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RESEARCH ARTICLE

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Brain areas activated in fMRI during self-regulation of slow cortical potentials (SCPs)

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Abstract In humans, surface-negative slow cortical potentials (SCPs) originating in the apical dendritic layers of the neocortex reflect synchronized depolarization of large groups of neuronal assemblies. They are recorded during states of behavioural or cognitive preparation and during motivational states of apprehension and fear. Surface positive SCPs are thought to indicate reduction of cortical excitation of the underlying neural networks and appear during behavioural inhibition and motivational inertia (e.g. satiety). SCPs at the cortical surface constitute summated population activity of local field potentials (LFPs). SCPs and LFPs may share identical neural substrates. In this study the relationship between negative and positive SCPs and changes in the BOLD signal of the fMRI were examined in ten subjects who were trained to successfully self-regulate their SCPs. FMRI revealed that the generation of negativity (increased cortical excitation) was accompanied by widespread activation in central, pre-frontal, and parietal brain regions as well as the basal ganglia. Positivity (decreased cortical excitation) was associated with widespread deactivations in several cortical sites as well as some activation, primarily in frontal and parietal structures as well as insula and putamen. Regression analyses revealed that cortical positivity was predicted with high accuracy by pallidum and putamen activation and supplementary motor area (SMA) and motor cortex deactivation, while differentiation between cortical negativity and positivity was revealed primarily in parahippocampal regions. These data suggest that negative and positive electrocortical potential shifts in the EEG are related to distinct differences in cerebral activation detected by fMRI and support animal studies showing parallel activations in fMRI and neuroelectric recordings.

Keywords Functional magnetic resonance imaging (fMRI) · Physiological regulation · Slow cortical potentials (SCPs)

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Introduction

Slow cortical potentials (SCPs) are direct current potential shifts of large neuronal assemblies of the cortex, lasting between several hundred milliseconds and several seconds. They are presumed to reflect the extent to which apical dendrites of the cortical pyramidal cells are depolarized. SCP amplitudes are regulated within tight limits by a negative feedback-loop consisting of a cortical-basal ganglia threshold regulation system that maintains cortical activation within acceptable medium limits (Birbaumer et al. 1990). The reduction of the excitation threshold of cortical assemblies leads to glutamatergic stimulation of mainly inhibitory GABAer-

gic structures within the basal ganglia, such as the putamen and pallidum (Braitenberg and Schütz, 1991) compensating cortical hyperexcitation via the basal ganglia and thalamus. Individuals can learn to voluntarily control SCPs through feedback and operant learning procedures. Combined recordings from the cortical surface and from single cortical cells at different depths and from different cortical layers (Caspers 1974; Rebert 1973; Requin et al. 1984; Stamm et al. 1975; Mitzdorf 1985) revealed a strong relationship between local field potentials (LFPs) near the tip of the electrode at the apical dendrites (layer I and II) and SCPs at nearby cortical surface locations (Birbaumer et al. 1990 and Speckmann and Elger, 1999 for reviews). The correlation between single and multi-unit activity (MUA) and SCPs is less pronounced because MUA is mainly present during the output-mode of the pyramidal layers in deeper cortical structures distant from the cortical surface. The interpretation of the neurophysiological basis of slow cortical positivities from scalp recordings is less clear cut (Mitzdorf 1985; Birbaumer 1999). A decrease of cortical positivity below baseline values may result from active inhibition of apical dendritic neural activity or simply from a reduction of firing of afferent inflow and subsequent reduced postsynaptic activity. In any case, slow cortical positivities do indicate decreased brain activity in the area under the electrode. For the blood oxygenation level-dependent (BOLD) signal, however, reduction of excitation or increase in inhibition may have different consequences. While reduced neuronal activity should be accompanied by attenuation of the BOLD signal, increased inhibitory action may cause an increase of the BOLD signal originating from the excitatory neuronal networks responsible for the decrease in the inhibited areas. Increased firing and depolarization of the cortical input structures and apical dendrites as reflected in surface negative SCPs appears mainly in experimental situations employing anticipatory attention and preparation (Rockstroh et al. 1989) or delayed response tasks (Stamm and Rosen 1972) and tasks using continuous stimulation of several seconds [such as those used by Logothetis et al. (2001) to compare BOLD response with nearby neuronal activity]. In humans, a reliable methodology to induce stable SCP recordings in both directions, positive and negative, consists of extensive training of self-regulation and voluntary control of SCPs (Birbaumer et al. 1990; Birbaumer 1999).

