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RAPID COMMUNICATION

Human Neocortical and Hippocampal Near-DC Shifts are Interconnected

Juergen Fell,[1]* Navah E. Fritz,[1] Wieland Burr,[1] Eva Ludowig,[1] Nikolai Axmacher,[1,2] Christian E. Elger,[1,2] and Christoph Helmstaedter[1]

ABSTRACT: Hippocampal DC shifts have been observed under various physiological and pathological conditions. Here, we studied the interconnection of slow shifts (0.01 Hz high-pass) in surface EEG and hippocampal shifts as emerging in an event-related EEG biofeedback paradigm. Hippocampal EEG activity was monitored by depth electrodes implanted in four epilepsy patients for presurgical evaluation. Trials were sorted according to the near-DC shifts occurring at the surface position Cz, which was the feedback electrode, into positive, indistinct (i.e., small or biphasic) and negative shifts. We found significant hippocampal near-DC shifts being positively or negatively correlated to the shifts in surface EEG in all four patients. The amplitudes of the hippocampal near-DC shifts were several times larger than the surface shifts. The polarity of the shifts appears to depend on the location of the electrode contacts with respect to the hippocampal subfields. The finding that neocortical and hippocampal near-DC shifts are interconnected may open new perspectives for the prediction and control of mediotemporal lobe seizures. © **2007 Wiley-Liss, Inc.**

KEY WORDS: hippocampus; neocortex; EEG; slow potential; bio-feedback

DC shifts or slow potentials have been observed in scalp recordings during a variety of cognitive tasks. These include the "lateralized readiness potential" preceding self-initiated movements (Kornhuber and Deecke, 1965), the "contingent negative variation" occurring during processing of two subsequent interdependent stimuli (Walter et al., 1964), and the DC potentials observed during visual and auditory working memory experiments (e.g. Lang et al., 1992). In general, scalp negative potentials are thought to correspond to neural activation, and scalp positive potentials to neural deactivation (e.g. Birbaumer et al., 1990; Speckmann and Elger, 1999; Vanhatalo et al., 2004). While slow potentials in the hippocampus have been reported during some cognitive tasks as well, for instance during long-term memory formation (Fernández et al., 1999), most reports of hippocampal slow potentials or DC shifts are related to pathological conditions like spreading depression (e.g., Herreras et al., 1994; Kunkler et al., 1998) or the termination of epileptic after discharges (Bragin et al., 1997). They might thus be related to the activation of large numbers of neurons, similar to, but more sustained than, hippocampal population bursts (De la Prida et al., 2006). A better comprehension of the mechanisms and functions of hippocampal DC shifts requires to understand whether they are interrelated to neocortical shifts or not, a question that has not been addressed so far. Therefore, we studied the interconnection of slow shifts in surface EEG and hippocampal shifts as emerging in an event-related EEG biofeedback paradigm.

During presurgical evaluation, intracranial EEG was recorded from four male patients (age: 47/35/46/37 yr) with pharmacoresistant unilateral temporal lobe epilepsy (TLE). Multicontact depth electrodes with platinum contacts had been implanted stereotactically along the longitudinal axis of the hippocampus (Van Roost et al., 1998). Patient 1, 2, and 3 had hippocampal sclerosis (right side) and were implanted with bilateral hippocampal depth electrodes. Only the EEG recordings from the contralateral side (left) were analyzed. Patient 4 had a parahippocampal dysplasia (left side) and was implanted with one hippocampal depth electrode on the same side. The experiments were undertaken with the understanding and informed consent of each patient. The individual placements of electrode contacts were ascertained by postimplantation magnetic resonance imaging (MRI) scans acquired in sagittal, axial, and coronal planes, adjusted to the longitudinal axis of the hippocampus. Electrode contacts were mapped by transferring their positions from MRI to standardized anatomical drawings (Van Roost et al., 1998). In patient 1, five contacts were unambiguously localized within the hippocampus, in patients 2 and 3, three contacts, and in patient 4, four contacts.

