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Do surface DC-shifts affect epileptic hippocampal EEG activity?

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Summary Despite considerable research on EEG-feedback of slow cortical potentials (SCPs) for seizure control in epilepsy, the underlying mechanisms and the direct effects on intracerebral pathological activity within the focal area remain unclear. Intrahippocampal EEG recordings from four patients with temporal lobe epilepsy and implanted electrodes were analyzed with regard to spike activity and power in 10 frequency bands (0.5–148 Hz) during SCP feedback based on surface recordings (position Cz). Trials with positive, negative and indifferent SCPs were contrasted. Three of the four patients showed changes in spike activity during SCPs, but these were inconsistent between patients, and resulted in increased and decreased activity in both positive and negative SCPs. Spectral analysis revealed that in all patients, positive surface shifts showed a bi-hemispheric higher power in the high-frequency activity above 40 Hz. Two patients showed a higher power also during negative shifts, both in high-frequency activity and one in most other frequency bands. Feedback-related power effects did not differ between focal and non-focal side. The inconsistent change in spiking activity and the lack of decrease of power in pathology associated frequency bands during SCPs show that these SCPs do not decrease pathological activity within the epileptic focus. A possible relation of higher power in high-frequency activity during positive SCPs to cognitive processes, such as memory functions, is discussed.

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Introduction

In search for alternative treatment methods for epilepsy, neurofeedback as a means to influence epileptogenic networks and thus prevent seizures has been object to research in the last decades (Walker and Kozlowski, 2005). Following the reinforcement of activity in a specific frequency band in the electroencephalogram (EEG) (Thompson and Baxendale, 1996), more recent research has been directed

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at the general level of excitability of the underlying cortex. This is represented by slow cortical potentials (SCP or DC-shifts) recorded from the surface (Rockstroh et al., 1989) and has been closely linked to epileptic activity. SCP recordings reach a large negative amplitude imminent to a seizure (Birbaumer et al., 1990; Speckmann et al., 1999). They have gained importance in the noninvasive lateralization and localization of the seizure focus, e.g. during presurgical workup (Miller et al., 2007; Vanhatalo et al., 2003) and may also be recorded intracranially in order to correctly localize the region of seizure onset (Ikeda et al., 1996). Slow positive potentials may also reflect sustained decreases of cellular activity (e.g. Schmitt et al., 2000). In hippocampal slices, DC-shifts may induce or enhance seizure activity (Gluckman et al., 2001). After analyzing penicillin-induced seizures in the hippocampus (Dichter and Spencer, 1969; Gloor et al., 1964), Dichter and Spencer as well as Gloor and colleagues suggested that seizures may be prevented from spreading widely by recurrent inhibitory action in the periphery (Gummit, 1974).

These findings from basic research have initiated clinical research on the feedback of SCPs, reinforcing the patient's ability to increase or decrease the cortical excitability. The intention is to enable patients to reduce their seizure frequency or seizure severity, yet the method is aimed at the single seizure and not at the epileptic condition itself. Clinical studies applying the reinforcement of positive SCPs (i.e. suppression of negativity) in order to achieve seizure control report a decrease in seizure frequency, with some patients with symptomatic as well as idiopathic epilepsy even becoming seizure free (Kotchoubey et al., 2001; Rockstroh et al., 1993; Strehl et al., 2005). In the latest of these studies, Strehl and colleagues reported that patients with left temporal lobe epilepsy had a lesser probability for seizure reduction. To what extent this variability may be influenced by cortical vs. mesial temporal lesions and their susceptibility to changes in excitability recorded from the surface remains unclear. The respective research group has also explored changes in EEG spectral power during 35 sessions of SCP training. Taking into account frequencies from 0.3 to 30 Hz, they found larger power values in the delta, theta and alpha bands when patient were required to produce positive

vs. negative SCP shifts. However the effects were too weak and unstable to be regarded as an immediate consequence of SCP dynamics (Kotchoubey et al., 1999).