In this training procedure, a graphic signal on a computer screen provides feedback of a person's ability to generate high amplitude shifts in the requested direction, producing cortical negativity (enhanced excitation) or positivity (reduced excitation). Voluntary regulation of SCPs has been shown to be a powerful treatment method for drug refractory epilepsy (Kotchoubey et al. 2001) and has also been used by patients with complete motor paralysis such as amyotrophic lateral sclerosis to communicate via computer-assisted spelling programs (Birbaumer et al. 1999). The study reported here is an observational one and explores the interrelationship between electrophysiological responses (SCP) of the human brain and fMRI. As different cognitive and emotional strategies lead to similar potential shifts at the vertex, the aim was the clarification of neural mechanisms underlying positivity and negativity.

Several studies have combined fMRI with electroencephalography (EEG) (Menon et al. 1997; Krakow et al. 2000a, 2000b; Bonmassar et al. 1999; Vitacco et al. 2002). These studies did not use SCPs but rather oscillatory activity (Arthurs et al. 2000 and 2002; Krakow et al. 2000) or event-related visual potentials (Menon et al. 1997; Bonmassar et al. 1999) or epileptiform activity were investigated. Often a relationship between measures of increased EEG activity such as high frequency responses or epileptic spiking and strength of the fMRI response was found (for a recent review see Heeger and Ress 2002). However, since modulations of negative SCPs precede and accompany states of high neural activity such as seizures or visual attention it is conceivable that fMRI activity is also correlated with the slow EEG changes that were excluded in these studies by bandpass filtering. Time constants below 1 s as used in those studies do not permit measurements of DC changes lasting several seconds with amplitudes between 1 and 50 μV. These and other methodological problems in comparing EEG and fMRI data were recently discussed by Horwitz and Poeppel (2002). In our study, functional fMRI and slow wave recordings of the EEG were used to observe the brain areas that are haemodynamically activated or deactivated when people produce electrocortical negativity or positivity. Based on previous work of our group (Elbert et al. 1991), a close relationship between the ability to regulate the slow cortical potentials shifts and activity in areas modulating cortical excitability (basal ganglia, thalamus, pre-frontal cortex, mesencephalic reticular formation) and areas around the active electrode comprising motor areas and the paracentral lobule was postulated. However, non-invasive neuroimaging methods available at that time did not allow measurement of activities in subcortical structures such as the basal ganglia and thalamus. With the availability of fMRI these hypotheses become testable. In addition, cortical negativity was thought to lead to a general increase and cortical positivity to an overall decrease of haemodynamic activity.

Methods

Participants and general procedure

We recruited 10 subjects (4 females, mean age 32.4, range 19–52) to take part in the study. Of them, five had no history of neurological disease, the other five were patients with focal epilepsies. Of the patients, four received anti-epileptic medication, mainly carbamazepine and one patient valproic acid. However, the comparison between the two groups revealed no difference in either population parameters (equal mean age, two females in each group, all strongly right-handed), or in their final (after training) ability to produce the required SCP shifts, as well as in their fMRI responses

(in detail, see below). Therefore, group statistics were computed with the pooled data of the ten subjects.

During training of SCP-regulation, at the beginning of each 8 s trial, the task was signalled by the presentation of the letters "A" for cortical negativity or "B" for positivity, respectively, and "C" for the passive viewing condition in the fMRI (see description of SCP-regulation). One week after completion of training the subjects participated in an fMRI session. To adapt the person to the fMRI environment, he or she practiced for one session in an fMRI simulator (dummy fMRI with identical visual and auditory environment) immediately before the actual fMRI recordings. In addition, the MRI environment creates artefacts for the electrophysiological recordings, therefore uncontaminated EEG acquisition was only possible in the simulator. To control the performance of voluntary SCP regulation, EEG was recorded inside the simulator. During the fMRI recording the discriminative stimuli (i.e. letters "A", "B" or "C") were presented in the same manner as during SCP-training and dummy-fMRI. Subjects were paid ($20) for participating in the fMRI sessions.