Furthermore, surface EEG was recorded with Ag/AgCl cup electrodes from position Cz (10–20 system). Surface, as well as depth electroencephalograms were referenced to linked mastoids (software), bandpass-filtered [0.01 Hz (6 dB/octave) to 70 Hz (12 dB/octave)], and recorded with a sampling rate of 1,000 Hz. Interelectrode impedances were below 5 kΩ. For the biofeedback task, EEG activity from position Cz was additionally recorded with a DC-compatible amplifier

[1] **Department of Epileptology, University of Bonn, D-53105 Bonn, Germany;** [2] **Life and Brain Center, D-53105 Bonn, Germany**
*Correspondence to: Dr. Juergen Fell, Department of Epileptology, University of Bonn, Sigmund-Freud-Str. 25, D-53105 Bonn, Germany.
E-mail: juergen.fell@ukb.uni-bonn.de
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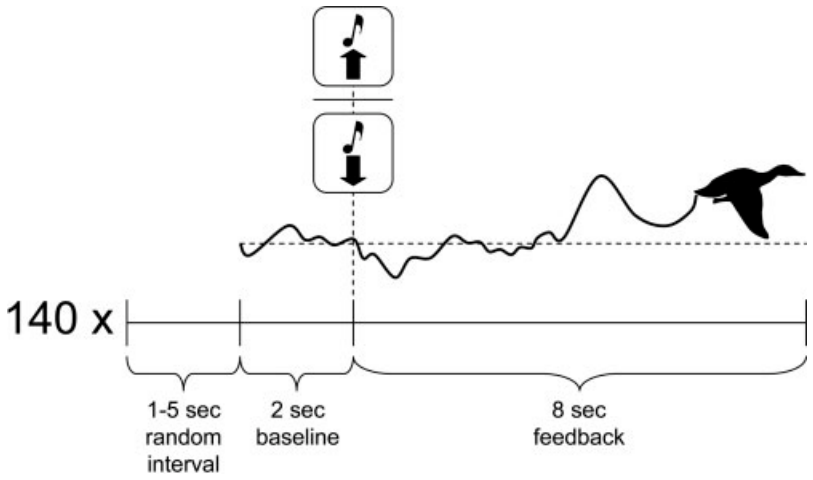

FIGURE 1. Schematic illustration of the EEG-Biofeedback paradigm.

