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Event-related desynchronization and synchronization in evoked K-complexes

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K-complexes – phenomena occurring in sleep EEG – pose severe challenges in terms of detection as well as finding their physiological origin. In this study, K-complexes (KCs) were evoked by auditory stimuli delivered during sleep. The use of evoked KCs enables testing the sleeping nervous system under good experimental control. This paradigm allowed us to adopt into the KC studies a method of signal analysis that provides time-frequency maps of statistically significant changes in signal energy density. Our results indicate that KCs and sleep spindles may be organized by a slow oscillation. Accordingly, KCs might be evoked only if the stimulus occurs in a certain phase of the slow oscillation. We also observed middle-latency evoked responses following auditory stimulation in the last sleep cycle. This effect was revealed only by the time-frequency maps and was not visible in standard averages.

Key words: ERD, ERS, sleep, K-complex, statistical significance

K-complexes (KCs) are phenomena known from sleep EEG. They were first described over 70 years ago (Loomis et al. 1938), and later became part of the standard criteria for sleep staging (Rechtschaffen and Kales 1968). They are believed to represent a response evoked in the sleeping brain (Loomis et al. 1938). In spite of their established position among sleep EEG transients, their functional role and mechanisms of generation are not clear (Colrain 2005). Therefore, we decided to study this phenomenon in a controlled setup as potentials evoked by auditory stimuli in sleep EEG.[1]

The standard, commonly-used method to quantify brain activity evoked by a stimulus is based on simple averaging in the time domain of subsequent repetitions of evoked responses aligned to the instant of the stimulus. It was first applied by Dawson (1954); later, the application of digital computers greatly facilitated this task. The introduction of averaging technique to KCs by Ujszaszi and Halasz (1986, 1988), Campbell and coauthors (1990), and Bastien and Campbell (1992) was used to investigate the role of KCs in information processing during sleep, and resulted in many subsequent findings relating the properties of the averaged KC to age, illness, and scalp topography. This methodology is most commonly used to date although it is limited to the analysis of components that are phase locked to the stimulus. A further step in the analysis of event-related brain activity revealing both phase-locked and non phase-locked responses was made possible by the introduction of Event Related Synchronization (ERS) and Desynchronization (ERD) (Pfurtscheller and Arnibar 1979), which can be estimated as relative changes of mean spectral power in a given frequency band induced by an event. Recently the methodology was extended to the evaluation of statistically significant changes in the time-frequency plane (Durka et al. 2004, Kamiński et al. 2005, Żygierewicz et al. 2005).

The aim of the paper is to assess the applicability of ERD/ERS methodology to evoked KCs and related sleep EEG transients. Therefore, our first application of ERD/ERS analysis approach concerns a small data set. This allows us to analyze each individual case in

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[1] The name "K-complex" was probably derived from the word "knock" – their first occurrences were linked to the knocking on the door (Conant 2002).

great detail. In this way we identify features of the event-related responses exposed by the proposed type of analysis, which may be of potential significance for deeper understanding of the mechanisms of KC generation. Among others, our observations of power changes in the whole spectrum range (0–50 Hz) revealed noticeable relations between different EEG transients that were undetected using traditional methodology. We relate our observations to the hypothesis that KCs and sleep spindles are temporally organized by a slow oscillation.

Healthy subjects (3 males, aged 22, 23 and 25 years) were included in the study. An informed consent was obtained from all the subjects. The study was approved by the University Ethics Committee. The data were acquired from 23 EEG channels including 10/20 derivations, and Fpz, Oz, A1, and A2. A reference electrode was placed between Cz and Fz. The EOG and EMG were recorded according to Rechtschaffen and Kales' rules (Rechtschaffen and Kales 1968). The signal was filtered with an analog anti-aliasing filter and then sampled with frequency 128 Hz. An analog-digital 12-bit converter was used. Silver electrodes were applied with collodion. The maximal resistance was 5 kΩ. The visual analysis of sleep EEG was performed from standard polysomnographic derivations, according to Rechtschaffen and Kales' criteria, by experienced sleep researchers.