Despite considerable research on the mechanisms and effectiveness of EEG feedback, the interaction of neocortical DC potentials recorded with scalp EEG and activity in the epileptogenic area in deeper structures is still unclear. In a recent study of four epilepsy patients, we addressed the question whether SCPs recorded from the surface interact with slow potentials recorded intracranially from temporo-mesial structures (Fell et al., 2007). We were able to show that neocortical and hippocampal SCPs were in fact interconnected and occurred with greater amplitude in the temporo-mesial structures. However, the polarity of the slow potentials within the hippocampus was not uniformly coupled to the cortical signals.

The current paper aims to address the following questions: First, are SCP shifts related to changes in interictal electrophysiological pathology recorded in the hippocampus? Based on previous studies on patients with symptomatic as well as idiopathic epilepsy (Kotchoubey et al., 2001; Rockstroh et al., 1993; Strehl et al., 2005), we hypothesized that positive SCPs should be correlated with a decreased incidence of interictal spikes. Furthermore we expected an overall decrease in spectral power during positive SCPs. Second, are changes in specific frequency bands of temporo-mesial EEG activity associated with positive and negative SCPs? We predicted that hippocampal gamma-band activity (>32 Hz), which is closely linked to inhibitory activity in the hippocampus (Whittington et al., 1995) and probably also in the neocortex (Axmacher et al., 2008), correlates with positive DC shifts.

Material and methods

Patients

All four patients (age 34–46 years) suffered from temporal lobe epilepsy and underwent intracranial EEG recording during pre-surgical evaluation (for patient characteristics see Table 1). Multicontact depth electrodes with platinum

Table 1 Patient characteristics.

	Patient 1	Patient 2	Patient 3	Patient 4
Age (years)	46.8	34.5	45.7	36.5
Sex	Male	Male	Male	Male
Temporal pathology	Hippocampal sclerosis	Hippocampal sclerosis	Hippocampal sclerosis	Parahippocampal dysplasia
Side of pathology	Right	Right	Right	Left
Side of implanted electrodes	Bilateral	Bilateral	Bilateral	Left
Number of included electrode contacts in the hippocampus (left/right)	7/5	4/5	3 ^a /3 ^b	4/-
Number of included feedback trials	126 ^c	134	130	139
Mean number of trials with spikes per contact (left/right)	68.7/75.8	2/41	53.3/49.3	103/-

^a One of the former four electrode contacts was excluded, because it was defect (constant high frequency firing).

^b Two of the former five electrode contacts had to be excluded because of invariant pathological firing.

^c Two subclinical seizures during the 140 conducted trials were excluded in all contacts.

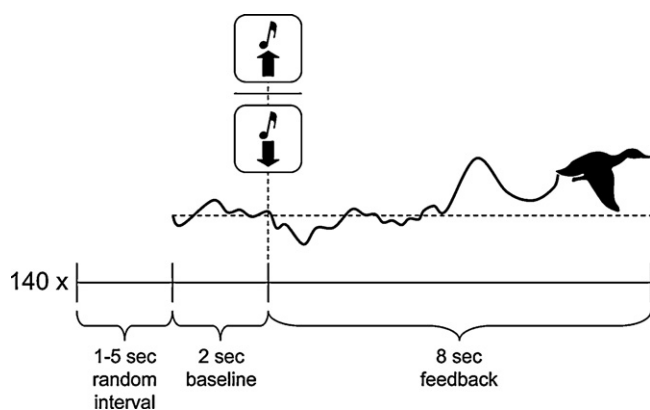


Figure 1 Schematic illustration of biofeedback paradigm. Reproduced with permission of John Wiley & Sons, Inc.

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. 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 post-implantation magnetic resonance imaging (MRI) scans acquired in sagittal, axial, and coronal planes, adjusted to the longitudinal axis of the hippocampus (Fell et al., 2007). Electrode contacts were mapped by transferring their positions from MRI to standardized anatomical drawings (van Roost et al., 1998). The number of contacts, which were unambiguously localized within the hippocampus and therefore considered for analysis, is shown in Table 1.