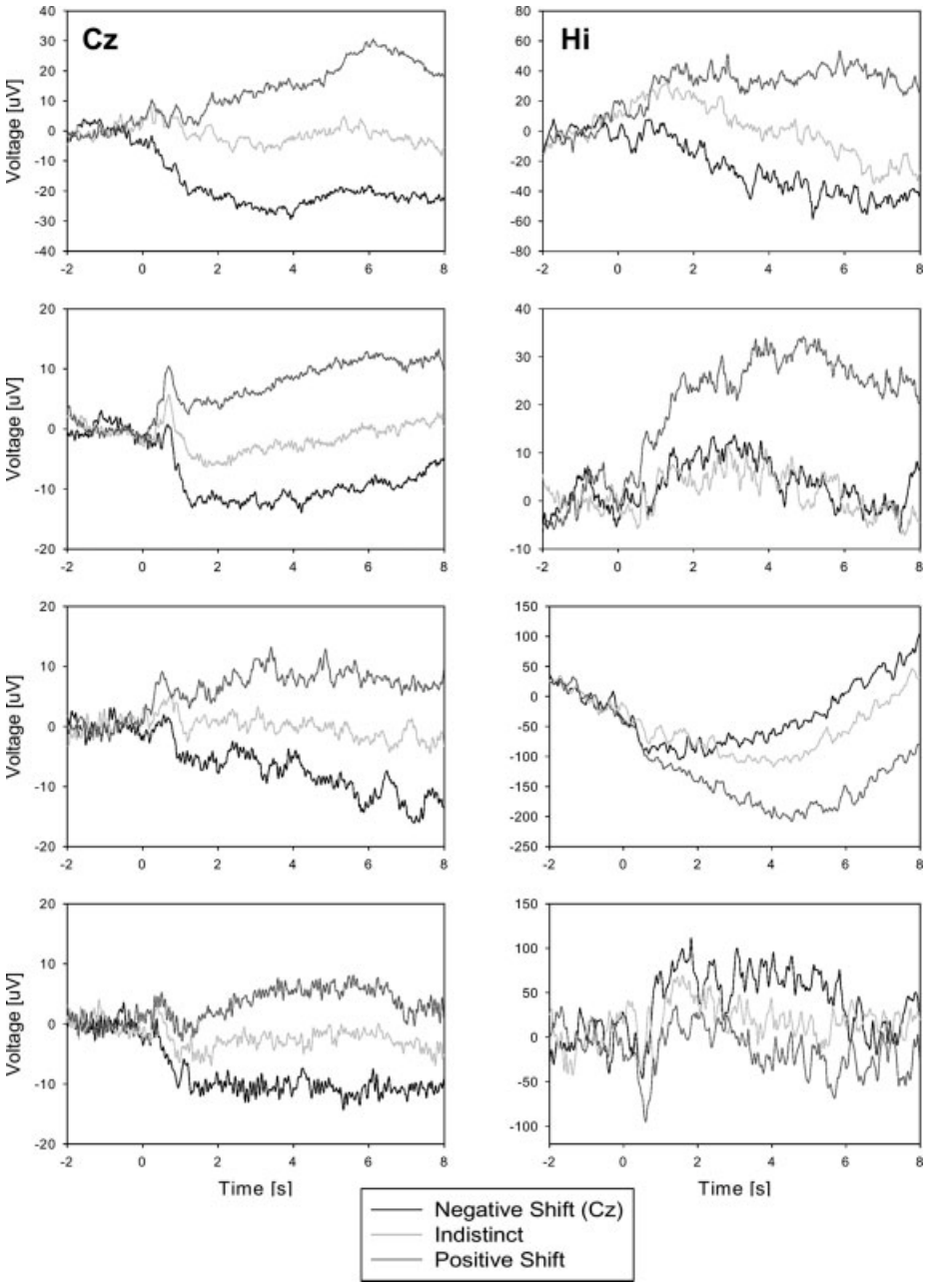

FIGURE 2

(sampling rate: 128 Hz). The biofeedback experiment consisted of 140 trials of 10 s length, separated by randomized intertrial intervals of 1–5 s length (Fig. 1). Patients watched a computer screen providing the feedback. After 2 s of baseline EEG recording, an arrow appeared on the screen together with an auditory cue. The arrow indicated the direction (positive or negative) towards which patients should move the amplitude of their EEG. Feedback of the EEG amplitude at position Cz was supplied with a delay of around 150 ms by a moving figure (airplane, bird, etc.) for 8 s.

All EEG trials were visually inspected for movement artifacts and epileptiform activity, and artifact segments were discarded (six artifact trials in patient 2 and eight in patient 3). In patient 4, hippocampal EEG was continuously contaminated by low-frequency activity and all trials were kept for evaluation. Trials were sorted according to the average near-DC shifts (time window between 1 and 8 s after presentation of the visual/auditory cue) occurring at the surface position Cz, which was the feedback electrode, into positive, indistinct [i.e. small negative (patients 2 and 4) or biphasic (patients 1 and 3)] and negative shifts (each category one third of the total trial number). For the hippocampal recordings three corresponding trial groups were composed, which contained the same trials as the groups selected for position Cz.

In all four patients, we observed prominent near-DC shifts within the hippocampus, which accompanied the surface shifts (Fig. 2). In patients 1 and 2, the hippocampal shifts had the same polarity as at position Cz, whereas hippocampal and Cz shifts had opposite polarity in patients 3 and 4. In patient 1, hippocampal near-DC shifts were detected for all five hippocampal positions (Fig. 3). In patient 2, hippocampal near-DC shifts occurred at one of three hippocampal positions, and only the positive shifts deviated markedly from the indistinct and negative shifts. In patient 3, we found hippocampal near-DC shifts with opposite polarity as compared with the position Cz at one of three hippocampal positions. Finally, patient 4 exhibited hippocampal near-DC shifts with opposite polarity as compared with the shifts at Cz at all four hippocampal positions.