At random moments during sleep, a technician generated a knock. The time of the auditory stimuli was recorded in a separate channel. The intensity of the stimulus was 43.58 ± 0.05 dB relative to the background noise. The typical form of the acoustic stimulus is presented in the bottom of Fig. 1. The intervals between stimuli ranged from 0.5 s to 4 200 s. Total number of stimuli presented to the three subjects was 167, 556 and 693, respectively. Cases in which more than one stimulus was present within 11 s epoch – consisting of 5 s before and 6 s after the stimulus – were removed from the study, resulting in 130, 192 and 258 valid epochs, respectively. From the all-night sleep recording, epochs belonging to stage 2 sleep were selected, leaving 79, 123 and 156 epochs, respectively. The epochs were visually classified into 3 categories according to Rechtschaffen and Kales' (1968) criteria: those where the stimulus was followed by a KC, those where the stimulus was followed by vertex slow waves, and those where according to visual inspection there was no change in the EEG. Due to the well-known issue of low inter-expert agreement in visual detection [e.g., Bremer et al. (1970) report 50% agreement between two experts] only the epochs with unquestionable KCs were selected for further analysis.

The time-frequency energy density was estimated for each epoch. In this study we followed a standard approach to the estimation of energy density in the time-frequency plane which relies on the spectrogram – the squared magnitude of the short-time Fourier transform (STFT):

$$|F\ s(u,f)|^2 = \left| \int_{-\infty}^{\infty} s(t)\, w(t-u)\, e^{-2\pi i f t}\, dt \right|^2$$

where w is a window function (in this study Hann window of length 0.25 s) and u denotes translation along the time axis. Next, the maps of energy density were aligned to the stimulus and averaged (Fig. 1A). Subsequently, maps of relative power changes – event-related desynchronization (ERD) and synchronization (ERS) – defined as relative changes of the average energy of (post-stimulus) signals in selected frequency bands in relation to the baseline period (Pfurtscheller and Arnibar 1979) were investigated (Fig. 1B). In this study, we selected a baseline period from 4.5 to 2 s before the stimulus. Using time-frequency estimates of the energy density of signals, we eliminated the prior assumptions on the reactive bands and computed complete time-frequency maps of ERD/ERS.

To focus only on the repetitive effects, statistical significance of the energy changes was computed. We started by dividing the time-frequency plane into rectangular resolution elements (resels); in this study the time and frequency spread of the resel were 0.25 s and 1.94 Hz, respectively. Then, the values of energy in each resel were transformed by the Box-Cox transform (Box and Cox 1964) to approximately normal distribution, allowing application of the parametric Welch *t*-test, which corrects the number of degrees of freedom to account for possible heteroscedasticity (i.e., differences in the variances of the populations of resels). At each resel, a null hypothesis of no change with respect to the reference period in the same frequency band was tested. The error of falsely rejecting the null hypothesis due to the problem of multiple comparisons was controlled by False Discovery Rate (FDR) (Benjamini and Yekutieli 2001) with $q=0.05$. After FDR correction of the significance level, only those resels at which the null hypothesis was still rejected were assumed significant (Fig. 1C). In Fig. 2 and 3 only significant changes are displayed. Details