Physiological regulation training of SCP

For the five patients with epilepsy, training sessions were subdivided into a three-week phase of 20 sessions and a two-week phase of 15 sessions, respectively. Each session consisted of 145 trials and lasted about 90 min. The two phases were separated by an eight-week phase during which the people were instructed to practice at home the strategies they had learned during the first training phase. For the five healthy subjects 10 daily identical sessions were conducted within two weeks.

During a training session, the persons' SCPs were recorded at the vertex (Cz), referred to as the average potential of the two mastoid electrodes measured separately. The time constant was set to 16 s. Mean EEG amplitudes over 500 ms intervals sliding with a 100 ms moving average were presented as a moving cursor on a computer screen over a period of 8 s in each trial. They were corrected on-line for blinks and vertical eye movements (Rockstroh et al. 1993; Kotchoubey et al. 1996) Each trial began with the presentation of the letter "A" or "B", chosen in a pseudo-randomized order, that served as a discriminative signal informing the subject whether the cortical potential should be changed to a negative ("A") or positive ("B") polarity compared to baseline (first 500 ms of each trial). Rightward movements of the feedback cursor indicated an SCP change in the required direction, and leftward movement changes in the opposite direction (i.e. a positive SCP shift, when negativity was required, or vice versa). After 8 s, the letter and feedback signal disappeared, indicating the end of the trial. Inter-trial intervals varied randomly between 2 s and 5 s. To assist the transfer of the acquired self-regulation skill to every day life, "transfer trials" were employed where the participants were prompted by the letters "A" and "B" but received no feedback.

Practice session in the fMRI simulator

The fMRI simulator consisted of a "dummy" fMRI providing a comparable environment (including patient table and head-coil) as the actual measurement but without the magnetic field and RF pulses. The scanning noise of the EPI sequences used in the experiment were recorded on CD and presented in the simulator. This permitted undisturbed recording of the EEG and the vertical EOG while transfer trials without feedback were performed similar to the actual fMRI session. Previous studies using extended training of slow cortical potential control revealed high intra-individual stability of the learned polarity even after several years. In a follow-up study, 37 patients with intractable epilepsy were trained for SCP self-regulation. After a break of half a year, follow-up studies demonstrated high stability in SCP differentiation and control (Kotchoubey et al. 1997).

Thus, satisfactory performance during the actual fMRI recording was likely obtained. A third condition where the persons passively viewed the screen was introduced to control for non-specific task effects (e.g. attention, visual processing of the stimuli) in the fMRI experiment. Passive viewing trials followed each active task trial and one run consisted of 25 trials for task "A", 25 trials for task "B" and 50 passive viewing trials. We carried out three to five runs in the simulator before the actual fMRI session.

fMRI session

The same procedure was used for the subsequent fMRI session but without the EEG recording. The participants were prompted to produce positive, negative, or no SCP shifts for 90 8 s trials. Similar to the simulator session, each trial with a task was followed by a passive viewing condition signalled by the letter "C". The visual stimuli were displayed by an LCD video projector on a screen attached to the foot of the patient table. A non-magnetic mirror attached to the head coil permitted the subjects to view the stimuli. The session was subdivided into three experimental blocks. Each block consisted of 10 trials per condition presented in counterbalanced (pseudo-randomized) order thus yielding a total of 30 trials for each condition. Imaging was performed with a 1.5 T Magnetom Vision (Siemens, Erlangen, Germany) whole body MRI system equipped with a standard head coil system. T2* weighted echo-planar images were acquired in axial orientation (TR=4.5 s, TE=64 ms, flip angle 90°, FOV=160×256 mm, 28 slices, slice thickness 4 mm, 1 mm gap, voxel dimension 2×2×4 mm^3) covering the whole brain. An improved storage system was used (Klose 1999). For each subject 384 images were acquired. Additionally, a T1-weighted 3D dataset containing 128 sagittal slices (slice thickness 1.5 mm, matrix 224×256, FOV 250, TR=9.7 ms) was acquired.

Image processing and statistical evaluation

Pre-processing and statistical analyses of the data were carried out with SPM99 (Welcome Department of Cognitive Neurology, London, UK). All images were realigned to the first image of the time series using a rigid body spatial transformation (actual head movements were smaller than 1.5 mm in all subjects). The realigned and re-sliced images were then corrected for differences in acquisition time. A mean image was created and co-registered to the T1 structural image. The anatomical image was then normalized into a standard stereotactic space using the T1 MNI template (Montreal Neurological Institute, Quebec, Canada). The non-linear transformation parameters were also applied to the functional images. Finally, the data were smoothed with a 12 mm (full width half maximum) Gaussian kernel.