Figure 4 shows six consecutive trials recorded from position Cz and from hippocampus, as well as a scatter plot of the average near-DC shifts at position Cz versus hippocampus for patient 1. Furthermore, spectral coherence between Cz and hippocampus for the joined intertrial/baseline intervals and for the task execution interval [0–8 s poststimulum] is depicted. Indeed, spectral coherence appears to be more pronounced in the frequency range below 1 Hz than in the theta, alpha, or beta range. This is the case not only during task execution, but also during the intertrial/baseline phase. During the intertrial/baseline interval possibly a back-regulation of near-DC shifts towards base level occurs.

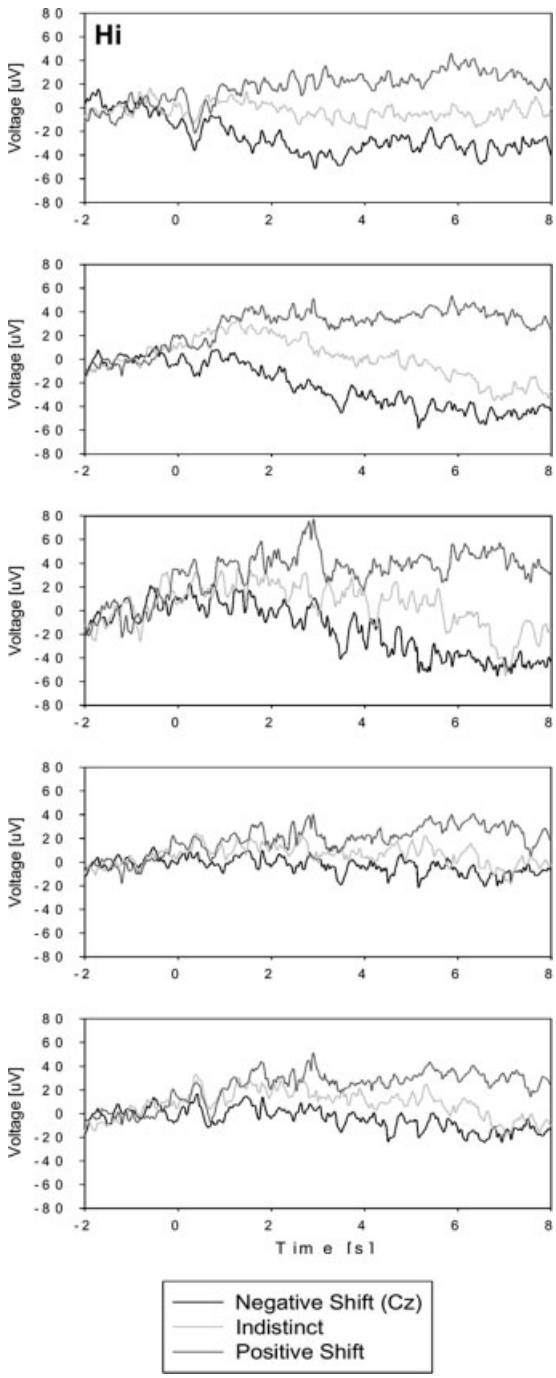

FIGURE 3. Near-DC shifts at all five hippocampal positions for patient 1. Time with respect to the presentation of the auditory/visual cue is depicted on the *x*-axis and Voltage [μV] is depicted on the *y*-axis.

FIGURE 2. Near-DC shifts at surface position Cz (left column) and corresponding shifts within hippocampus (Hi, right column) for patients 1–4. Time with respect to the presentation of the auditory/visual cue is depicted on the x-axis and Voltage [μV] is depicted on the *y*-axis.