EEG specifications and feedback paradigm

Surface EEG was recorded with Ag/AgCl cup electrodes from position Cz (10–20 system) during presurgical intracranial recordings. Surface, as well as depth electroencephalograms were referenced to linked mastoids contralateral to the focus, bandpass-filtered [0.01 Hz (6 dB/octave) to 300 Hz (12 dB/octave)], and recorded with a sampling rate of 1000 Hz. Interelectrode impedances were below 5 k Ω . For the biofeedback task, EEG activity from position Cz was additionally recorded with a DC-compatible amplifier (sampling rate: 128 Hz). Yet, the latter recording did not enter analysis and only served for the computation of the signal shown to the patients as feedback of their SCPs.

The biofeedback experiment consisted of a maximum of 140 trials of 10 s length each. The trials were separated by randomized intertrial intervals of 1–5 s length (see Fig. 1) adding up to a session of approx. 25 min. 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 were supposed to 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,

Table 2 EEG frequency bands considered for analysis.

Notation	Frequency (Hz)
Delta	0.5–3
Theta	3–8
Alpha	8–12
Beta1	12–16
Beta2	16–24
Beta3	24–32
Gamma1	32–40
Gamma2	40–48
Gamma3	52–98
Ripple band	102–148

etc.) for 8 s (see Fig. 1). All trials were visually inspected for movement artifacts and epileptiform activity. Artifact segments were discarded leading to a different number of trials for each patient (see Table 1).

Analogous to the procedure in the preceding publication (Fell et al., 2007), trials were sorted according to the average SCP (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. Accordingly, categories with positive, indistinct (small or biphasic) and negative shifts were formed (each category containing one third of the total trial number). The first second after cue presentation was excluded from the SCP average in order to avoid a bias caused by transient evoked potentials. For the hippocampal recordings, three corresponding trial groups were established containing the same trials as the groups selected for position Cz.

EEG measures and statistical analysis

For all included contacts, trials were checked whether they contained spikes or not (time window between 1 and 8 s after presentation of the visual/auditory cue; 5 Hz high-pass filter, 12 dB/octave). For this purpose, waves with either at least twice the amplitude (peak to peak) of the mean amplitude of the preceding 3 seconds (background activity) and a maximum duration of 70 ms or 80 ms if the amplitude exceeded the background activity by a factor of more than three were considered as spikes (the mean number of the trials with spikes per electrode contact are depicted in Table 1). The number of trials with and without spikes in trials with negative or positive DC shifts was compared to those with indistinct shifts using the χ^2 -test for each patient (exact *p*-values, threshold *p* < 0.05, tendencies *p* < 0.1). In order to reduce the number of conducted tests, we carried out χ^2 -tests with all three conditions, interpreting only the differences between the positive/negative vs. indistinct trials. In case of significant overall results, χ^2 -tests were conducted separately for each hemisphere.

Secondly, for each patient, a spectral analysis (fast Fourier transformations with cosine windowing and zero padding) was carried out including 10 EEG-bands from 0.5 to 148 Hz (see Table 2). Activity in the high-frequency range above 100 Hz is probably due to mechanisms different from gamma-band activity and has been referred to as "ripple band" (Bragin et al., 1999a,b; Buzsaki et al., 1992; Draguhn

Table 3 Results of three-way ANOVAs for each patient.