The haemodynamic responses were modelled with a delayed box-car function convolved with a canonical haemodynamic response as well as their time derivatives. The (first order) rigid body transformation parameters (translation and rotation) were employed as additional regressors. We defined three event types: negativity, positivity, and passive viewing. The epoch length for all conditions was two scans. Each subject's data set was high-pass filtered (cut-off frequency 0.39 Hz per min) to remove low-frequency drifts.

Since each subject used different cognitive strategies for physiological control, a fixed effects analysis was carried out. Separate t-contrasts for the parameter estimates for negativity and positivity (exclusively masked with passive viewing, $P<0.05$ (uncorrected) to control for unspecific task effects) for each subject were conducted. In addition to the fixed effects analysis, a random effects analysis was performed. Although a random effects analysis is less powerful, especially with small sample sizes, it considers the inter-subject variability and hence the results can be generalized to other samples. In the random effects analysis, mean subject-specific functional images were computed for every contrast (negativity, positivity, negativity vs positivity) and subject. These individual contrast images were then entered into a second level analysis using a one-sample t-test. Based on a priori anatomical hypotheses, a small volume correction was applied in the basal ganglia and the

thalamus using separate masks that contained the putamen, pallidum, caudate nucleus and the thalamus.

A linear regression between SCP performance and the haemodynamic response was calculated using the individual SCP-shifts during the dummy session as predictors to identify those brain areas that showed a relationship between SCPs and the BOLD response. The individual contrast images for negativity, positivity and the difference between negativity and positivity (adjusted for global effects) were used as dependent variables. Masks for the predefined regions of interest were created using the parcellated brain of Tzourio-Mazoyer et al. (2002).

Correlation coefficients for the difference in microvolts between required positivity or required negativity and the individual parameter estimates for negativity, positivity, negativity compared with positivity and deactivations during positivity were calculated. The emphasis was on positivity training because clinical applications of SCP-regulation (Kotchoubey et al. 2001) rely on positive polarity of SCPs because of their presumable anticonvulsive effect.

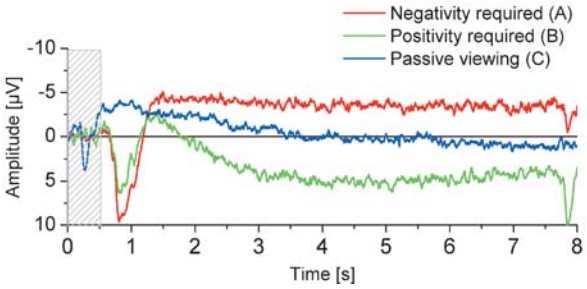

Fig. 1 Grand average of the EEG trace during transfer trials inside the dummy-fMRI for all 10 people. 760 trials (condition A), 760 trials (B) and 1667 trials (C) were averaged for each task separately. For active tasks (production of negativity or positivity) an event-related positive potential (P300) appears after the baseline (*grey shaded area*)

Results

SCP regulation training

After the feedback training, subjects were able to voluntarily control their SCPs with and without feedback. The feedback training resulted in an average SCP differentiation (positivity minus negativity) of 12 μV ($t_{\text{Feedback}(9)}$=3.7, P<0.01) while in the transfer condition, a differentiation of 8.8 μV ($t_{\text{Transfer}(9)}$=2.9, P<0.01) was achieved. The performance of SCP control relevant for this study was evaluated in the fMRI simulator session.

fMRI simulator session

The mean SCP amplitude during the last 4 s of an 8 s trial was analyzed. The differentiation during the training session in the dummy-fMRI over all subjects amounted to 8.3 μV ($t_{(9)}$=2.64, P=0.03). Differentiation over all subjects analyzed on a trial basis (n=760 per task) was highly significant ($t_{\text{pos-neg}(759)}$=8.38, P<0.001) demonstrating successful learning of SCP self-control. Eye movement-related potential shifts, the most critical sources for artifacts, showed no significant differentiation between positivity and negativity ($t_{(759)}$=−1.42, n.s.). For the positivity task, the average SCP potential shift for all subjects was 4.6 μV ($t_{(9)}$=3.31, P<0.01), and for the negativity task it was −3.7 μV ($t_{(9)}$=1.94, n.s.). Of the ten participants, eight could produce significant SCP differentiation in the simulator. Fig. 1 illustrates the EEG trace averaged over all ten subjects for the three conditions A, B and C inside the dummy fMRI. The active tasks A and B were indicated after a baseline period of 0.5 s. Even in trials without feedback (transfer trials) a strong positive event-related potential occurred 300–400 ms after the baseline. The higher positive evoked potential at the beginning of the negativity condition is in line with the theory of an increased cortical excitability during the production of cortical negativity.