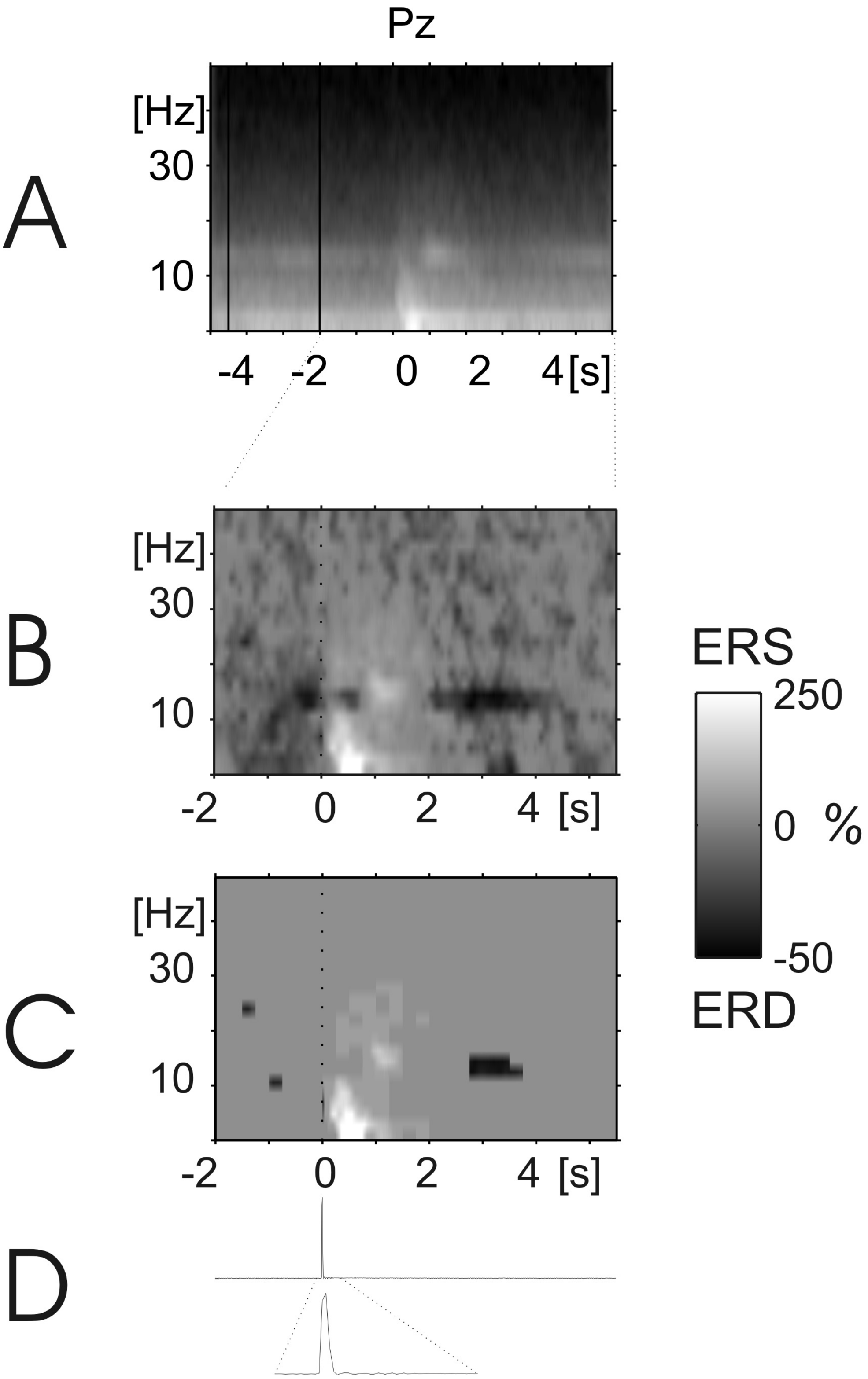

Fig. 1. Illustration of data analysis steps: (A) Averaged time-frequency energy density maps of epochs centered on stimulus. Vertical lines indicate baseline period. (B) Map of raw ERD/ERS-relative changes of energy with respect to the baseline period. Vertical line marks the stimulus. (C) Significant (FDR *q*=0.05) changes from B. (D) Stimulus envelope.

of this procedure are given in Durka and colleagues (2004) and Żygierewicz and others (2005).

In this study we observed three types of reaction to the auditory stimulus. Large amplitude waveforms with a well-delineated negative sharp wave that was immediately followed by a positive component – and exceeded 0.5 s were classified as KCs (Rechtschaffen and Kales 1968). They constituted 19%, 24% and 36% of cases in each subject (in absolute numbers: 15, 29, and 57 out of 79, 123, and 156). Responses in the form of a large negative sharp waveform of duration not exceeding 0.5 s were classified as vertex slow waves (VSW) and constituted 52%, 31%, and 49% (in absolute numbers: 41, 38 and 76 out of 79, 123, and 156) of cases. In remaining 29%, 45%, and 15% (in absolute numbers: 23, 56 and 23 out of 79, 123, and 156) cases, neither of the above described waveforms was observed. In these cases, also the ERD/ERS revealed no statistically significant changes in any frequency band. Coherence of both the classical and new results may indicate, that in these cases indeed no observable response was present in the EEG. In the following, we will present results of analysis of trials that resulted in evoked KCs.

In Fig. 2 we show topographic distribution of time-domain averaged responses and of the significant changes of spectral power relative to baseline in form of time-frequency maps obtained for one of the subjects. The results for other subjects were analogous unless stated otherwise.

The initial part of the KC was expressed as an ERS in the frequency band 0–10 Hz during the first second after the stimulus. It continued as a weaker ERS until the end of the next second in the F3, Fz, F4, C3, Cz, C4, P3, Pz, P4 and Oz channels.

Evoked KCs were followed by a transient ERS at spindle frequency range, i.e., 12–14 Hz between seconds 0.5–1.5. Subsequently in two of the subjects, around second 3.5, an ERD at spindle frequency occurred. The topographic distribution of this effect was widespread with its maximum in posterior and central electrodes. A similar ERD at spindle frequency was visible also about 0.5 s before the stimulus in all three subjects. Since the ERD/ERS are computed as changes of power relative to the reference period level, for such a pattern to occur there should have been some power in the frequency band of spindles during the reference period. The pattern of ERS and ERD in spindle frequency range, with two consecutive ERD centered at times −0.5 s and 3.5 s, indicates that sleep spindles tend to occur at a rhythm of about 0.25 Hz.

