phase coupling interactions were enhanced in the visual cortex compared to parietal and frontal responses. Spectral amplitude differences were less pronounced between cortical regions. Time delay estimation showed a delay between light stimulus and visual cortex of 118 ± 21 ms, significantly higher than the delay between stimulus and frontal or parietal lobes.

Discussion

This study demonstrates the potential of using sum-of-sinusoid light stimulation and quantitative nonlinear EEG analysis to identify higher-order nonlinear dynamics of visual processing. We foresee that application of the described frequency interaction analyses can further our insight in the nonlinear dynamics of visual processing not only in healthy subjects, but also with respect to the pathophysiology of neurological diseases with visual manifestations that relate to cortical hyperexcitability, like migraine and epilepsy.

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A44

Whole-brain time-frequency analysis of event-related potentials for the assessment of pharmacodynamic effects in the human brain

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We are developing Whole Brain Time-Frequency (WBTF) analysis as a new physiological biomarker for clinical trials of pharmacodynamics of novel drugs. WBTF analysis expands the power of event-related potential (ERP) assessment by using wavelets to measure both evoked (phase-locked) and induced (non-phase-locked) activity. Unlike traditional ERP measures, which are indexed by specific electrodes and peak latencies, WBTF analysis measures integrated change in brain responses across time, frequency and space to infer whether a drug has a significant effect. WBTF analysis also uses permutation tests and multiple comparison corrections to identify important within-subject changes between conditions and rule out differences arising from recording noise, artifacts or random variability.

The specific aim of this study was to assess the sensitivity and specificity of WBTF analysis to drug effects that are typically measured with ERP amplitudes and latencies. We simulated effects of dose-related changes in N1-P2-P3 ERP components and 40-Hz induced gamma bursts at 24 electrodes. Simulations included a range of amplitude effects, latency effects and signal-to-noise ratios, serving to define the sensitivity and specificity of WBTF analysis to ERP differences.

The simulations allowed us to optimize parameters for WBTF analysis, including choice of analyzing wavelets, energy normalization, baseline correction, measures of evoked and induced activity, and method of testing significant differences. We found that WBTF analysis reliably detects small differences in evoked activity (on the order of 10 %) in realistic noise and background EEG conditions. We found similar detectability of small differences in induced 40-Hz gamma bursts.

It is the goal of the further studies to investigate the clinical relevance of these observed differences using WBTF analysis, and to relate the evoked and induced components ERP differences to mechanisms of drug action. Currently we are applying WBTF analysis to data from three Phase 1 clinical trials of novel compounds for schizophrenia in both healthy controls and schizophrenia patients.

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Dysregulation of hyperpolarization-activated inward cation current (I_h) affects thalamocortical oscillations: the role of the auxiliary subunit TRIP8b on HCN channel function in thalamic and cortical neurons

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Background

The family of hyperpolarization-activated cyclic nucleotide-gated cation (HCN) channels consisiting four different isoforms (HCN1-4) have a major role in controlling neuronal excitability and generation of rhythmic oscillatory activity in individual neurons and neuronal networks [1, 2]. These channels activate in response to hyperpolarizing potentials negative to −50 to −60 mV and depolarize the resting membrane potential. HCN channels are regulated by small molecules like cyclic nucleotides and different accessory proteins. TRIP8b is a brain-specific accessory subunit of HCN channels which controls the gating, surface expression and trafficking of different HCN channels subunits in many regions of brain [3–5]. The role of this protein for I_h characteristics in thalamic and cortical neurons and the functional consequences of TRIP8b dysregulation for thalamocortical oscillations however is not yet fully understood. The present study aimed at providing a better understanding of the functional role of TRIP8b in the thalamocortical system and shedding some light on possible dysfunctional aspects by combining in vitro and in vivo electrophysiological approaches.

In this study, I_h was measured in whole cell patch clamp recordings from thalamocortical (TC) neurons of different thalamic nuclei, as well as pyramidal neurons in layer V and VI of the somatosensory cortex of TRIP8b-deficient (TRIP8b$^{-/-}$) and control (C57Bl/6 J) mice (p15 – p90). Effects of TRIP8b-dependent dysregulation of I_h on thalamocortical oscillations was monitored by local field potential (LFP) recordings from the ventral-posterior medial complex of the thalamus (VPM) and somatosensory cortex (p 90 – p120), regions which are known to be involved in generation of normal and also pathological thalamocortical oscillations.

Results

Characterization of I_h in the thalamocortical system in the absence of the auxiliary subunit TRIP8b showed a significant decrease in I_h density and changes in intrinsic properties and firing patterns of TC and cortical pyramidal neurons. These changes were accompanied by an increase in cAMP sensitivity in TC neurons. Dysregulation of I_h in the thalamocortical system of TRIP8b$^{-/-}$ mice was associated with altered thalamocortical oscillations revealing a significant increase in slow oscillations in the delta frequency range (0.5-4 Hz) during episodes of active-wakefulness.

Conclusion

The results of our study point to the importance of TRIP8b, as a brain-specific auxiliary subunit of HCN channels, in regulation of cell and network oscillations. It was demonstrated here that the presence of TRIP8b is necessary for modulation of thalamocortical delta oscillations due to its direct effect on HCN channels protein expression in the thalamocortical system.

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