	Effect	<i>F</i>	Hypothesis <i>df</i>	Error <i>df</i>	<i>p</i>
Patient 1	“Frequency band”	132.6	9	1498	<0.001
	“Frequency band” × “type of trial”	1.7	18	2998	0.037
	“Frequency band” × “side of electrode contact”	13.9	9	1498	<0.001
	“Frequency band” × “type of trial” × “side of electrode contact”	2.0	18	2998	0.008
Patient 2	“Frequency band”	896.6	9	1192	<0.001
	“Frequency band” × “type of trial”	3.4	18	2386	<0.001
	“Frequency band” × “side of electrode contact”	78.0	9	1192	<0.001
	“Frequency band” × “side of electrode contact” × “type of trial”	1.3	18	2386	0.163
Patient 3	“Frequency band”	184.6	9	766	<0.001
	“Frequency band” × “type of trial”	2.6	18	1534	<0.001
	“Frequency band” × “side of electrode contact”	46.4	9	766	<0.001
	“Frequency band” × “type of trial” × “side of electrode contact”	1.5	18	1534	0.068
Patient 4	“Frequency band”	120.3	9	545	<0.001
	“Frequency band” × “type of trial”	2.2	18	1092	0.003

ANOVA with repeated measurement factor: “frequency band” and fixed factors: “type of trial” and “side of electrode contact”.

et al., 1998). The mean power in the different bands entered a three-way analysis of variance (ANOVA) with the repeated factor “frequency band” and “type of trial” as well as “side of electrode contact” as fixed factors. This analysis yielded significant interactions between “frequency band” and “type of trial” in all four patients; which are described in the results section for each patient (for detailed statistical measures see Table 3). We therefore subsequently conducted separate ANOVAs for the power in all 10 EEG bands as dependent variables and “type of trial” as well as “side of electrode contacts” as fixed factors (*F*-, *p*-values and degrees of freedom are given in the text). For “type of trial” subsequent post-hoc test were conducted in case of significant results (Scheffé-test).

Alpha was set to 5%. Because of the study’s explorative character, *p*-values < 0.1 were regarded as tendencies; because of the decreased power with repeated testing tendencies were disregarded for the ANOVAs conducted for each of the 10 frequency bands. Results are discussed for each patient separately and summarized in Table 4. Statistics were calculated using SPSS (SPSS Inc., Chicago, Illinois).

Results

Patient 1

The occurrence of spikes did not differ between the trials categorized by surface shifts (negative: 57%, *n* = 289; indistinct: 56%, *n* = 270; positive 57%, *n* = 301; $\chi^2 = 0.1$; *df* = 2; *p* = 0.942).

The ANOVA with “frequency band” as a repeated measure showed a significant main effect for this within subject factor (*p* < 0.001), as well as its interaction with “type of trial” (*p* = 0.037), “side of electrode contacts” (*p* < 0.001) and a three-way interaction of “frequency band” with “type of trial” and “side of electrode” (*p* = 0.008). The subsequent ANOVAs showed a significant effect for high fre-

quency oscillations (gamma3, *F* = 3.3; *df* = 2; *p* = 0.037, see Fig. 2) with a higher power in trials with positive compared to indistinct surface shifts (Scheffé-test *p* = 0.055). Delta-, theta- and gamma2-band showed a higher power on the left side compared to electrode contacts on the right side (all *p* ≤ 0.001 and *df* = 1; delta, *F* = 65.4; theta, *F* = 17.1; gamma2, *F* = 12.0).

Patient 2

More trials with hippocampal spikes occurred during positive surface shifts (22%; *n* = 86) as compared to 14% (*n* = 58) of the trials with indistinct and 17% (*n* = 69) with negative surface shifts ($\chi^2 = 7.7$; *df* = 2; *p* = 0.021). This effect persisted when accounting for side of electrode contacts (right: $\chi^2 = 5.9$; *df* = 2; *p* = 0.054; left: $\chi^2 = 11.2$; *df* = 2; *p* = 0.002).