Additionally, in two of the subjects, in stage 2, in epochs from the last sleep cycle, there was a marked increase (ERS) of higher frequencies (>20 Hz) around the time of the stimulation in frontal and occipital electrodes (Fig. 3). In standard averages (Fig. 3, lower panel) these higher frequency components were not noticeable. These structures may correspond to Middle Latency Response (MLR). They appeared in one of the subjects at Fz, Cz, C4, and F4, and at Fz and Oz in the other subject. These evoked responses were not present in trials during other sleep cycles but the last.

Comparison of upper and lower panels of Fig. 2 reveals that the topography of the KCs viewed in the standard way (as average EP) and in the ERS maps is the same. In contrast, the sleep spindle is clearly visible as an ERS in the central and posterior locations, and only a closer examination, e.g., at electrode Cz (insert in Fig. 2), allows one to see the weak trace of the sleep spindle riding on the average KC trace in the standard EP. However, there is one feature of the EEG surrounding the evoked KCs that is uniquely expressed in the ERD/ERS maps – the ERDs in spindle frequency band.

The slow rhythm of sleep spindles occurrence suggested by Fig. 2 (upper panel) may be due to spindle recovery period as documented in animals (Steriade and Deschenes 1984), in humans (Żygierewicz et al. 1999) and in computational models, e.g., Destexhe and Babloyantz (1993), and Żygierewicz and coworkers (2001). Steriade and Amzica described the effects of slow cortical rhythm on grouping of sleep spindles and KCs (Steriade and Amzica 1998, Amzica and Steriade 2000). It is known that the slow rhythm influences the probability of sleep spindle generation, and that the spindles have greater probability of appearance in the depolarizing phase of that rhythm (Mölle et al. 2002). The pattern of ERD/ERS in spindle frequency band and ERS of the evoked KC observed in the current study can be explained if we assume that the probability of evoking a KC also depends on the phase of the slow rhythm and that the phases corresponding to these two phenomena have a stable relationship within an oscillation cycle. The evoking stimulus was delivered randomly in time, hence it occurred at random phases of the on-going slow oscillation. If we assume that at some phase of the slow oscillation the probability of evoking KCs is big while this probability is small at other phases, it might explain why some stimuli were