For the hippocampal contacts showing the most pronounced near-DC shifts (Fig. 2), we performed an analysis quantifying the average shifts at position Cz and within the hippocampus across single trials (Fig. 5). Hippocampal near-DC shifts between the three conditions (negative/indistinct/positive shift

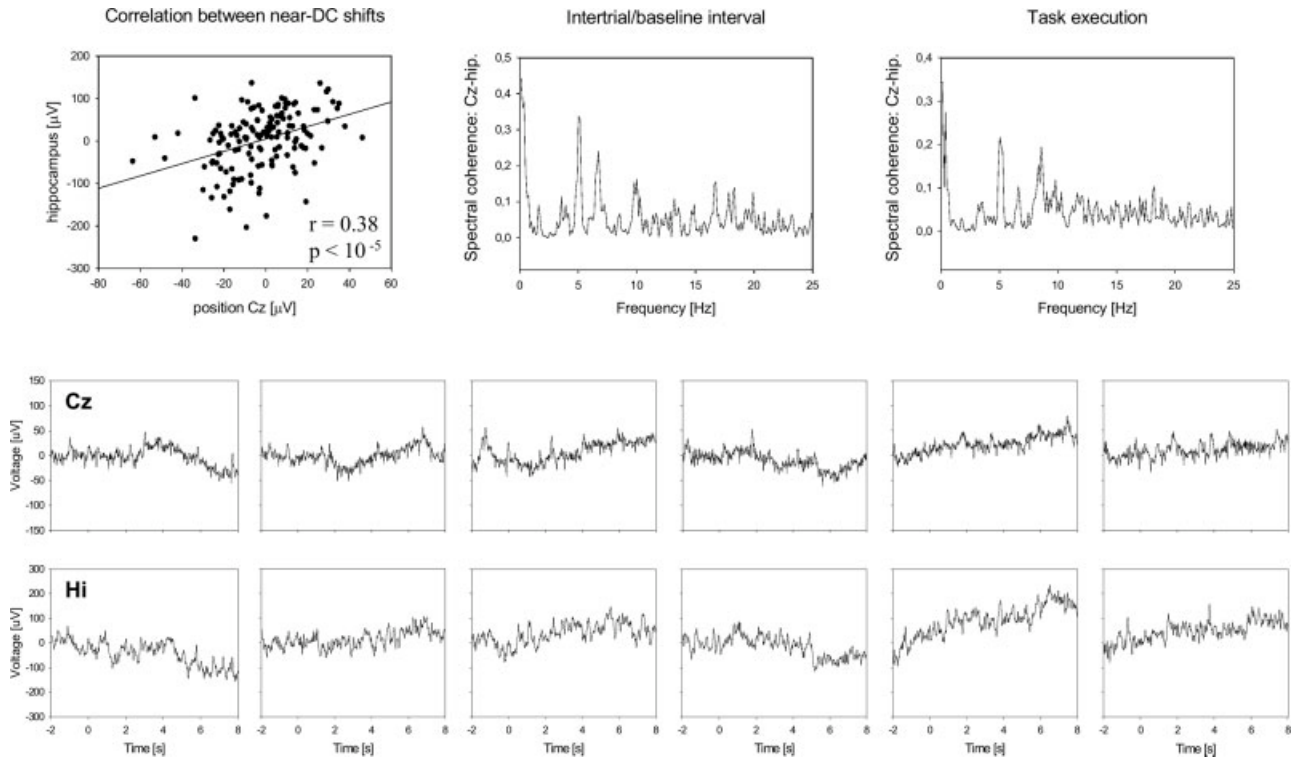

FIGURE 4. Cz-hippocampus correlation for patient 1. Below: Six consecutive trials recorded from position Cz and from hippocampus. Above left: Scatter plot of average near-DC shifts at position Cz vs. hippocampus. Above middle: Spectral coherence between position Cz and hippocampus during the intertrial/baseline interval. Above right: Spectral coherence between position Cz and hippocampus during task execution.