The ANOVA showed a significant main effect for the repeated measurement factor “frequency band” (*p* < 0.001), as well as its interaction with “type of trial” (*p* < 0.001) and “side of electrode contacts” (*p* < 0.001). The three-way interaction of “frequency band” with “type of trial” and “side of electrode” was not significant. Therefore, results concerning this interaction were disregarded in the subsequent ANOVA. The subsequent ANOVA revealed significant effects in all high-frequency bands above 40 Hz (all *p* < 0.001 and *df* = 2; gamma2, *F* = 9.3; gamma3, *F* = 18.4; ripple band, *F* = 17.9) indicating a higher power for trials with positive as well as negative surface shifts compared to indistinct trials (Scheffé-test: gamma2, positive *p* = 0.036; negative *p* < 0.001; gamma3, positive *p* < 0.001; negative *p* < 0.001; ripple band, positive *p* < 0.001; negative *p* < 0.001). While the frequency bands below 40 Hz showed a higher power on the right side, no differences between right and left electrode contacts were observed for frequencies above 40 Hz (all *p* < 0.001 and *df* = 1; delta, *F* = 19.6; theta, *F* = 374.6; alpha, *F* = 283.7; beta1, *F* = 288.6; beta2, *F* = 331.1; beta3, *F* = 278.6; gamma1, *F* = 77.0).

Table 4 ANOVA results for all patients.

Frequency Band [Hz]	Patient 1			Patient 2			Patient 3			Patient 4	
	Type of Trial	Side of Contacts	Interaction trial* side	Type of Trial	Side of Contacts		Type of Trial	Side of Contacts		Type of Trial	Type of Trial
delta, 0.5-3	n.s.	**right < left	n.s.	n.s.	**right > left		n.s.	**right < left		n.s.	n.s.
theta, 3-8	n.s.	**right < left	n.s.	n.s.	**right > left		**pos↑+ neg↑↑↑	**right < left		n.s.	n.s.
alpha, 8-12	n.s.	n.s.	n.s.	n.s.	**right > left		**neg↑↑↑	**right < left		n.s.	n.s.
beta1, 12-16	n.s.	n.s.	n.s.	n.s.	**right > left		*neg↑↑↑	**right < left		n.s.	n.s.
beta2, 16-24	n.s.	n.s.	n.s.	n.s.	**right > left		n.s.	**right < left		n.s.	n.s.
beta3, 24-32	n.s.	n.s.	n.s.	n.s.	**right > left		**neg↑↑	**right < left		n.s.	n.s.
gamma1, 32-40	n.s.	n.s.	n.s.	n.s.	**right > left		**neg↑↑↑	**right < left		n.s.	n.s.
gamma2, 40-48	n.s.	**right < left	n.s.	**pos↑ neg↑↑↑	n.s.		**neg↑↑↑	**right < left		n.s.	n.s.
gamma3, 52-98	* pos↑+	n.s.	n.s.	**pos↑↑↑ neg↑↑↑	n.s.		**neg↑↑↑	**right < left		n.s.	n.s.
ripple band, 102-148	n.s.	n.s.	n.s.	**pos↑↑↑ neg↑↑↑	n.s.		**pos↑↑↑ neg↑↑↑	n.s.		n.s.	**pos↑↑↑

ANOVA: *p < 0.05; **p ≤ 0.001.
 Type of trial: pos/neg: trials with positive/negative surface shifts; ↑/↓: higher/lower power compared to trials with indistinct surface shifts.
 Posthoc Scheffé tests; ↑+: p < 0.1. ↑/↓: p < 0.05; ↑↑/↓↓: p < 0.01; ↑↑↑/↓↓↓: p < 0.001.
 Side of electrode contact: </> : more/less power.

Patient 3

More trials with hippocampal spikes occurred during negative surface shifts (46%, n = 116) as compared to trials with indistinct (37%, n = 101) as well as positive (35%, n = 91) surface shifts ($\chi^2=6.9$; $df=2$; $p=0.031$). When separated by side of electrode contact, this effect did not become apparent.

