual perception of stimuli close to the detection threshold (Busch et al., 2009; Mathewson et al., 2009). Importantly, it has been demonstrated that transcranial alternating current stimulation modulates visual and acoustic detection thresholds depending on local phases and phase differences between regions suggesting a causal role of phase dynamics (Neuling et al., 2012; Helfrich et al., 2014).

With regard to memory operations it is well-known that the phase of theta oscillations within the hippocampus determines the direction and magnitude of synaptic plasticity. In rats, electrical stimulation at the peak of hippocampal theta oscillations facilitates long-term potentiation, whereas stimulation at the trough induces long-term depression (Pavlides et al., 1988; Huerta and Lisman, 1993). Moreover, stimulus-related phase reset of low-frequency oscillations has been reported to

* Corresponding author at: Department of Epileptology, University of Bonn, Sigmund-Freud-Str. 25, D-53105 Bonn, Germany.
*E-mail address:* juergen.fell@ukb.uni-bonn.de (J. Fell).

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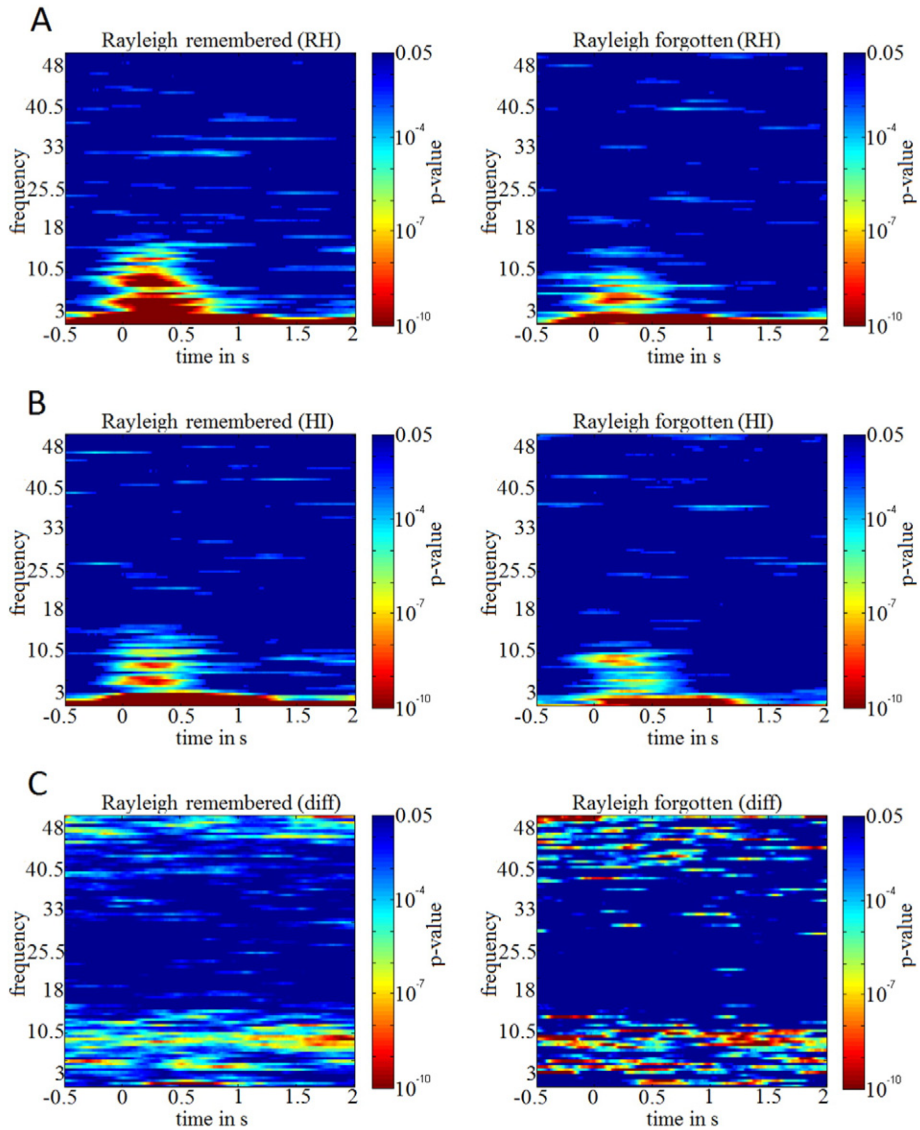


**Fig. 1.** Results of the Rayleigh tests. The figure shows the Fisher combined p-values of Rayleigh tests for the phase values within rhinal cortex (A) and hippocampus (B) as well as for the phase differences between rhinal cortex and hippocampus (C) under the conditions "later remembered" (left column) and "later forgotten" (right). Colors indicate p-values according to a logarithmic scale, with all values >0.05 colored in dark blue.

be an essential characteristic of memory operations (e.g. Rizzuto et al., 2003; Mormann et al., 2005; Haque et al., 2015). Furthermore, phase information derived from mediotemporal lobe (MTL) recordings in epilepsy patients was found to be superior to amplitude information for a classification of correct versus incorrect trials in a card-matching task (Lopour et al., 2013).

In a previous study, we have investigated how closely different mediotemporal EEG measures are related to memory formation (Fell et al., 2008). For this purpose, we analyzed intracranial data from 31 epilepsy patients performing a continuous word recognition paradigm. EEG measures comprised traditional average event-related potential (ERP) characteristics, rhinal and hippocampal power changes within different frequency bands, as well as inter-trial phase locking and rhinal-hippocampal phase synchronization. This analysis revealed that phase-based measures (i.e. inter-trial phase-locking and phase-synchronization), which reflect the stability of phase values and phase differences across trials, are better suited to distinguish subsequently remembered from forgotten trials than ERP or amplitude-based measures. Based on theoretical considerations there should be an optimal phase, as well as less optimal or unsuitable phases with regard to the facilitation of neural communication and plasticity (e.g. Fell and Axmacher, 2011). This suggests that phases for subsequently remembered compared to forgotten trials may be centered around different values, which, however, cannot be deduced from the previous finding that phases are more strongly accumulated for later remembered trials (they nevertheless could be centered around the same value). Thus, it remained an open question whether single-trial phase values per se are predictive for memory encoding.

For the present study, we therefore reanalyzed encoding-related responses for subsequently remembered and forgotten words in the same paradigm (Fell et al., 2008, 2011). In a first step, we identified time windows and frequencies with statistically significant phase clustering across patients. Then we determined for each patient time periods and frequencies for which the absolute phases and inter-electrode phase differences differ between the remembered and forgotten condition. Finally, a support vector machine (SVM) was trained by using the phases and phase differences from the most significant time windows and frequencies. Importantly, we aimed to employ a minimal set of features to predict subsequent memory, on the one hand, for ease of exposition, on the other hand, because such an approach is most closely related to possible practical applications (e.g. controlling one of the features by deep brain stimulation). Furthermore, we investigated whether prediction

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