at position Cz) were statistically significant (two-tailed *t*-tests, $P < 0.05$) for all contrasts in patient 1, for the positive/indistinct contrast in patient 2 (trend for the positive/negative contrast), for the positive/negative contrast in patient 3 (trend for the positive/indistinct contrast) and for the positive/negative and positive/indistinct contrasts in patient 4 (trend for the indistinct/negative contrast). The magnitudes of the positive and negative hippocampal near-DC shifts with respect to the indistinct condition were about a factor 1.5–11 larger as compared with the surface shifts (patient 1: 1.50, 1.96; patient 2: n.s., 2.18; patient 3: n.s., −10.97; patient 4: −5.45, −3.72). Pearson's correlations between hippocampal and surface shifts were for patient 1: 0.38 ($P < 10^{-5}$), for patient 2: 0.19 ($P < 0.05$), for patient 3: −0.15 ($P < 0.1$) and for patient 4: −0.27 ($P < 0.005$). We found no obvious relation between the Cz-hippocampus correlation and behavioral performance (patient 1: no training effect; patients 2 and 3: correct training effect; patient 4: inverted training effect). Figure 6 shows the positions of the selected hippocampal electrodes for the four patients in axial and coronal views. The electrodes of patient 1 and 2, where the near-DC shifts were in the same direction as at Cz, were located more centrally within the hippocampus (regarding its two curved neural layers), while the electrodes of the other two patients, where the near-DC shifts went in the opposite direction as compared to Cz, were located rather at the periphery.

To summarize, our findings indicate that slow shifts of hippocampal EEG activity are interconnected to neocortical near-DC shifts. Recently, similar interactions have been observed between slowly oscillating ($\leq$1 Hz) neocortical and hippocampal field potentials in rats (Wolansky et al., 2006), as well as between neocortical field potentials and the membrane potentials of CA1 interneurons in mice (Hahn et al., 2006). Slow oscillations in the neocortex have been related to cortical up- and down states (Hahn et al., 2006), that is, to states of modulated cellular excitability. Provided that hippocampal near-DC shifts reflect neural activation and deactivation, this may imply that information transfer from the hippocampus to the neocortex is greatly facilitated by the observed correlation of near-DC potentials. In contrast, neocortical slow oscillations have recently been shown to influence not only slow extracellular field potentials in the hippocampus, but also the firing rate of hippocampal neurons (Isomura et al., 2006). This indicates that also information transfer from the neocortex to hippocampus may be supported by the interconnection of near-DC shifts.

Prior data on DC potentials suggest that the polarity of hippocampal DC shifts may indeed depend on the exact location of the electrode contacts with respect to the hippocampal subfields. A radial dipolar profile had been observed in hippocampal shifts which were induced by repetitive perforant path stimulation in cats (Gloor et al., 1964; Gumnit, 1974). In this study, the polarity of the DC shifts inverted when the recording electrode was moved from a central location with regard to the two curved hippocampal layers towards more radial placements.