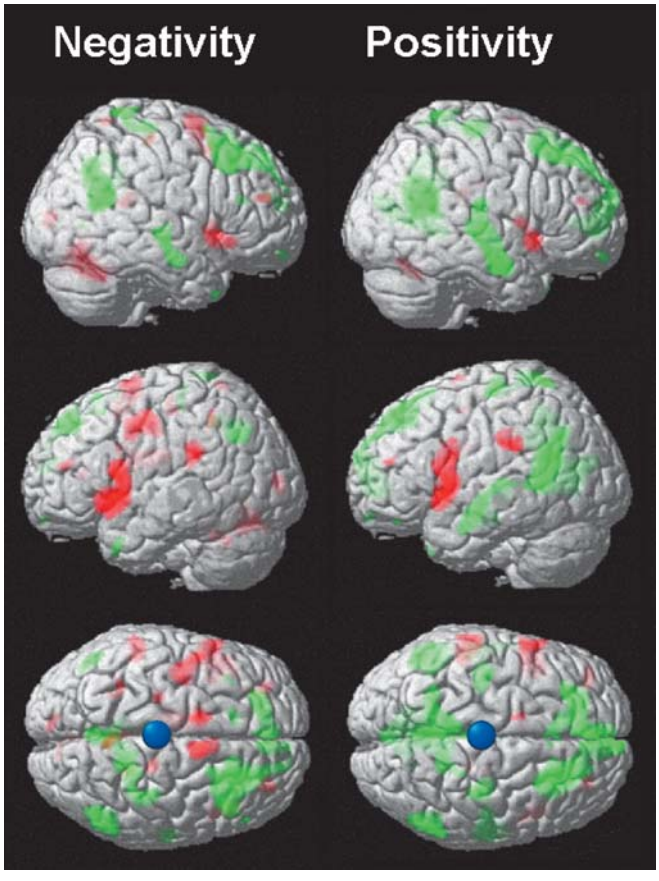

Fig. 2 Cortical activation maps of the significant effects during the negativity (*left*) and the positivity task (*right*) are projected on the surface of a standard volume-rendered brain (intensity cut-off at P=0.05, corrected). *Red* indicates significant activation, *green* indicates deactivation compared to baseline (masked with passive viewing thresholded at P=0.05, uncorrected). The positivity task shows deactivations in frontal and temporo-parietal areas. The *blue dot* in the bottom pictures marks the active central electrode position used for feedback

Table 1 Activation sites during negativity versus baseline (exclusively masked with passive viewing) A, Deactivations sites during negativity compared to baseline (exclusively masked with deactivations during passive viewing) B

	Coordinates			BA	*t* value
	x	y	z		
A: Activation during negativity					
Precentral gyrus left	–55	12	5	44	11.14***
Precentral gyrus left	–26	–19	49	4	5.73***
Precentral gyrus right	18	–21	54	4	5.70***
Postcentral gyrus right	6	–51	65	7	5.88***
SMA left	–14	7	64	6	9.63***
SMA right	8	7	59	6	7.03***
Middle frontal gyrus left	–48	6	40	6/8	6.49***
Insula left	–42	13	–4	44/13	7.35***
Insula right	48	14	–4	44/13	6.49***
Dorsolateral prefrontal cortex left	–32	43	16	10	6.28***
Dorsolateral prefrontal cortex right	30	43	13	10	5.60***
Supramarginal gyrus left	–55	–36	28	40	6.87***
Inferior parietal lobule left	–30	–46	43	40	6.09***
Cerebellum right	22	–69	–15	19	8.58***
Lingula gyrus right	14	–83	14	7/19	5.49***
Caudate body left	–10	3	16		7.52***
Putamen/Globus Pallidus left	–22	4	6		4.86**
B: Deactivation during Negativity					
Superior temporal gyrus right	57	–53	21	22/39	8.29***
Inferior parietal lobule left	–50	–60	38	39/40	6.09***
Superior frontal gyrus right	26	28	47	8	8.20***
Middle frontal gyrus right	2	49	40	8/9	7.71***
Dorsolateral prefrontal cortex left	–24	41	38	8/9	6.64***
Dorsomedial prefrontal cortex right	8	56	–15	11	6.42***
Dorsomedial prefrontal cortex right	6	57	10	10	5.30**
Middle temporal gyrus right	63	–20	–6	21	8.10***
Middle temporal gyrus left	–51	10	–27	21	5.21**
Superior frontal gyrus left	–14	26	56	6	5.86***
Paracentral lobule left	–4	–24	56	6	5.60***
Postcentral gyrus right	18	–39	72	3/5	8.07***
Precentral gyrus right	38	–22	60	4	6.31***
Precuneus left	–2	–58	42	7	6.81***
Lingula gyrus right	18	–66	5	19	5.07**