The ANOVA revealed a significant main effect for the repeated measurement factor "frequency band" ($p < 0.001$) as well as its interactions with "type of trial" ($p < 0.001$) and "side of electrode contact" ($p < 0.001$). The three-way interaction between these factors was not significant. The closer analysis of the 10 frequency bands as dependent variables in ANOVAs showed effects for 8 out of the 10 frequency bands, only beta2 and delta-bands were not affected by type of trial (all $p < 0.001$ and $df=2$; theta, $F=8.4$; alpha, $F=7.8$; beta1, $F=4.1$; beta3, $F=9.8$; gamma1, $F=12.0$; gamma2, $F=12.8$; gamma3, $F=16.6$; ripple band, $F=41.5$). In all 8 frequency bands affected by "type of trial", trials with negative surface shifts had a higher power compared to indistinct trials (Scheffé-test: beta1, $p=0.020$; all other bands $p < 0.001$: theta, alpha, beta3, gamma1, gamma2, gamma3, ripple band). In addition, a higher power for trials with positive shifts was observed in ripple band (Scheffé-test: $p=0.005$) and as a tendency in the theta-band (Scheffé-test: $p=0.099$). Concerning the "side of the electrode contacts", all frequency bands except the ripple band showed a higher power for left compared to right contacts (all $p < 0.001$ and $df=1$; delta, $F=41.3$; theta, $F=30.4$; alpha, $F=44.2$; beta1, $F=104.9$; beta2, $F=168.9$; beta3, $F=200.5$; gamma1, $F=220.6$; gamma2, $F=210.2$; gamma3, $F=100.8$).

Patient 4

Compared to 80% (n = 147) of the trials with indistinct surface shifts containing spikes, spikes were less frequent in trials with positive (71%; n = 130) and negative (72%; n = 135) shifts ($\chi^2=4.9$; $df=2$; $p=0.087$). In other words, spikes occurred slightly less frequent in trials with SCPs independent of their direction.

In this patient with only unilateral intracranial electrode contacts, the ANOVA showed a significant main effect for the repeated measurement factor "frequency band" ($p < 0.001$), as well as its interaction with "type of trial" ($p=0.003$). The following ANOVAs showed an effect in the power of ripple band ($F=10.5$; $df=2$; $p < 0.001$), indicating a higher power for positive compared to indistinct surface shifts (Scheffé-test: $p < 0.001$).

Summary of the results

Three of the four patients showed changes in spiking activity during SCPs as compared to intervals with no SCPs. However, these changes occurred both as decrease and as increase of spiking during positive as well as during negative surface shifts (see Table 5 for an overview).

The spectral analysis revealed more homogenous results across the four patients. During positive surface shifts, all four patients showed a higher power in the high-frequency