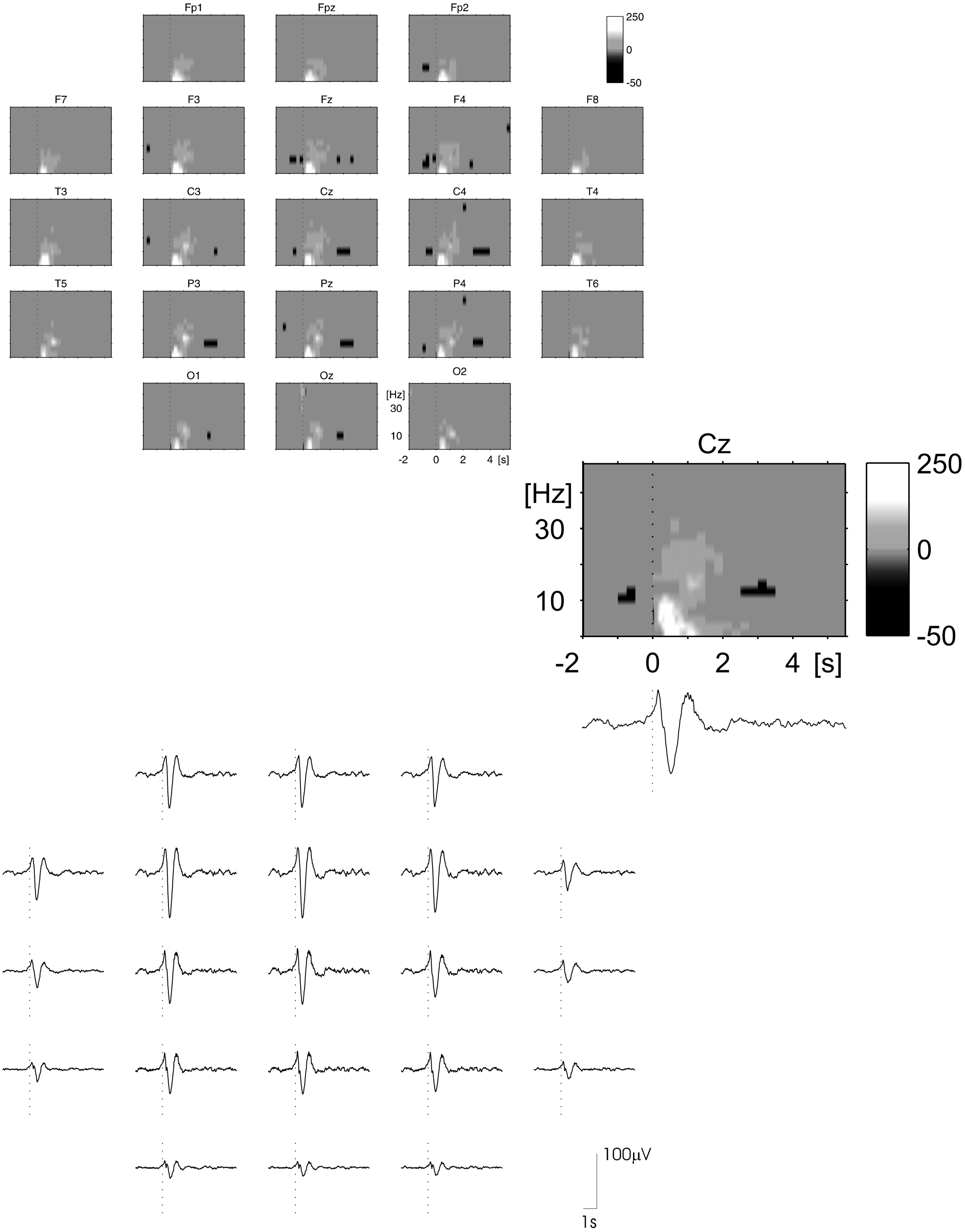

Fig. 2. Upper panel – Significant (FDR q=0.05) event-related changes in epochs where the KC was elicited. Lower panel – Averaged response for the same data. Insert displays expanded ERD/ERS map and EP for channel Cz.