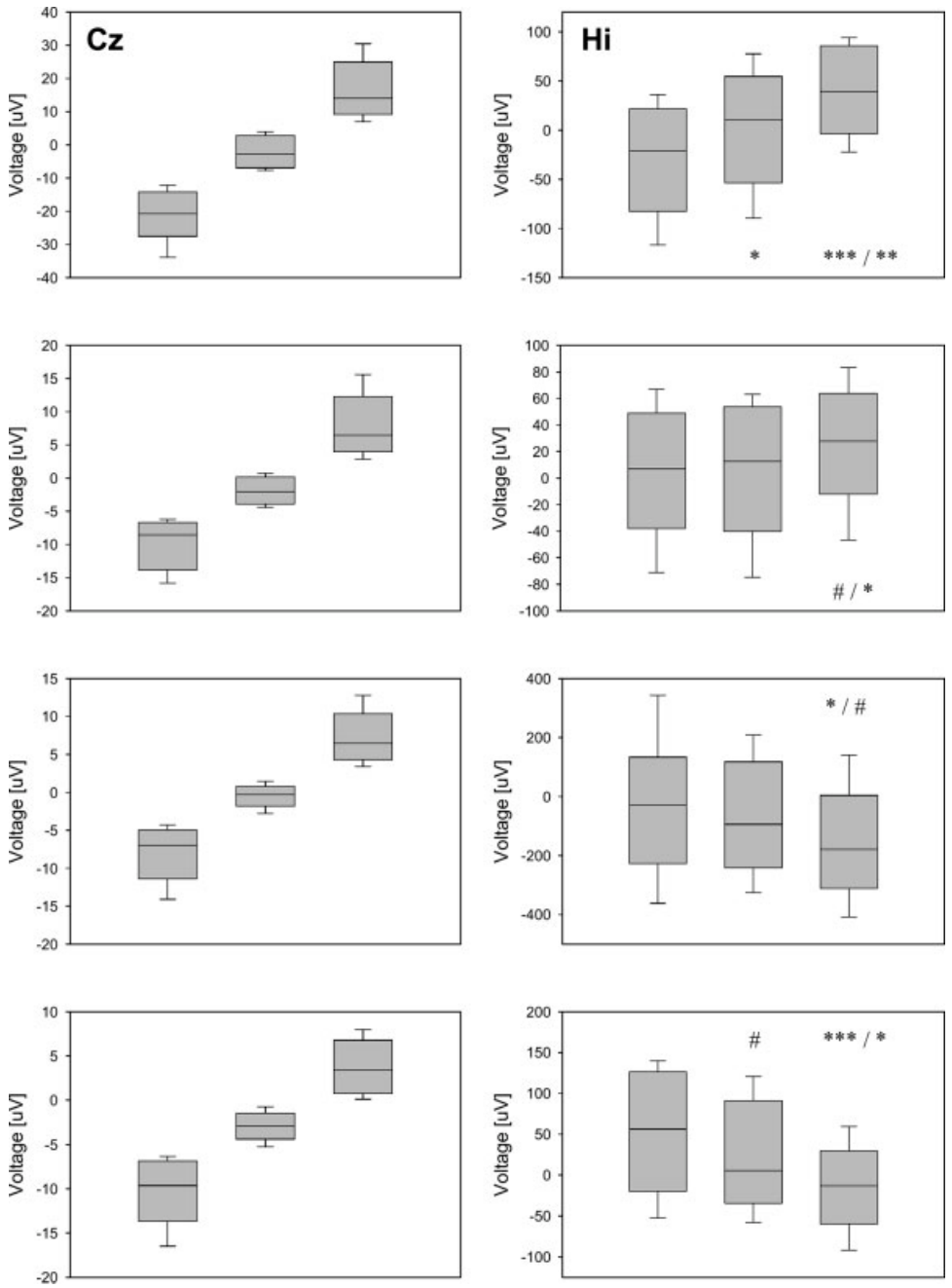

FIGURE 5. Single trial analysis of the near-DC shifts at position Cz (left column) and corresponding hippocampal shifts (right column). Whisker-Boxplots with 10th/25th/50th/75th/90th percentiles are shown. For the hippocampal shifts significant contrasts (paired two-tailed *t*-tests) between the indistinct vs. negative, positive vs. negative and positive vs. indistinct condition are depicted ($^{\#}P < 0.1$; $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.0001$).

A similar polarity inversion has, for instance, been observed for theta oscillations in rat hippocampus (Buzsáki, 2002). Nevertheless, our data do not exclude that the polarity relation between hippocampal and neocortical near-DC shifts may be subject-dependent.

The amplitudes of the hippocampal near-DC shifts were considerably larger as compared with those recorded at the scalp. In principle, the platinum electrodes suitable for permanent depth recordings, should, because of their high-pass characteristics, be less capable of detecting near-DC shifts than the silver chloride electrodes used for the scalp recordings (e.g. Cooper et al., 1980). The impedance of platinum electrodes depends inversely on the frequency f with a factor $1/f^m$, m being in the order of 0.75 (DeBoer and Oosterom, 1978). For instance, compared to 10 Hz, the impedance is about 5.6 times higher at 1 Hz and about 31.6 times higher at 0.1 Hz. This means that