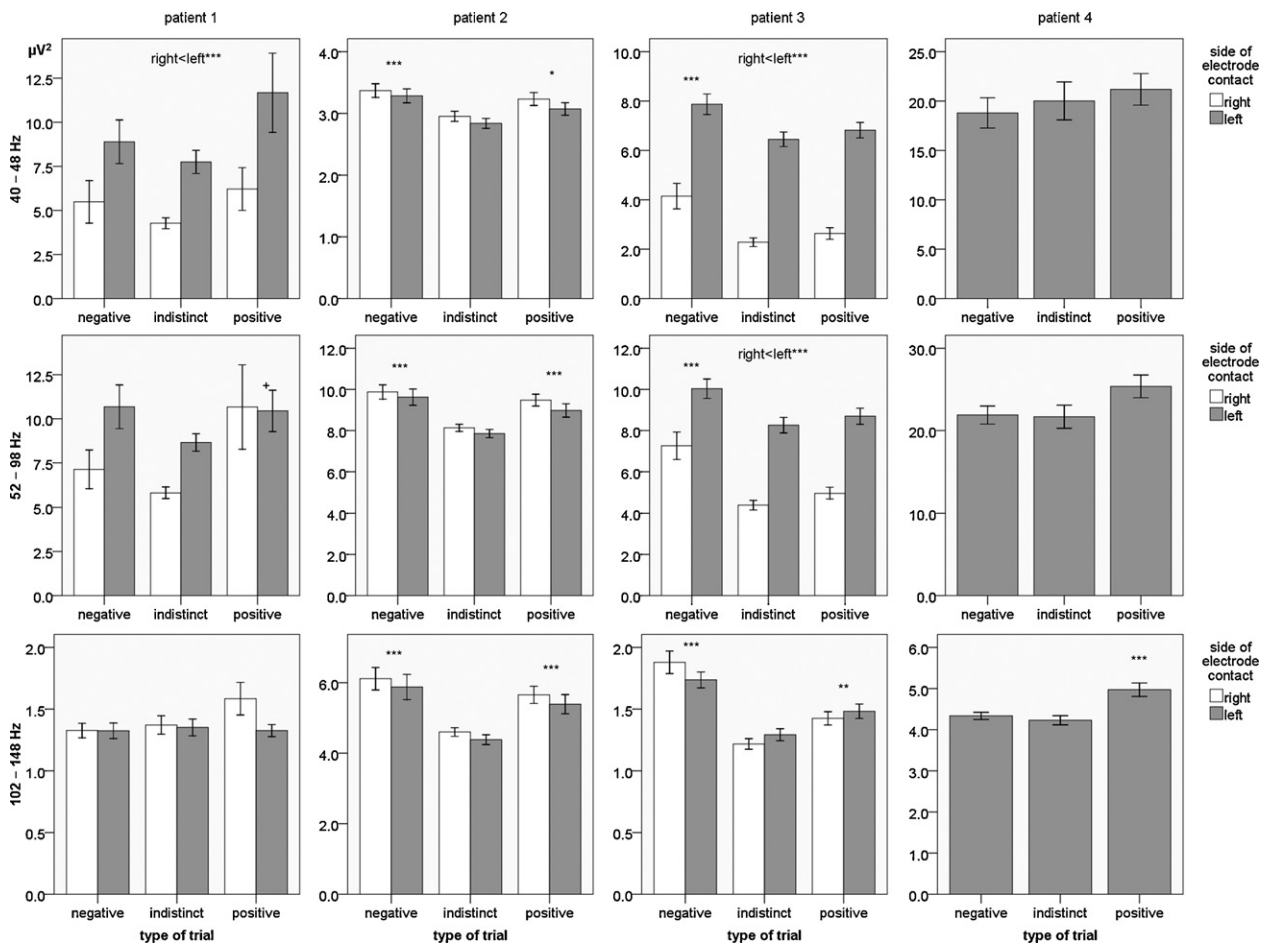


Figure 2 Means and SEM of the spectral power are shown for the three highest EEG bands (rows: gamma2, gamma3 and ripple band) for patients 1–4 (columns) with “type of trial” and “side of electrode contact” as fixed factors. For the hippocampal shifts significant contrasts between the negative and positive vs. indistinct condition (post hoc Scheffé tests) as well as between right and left hemisphere electrode contacts (ANOVA) are indicated (+ $p < 0.1$; * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$).

bands above 40 Hz (i.e., in the range of gamma-band activity or ripple band summarized as high-frequency activity, HFA, see Table 5). This effect was accompanied by an absence of differences in power between the two hemispheres. Two patients additionally showed a higher power of HFA during

negative shifts, one of which showed a higher power in most other frequency bands (theta, alpha, beta) during negative surface shifts as well. Concerning side of electrode contacts, patients showed intraindividually consistent but interindividually inconsistent effects: for two patients the power was

Table 5 Overview of results in spike activity and power of frequency bands for all patients (1–4).