P values are corrected for the whole brain (***$P<0.001$, **$P<0.01$). Only voxels with the highest *t* value per region and a minimal extent of 10 voxels were reported. Location was indicated by anatomical structures, by Brodmann's area (described by Talairach and Tournoux 1988) and Talaraich coordinates. The MNI coordinates were converted in Talairach coordinates using a non-linear transformation algorithm written by Matthew Brett (http://www.mrc.cbu.cam.ac.uk/Imaging/mnispace.html)

fMRI session

Fig. 2 shows the cortical activation (red) and deactivation (green) maps during required electrocortical negativity and positivity. The task to produce positivity resulted in similar but fewer significantly activated areas than the negativity task with the most pronounced differences in the dorsolateral pre-frontal cortex (DLPFC) and Broca's area. Deactivations were found in similar regions as in the negativity task (see below) but more pronounced. In most of the remaining cortical sites positivity was accompanied by deactivations including the central, temporal-hippocampal and prefrontal areas. A strong deactivation was seen in the middle and superior left temporal gyrus and the superior parietal lobule as well as the postcentral gyrus in the region next to the EEG electrode (Cz) that provided the feedback during training.

During self-produced negativity, highly significant activations in areas close to the location of the EEG electrode used for the SCP-feedback training were observed with the fixed effect analysis. These included the pre-central gyrus (bi-laterally), the middle frontal gyrus, and the supplementary motor area (SMA, bilaterally). Activations were also found in the insula (bilaterally), the DLPFC, and parietal areas such as the supramarginal gyrus (left) and the left inferior parietal lobule (see Table 1A). Significant deactivations (negative BOLD responses) were found in the temporal, parietal, frontal and pre-frontal areas as shown in Table 1B and Table 2.

The contrast negativity versus positivity showed activation sites focused around the location of the active EEG electrode and the temporal-hippocampal region (see Table 3).

The random effects analysis yielded significant activation of the left pallidum ($t_{(9)}=6.19$, $P=0.013$) during the negativity task as well as marginally significant activations of the left putamen ($t_{(9)}=5.57$, $P=0.072$) and the right pallidum ($t_{(9)}=4.43$, $P=0.065$). The positivity task led to a

Table 2 Activation sites during positivity versus baseline (exclusively masked with passive viewing) A, Deactivation sites during positivity compared to baseline (exclusively masked with deactivations during passive viewing) B