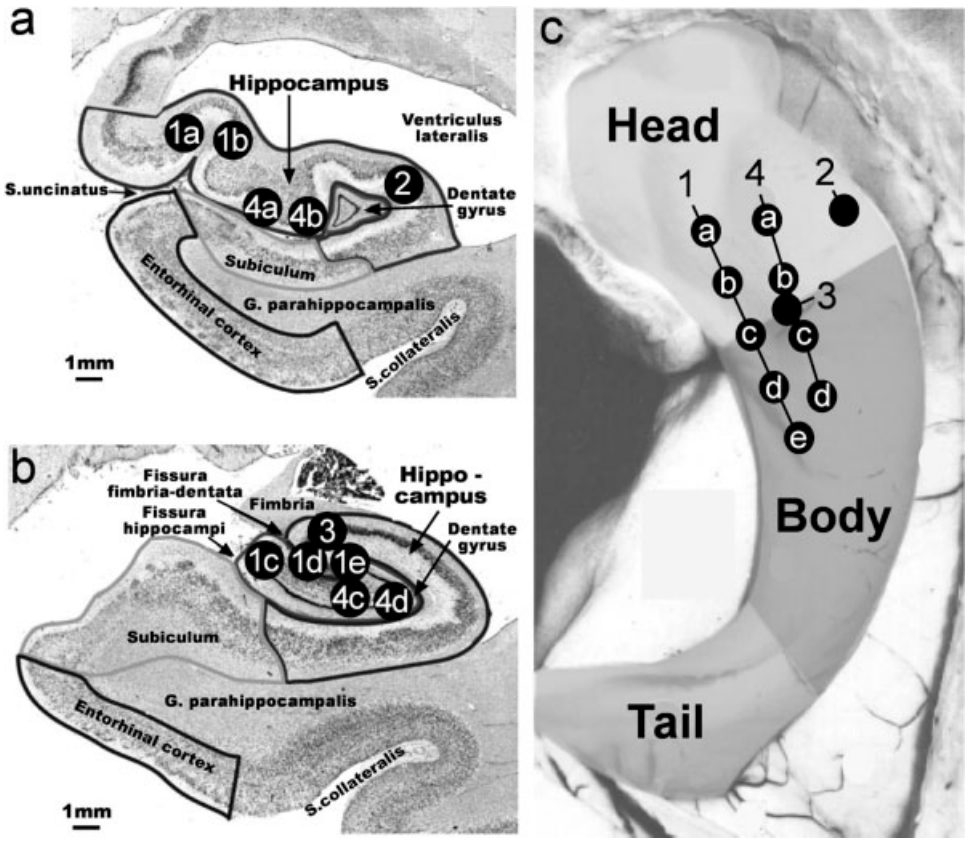

FIGURE 6. Localization of the hippocampal electrode contacts for patients 1–4. The quantitative analyses are based on recordings from electrodes 1b, 2, 3, and 4a. Left: Electrode placements displayed on cytoarchitecture images of the head (a) and the body (b) of the hippocampus (coronal view, adapted from Amunts et al. 2005). Right: Electrode loci superposed on an axial anatomical image of the hippocampus (adapted from Duvernoy 1988).

the hippocampal near-DC shifts may actually be even more pronounced. Hippocampal activity is known to be shielded towards the outside by the radial cylindrical arrangement of hippocampal pyramidal layers (e.g. Klee and Rall, 1977). Thus, it is unlikely, that hippocampal sources influenced the EEG signals recorded at position Cz.

DC shifts probably correspond to neural activation and deactivation associated with different levels of persistent neural firing (e.g., Birbaumer et al., 1990; Speckmann and Elger, 1999; Vanhatalo et al., 2004). The finding that neocortical and hippocampal near-DC shifts are interconnected may thus open new perspectives for the prediction and control of mediotemporal lobe seizures. Training of the self-regulation of slow potentials, which has been suggested as a method of seizure control, requires at least 20–30 sessions to be effective (Rockstroh et al., 1993). This means that the tight clinical schedule during presurgical evaluation of MTL epilepsies will generally not provide sufficient time to complete biofeedback training directly based on hippocampal recordings. Our data, however, suggest that even biofeedback training based on vertex recordings may be sufficient to regulate slow hippocampal potentials. The functional significance of hippocampal near-DC shifts and their interrelation to neocortical shifts during different cognitive processes remain important questions for further investigations.

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