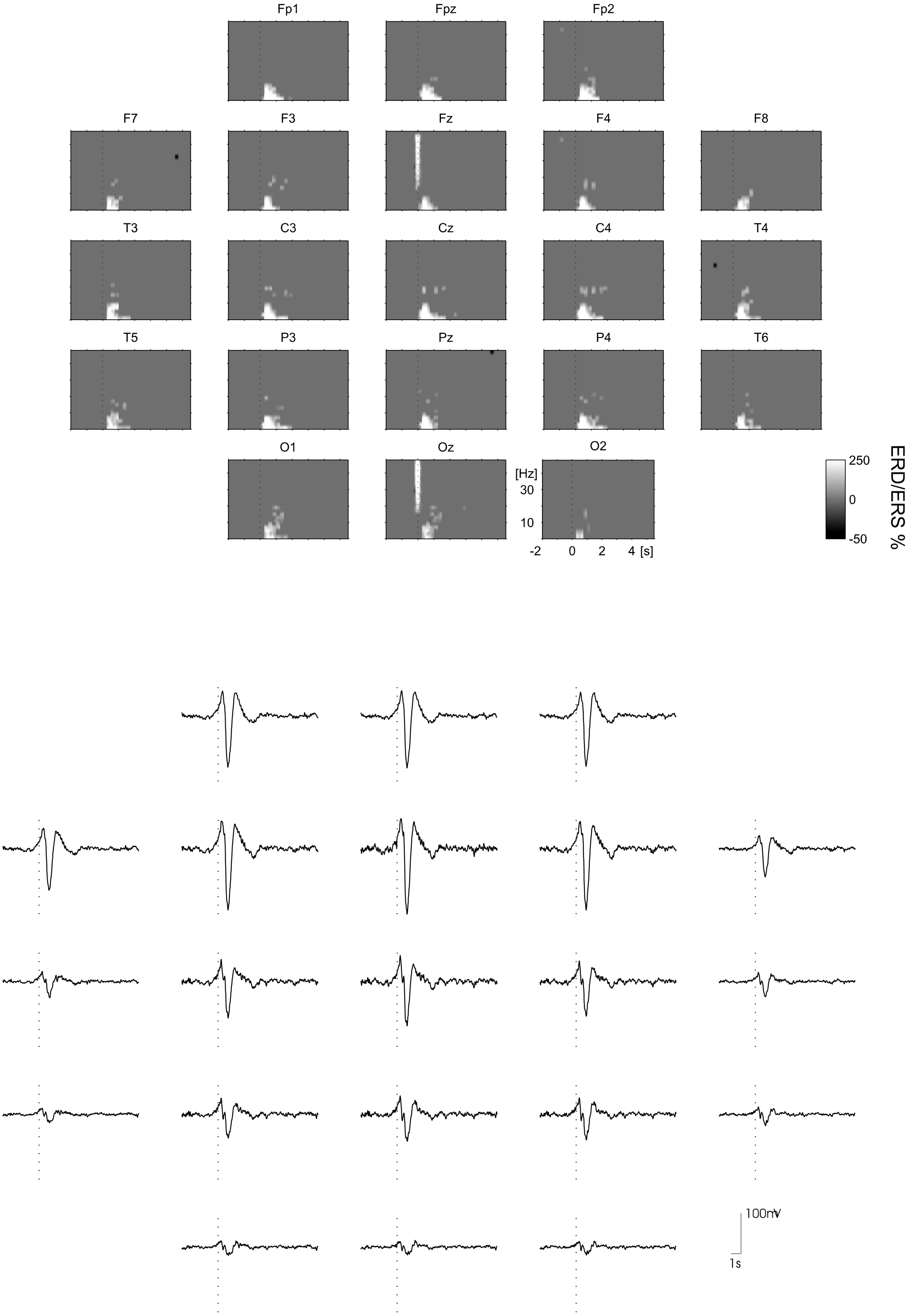

Fig. 3. Significant (FDR q=0.05) event-related changes in epochs where the KC was elicited in the last sleep cycle.

effective in evoking KCs, while some others were not. Furthermore, aligning all evoked KCs during the epoch extraction implies that the phases of slow oscillation were also aligned with respect to the probability of generation of KCs. Although the exact phases of the oscillation favouring KCs and sleep spindles are not necessarily the same, once we aligned the phase favouring KCs, the phases favouring spindles also became aligned. Accordingly, there should be more spindles around a certain moment in time closely related to the appearance of KCs and fewer spindles at half period of the slow rhythm before and after that moment. In Fig. 2 the KC precedes the sleep spindle by 0.5 s. It suggests that the phase of slow oscillations conducive to sleep-spindle generation is shifted in relation to the phase conducive to generation of KCs. Thus the pattern of ERD/ERS in spindle frequency band and ERS of the evoked KC, observed in the current study in human subjects (Fig. 2), is compatible with the hypothesis of grouping both spontaneous KCs and sleep spindles by the slow oscillation described in cats (Steriade and Amzica 1998) and humans (Achermann and Borbely 1997, Amzica and Steriade 1997, 2000). The latter hypothesis might also explain why on average only 25% of stimuli resulted in eliciting a KC.

The ERS (>20 Hz) shown in Fig. 3 are best seen in midline derivations (Fz, Oz). They were all elicited during stage 2 of the last sleep cycle. Their expression very close to the stimulation time and frequency band >20 Hz suggests that they may reflect MLR. Such auditory responses, as described by Picton and colleagues (1974), consist of a sequence of alternating negative and positive components: N0 (latency about 8 ms), P0 (12 ms), Na (18 ms), Pa (30 ms), Na (40 ms) and P1 (or Pb) (50 ms). The interval between consecutive positive components is around 20 ms, which translates to an instantaneous frequency around 50 Hz.

Scalp topography of ERS >20 Hz band in the present study seems to be consistent with animal and human models showing activation of non-primary auditory pathway (Kraus and McGee 1995, Kraus and Nicol 2005). Since MLR depends on the level of arousal it is not coincidental that ERS changes appeared at the end of sleep. It links MLR to sleep-wake cycle and is consistent with the concept of the functional relation of MLR generators to state of arousal (Erwin and Buchwald 1986).

EEG transients may be viewed as EEG power changes in reaction to some external or internal stimuli. By applying time-frequency ERD/ERS methodology to evoked KCs we were able to observe power changes in the whole spectrum range and relations between different EEG transients. Specifically, our results support the hypothesis that KCs and sleep spindles are organized by a slow oscillation. Accordingly, KCs might be evoked only if the stimulus occurs in a certain phase of the slow oscillation. These novel findings should be confirmed on a larger group of subjects. The proposed paradigm opens a way to quantitative and statistically-sound investigation of new hypotheses relating K-complexes to other EEG transients or rhythms.

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