	Spikes	Spectral power
Positive surface shifts	<ul style="list-style-type: none"> ↑ patient 2** ↓ patient 4* 	<ul style="list-style-type: none"> ↑ patient 1: gamma3+ ↑ patient 2: gamma2*, gamma3***, ripple band*** ↑ patient 3: theta+, ripple band** ↑ patient 4: ripple band***
Negative surface shifts	<ul style="list-style-type: none"> ↑ patient 3* ↓ patient 4* 	<ul style="list-style-type: none"> ↑ patient 2: gamma2***, gamma3***, ripple band*** ↑ patient 3: theta***, alpha***, beta1***, beta3**, gamma1–3***, ripple band***

↑/↓: higher/lower spike activity/power compared to trials with indistinct surface shifts. Detailed information on statistical procedures is provided in the text as well as in Table 3. Levels of significance refer to χ^2 -tests for spikes and to post hoc Scheffé tests for spectral power:

- + $p < 0.1$.
- * $p < 0.05$.
- ** $p < 0.01$.
- *** $p < 0.001$.

higher on the non-lesional side and one patient had a higher power on the lesional side.

Discussion

Little research has clarified the underlying mechanisms of neurofeedback of SCPs and its possible effect on epilepsy. In our previous study we were able to show in four patients that neocortical and hippocampal SCPs are effectively interconnected, with a greater amplitude and partially inversed polarity in the temporo-mesial structures (Fell et al., 2007). In this paper, we investigated whether the observed shifts in these patients are related to change in interictal electrophysiological pathology as well as oscillatory measures and if so whether this change is related to a certain direction of the shift. We therefore compared spike activity and power of frequency bands for positive and negative surface shifts to trials with indistinct shifts.

Changes in spiking activity occurred in most but not in all patients and these changes were inconsistent between subjects regarding both their dependency on the direction of the shifts as well as the nature of the effect on spike frequency (increase/decrease). Therefore, our results do not support the hypothesis that SCP training may decrease epileptic EEG activity. Yet, the intra-individual reliability of the effects cannot be judged from the present data, because only data from a single test session could be obtained. In addition, the lack of a direct relationship between the incidence of hippocampal spikes and shifts of SCPs in surface EEG might be explained by the fact that the spike rate depends on various factors including action potential frequency, the ratio of excitation to inhibition, the amount of synchronization, and overall synaptic activity as reflected by SCPs (Zschocke, 2002).

While clinical studies frequently report seizure frequency as their relevant outcome variable, the relation between spiking activity and seizure occurrence is rather variable (Lange et al., 1983; Zschocke, 2002). Our results may therefore not be drawn upon to justify EEG-feedback as a means of seizure reduction, yet, they also do not rule out such a relationship.

Spectral analysis revealed that all patients showed a higher power in the high-frequency activity above 40 Hz during positive surface shifts. An increased gamma-band activity (40–60 Hz) often precedes epileptic discharge in patients and in some animal models (Fisher et al., 1992; Medvedev, 2002). Medvedev suggested that fast activity may be desynchronized and suppressed by spike activity. One may speculate that the establishment of increased hippocampal HFA outside pre-seizure states may readjust seizure thresholds.

Previous findings suggest that both gamma-band activity and ripple band are closely linked to activity of interneurons and thus to inhibition in the hippocampus and the neocortex (Axmacher et al., 2008). In memory formation, during successful encoding of items, the hippocampus shows an increase in higher gamma-band activity (44–64 Hz) (Sederberg et al., 2007) and an increased positive potential (Fernandez et al., 1999), probably linked to decreased cellular activity (Speckmann et al., 1999). In the neocortex, memory formation is accompanied by increased slow

positive potentials (Fernandez et al., 1998), which are also linked to inhibition. Thus, it is likely that hippocampal gamma-band activity is coupled with decreased overall hippocampal and neocortical activity during memory formation. Memory processes play an important role during various cognitive tasks and even during resting state (Hasson et al., 2007).

Thus, while we did not find supportive evidence for a therapeutical approach with DC-shifts in epilepsy, one may well speculate that parts of the current experimental setting activated hippocampus-related memory processes. Evaluation of this interesting hypothesis will be the issue of further investigation.

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