	Coordinates			BA	*t* value
	x	y	z		
A: Activation during positivity					
Precentral gyrus left	–53	12	3	44	8.90***
Precentral gyrus right	51	8	3	44	5.50***
SMA left	–14	1	66	6	5.44***
Insula right	46	13	–7	44/13	6.53***
Dorsolateral prefrontal cortex left	–36	43	11	10	5.50***
Dorsolateral prefrontal cortex right	28	45	12	10	5.45***
Inferior parietal lobule left	–55	–28	33	40	6.66***
Putamen right	30	–4	0		4.63**
B: Deactivation during positivity					
Dorsomedial prefrontal cortex left	–2	47	42	8	8.95***
Medial orbitofrontal cortex right	6	52	–6	10	8.44***
Middle temporal gyrus right	55	–12	–15	21/20	9.34***
Middle temporal gyrus left	–57	–14	–9	21	8.33***
Superior temporal gyrus left	–51	–51	23	39/40	7.79***
Superior temporal gyrus right	57	–51	21	22/40	7.77***
Superior temporal gyrus left	–46	20	–33	38	5.93***
Inferior parietal lobule left	–48	–58	36	39/40	5.69***
Superior parietal lobule left	–22	–51	65	7	6.52***
Postcentralis gyrus left	–10	–41	68	3/5	7.00***
Postcentral gyrus right	14	–41	72	3/5	5.96***
Precentral gyrus left	–38	–18	62	4/6	6.72***
Precentral gyrus right	36	–16	60	4/6	6.53***
Parahippocampal gyrus right	20	–47	2	30	6.98***
Parahippocampal gyrus left	–18	–54	6	30	6.84***
Hippocampus left	–24	–20	–16	35/28	5.31***
Pulvinar left	–10	–27	0		5.53***
Amygdala left	–22	–3	–18		4.91*
Putamen left	–18	12	–6		4.82*

P values are corrected for the whole brain (***$P<0.001$, **$P<0.01$, *$P<0.05$). Only voxels with the highest *t* value per region (extent threshold 10 voxels) were reported

Table 3 Activation sites during negativity versus positivity

	Coordinates			BA	*t* value
	x	y	z		
Negativity versus positivity					
Precuneus left	–2	–41	67	7	6.33***
Precuneus right	–4	–52	56	7	5.72***
Caudate body left	–10	3	15		5.67***
Superior temporal gyrus left	–57	–25	5	21/22	5.14**
Parahippocampal gyrus right	18	–20	–14	35/28	5.02**
Hippocampus left	–26	–20	–11	28	4.78*

P values are corrected for the whole brain (***$P<0.001$, **$P<0.01$, *$P<0.05$)

marginally significant activation in the left thalamic region ($t_{(9)}$=5.76, P=0.058). It should be noted that the pallidum and putamen (both bi-laterally) as well as the left thalamus were highly significantly activated during all active tasks when the less stringent criterion of uncorrected *P* values was used.

Regression analyses between SCP performance and BOLD response during self-produced positivity revealed that the activations of the pallidum and the putamen were the best predictors for successful SCP control (see Table 4). SCP task performance was also correlated with deactivation during self-produced positivity visible in the SMA, the cuneate and the right dorsomedial pre-frontal cortex. Correlations between achieved SCP changes and BOLD contrasts ranged between 0.88 and 0.98. Prediction of the difference between cortical negativity and positivity revealed activity in the dorsomedial pre-frontal area and parahippocampal gyri (see Table 4). A strong positive correspondence between self-produced negativity and BOLD contrasts was found in the hippocampus and the SMA. Correlations ranged between 0.84 and 0.92 (Fig. 3, Fig. 4).

Discussion

The data of this study support the hypothesis of the relationship between the fMRI signal and SCPs in

Table 4 Activation, deactivation sites associated with task performance during the fMRI-simulator session during negativity and positivity

	Coordinates			Beta	*t* value	R
	x	y	z			
Activation during positivity						
Pallidum right	19	–4	0	0.47	6.29*	0.92
Putamen right	24	–2	9	0.48	5.49*	0.90
Deactivation during positivity						
SMA right (BA 6)	2	18	58	–1.59	–11.75*	0.98
SMA left (BA 6)	–4	–14	66	–2.05	–8.65*	0.96
Cuneus right (BA 17)	2	–77	11	–2.76	–6.53*	0.93
Dorsomedial prefrontal right (BA 9)	4	52	31	–1.82	–5.48*	0.90
Activation during negativity						
SMA left (BA 6)	–8	6	68	–0,97	–4.40*	0.84
Parahippocampal gyrus right (BA 28)	20	–32	–14	–0,66	–6.05*	0.92
Negativity versus Positivity						
Dorsomedial prefrontal right (BA 10)	8	62	10	0.50	9.41*	0.96
Parahippocampal gyrus right (BA 28)	24	–18	–14	0.48	8.62*	0.95
Parahippocampal gyrus left (BA 30)	–24	–32	–6	0.45	6.76*	0.92

Beta represents the slope of the regression line with the corresponding *t* value and the correlation coefficient R. *All activations are significant at$P<0.05$, corrected for multiple comparisons

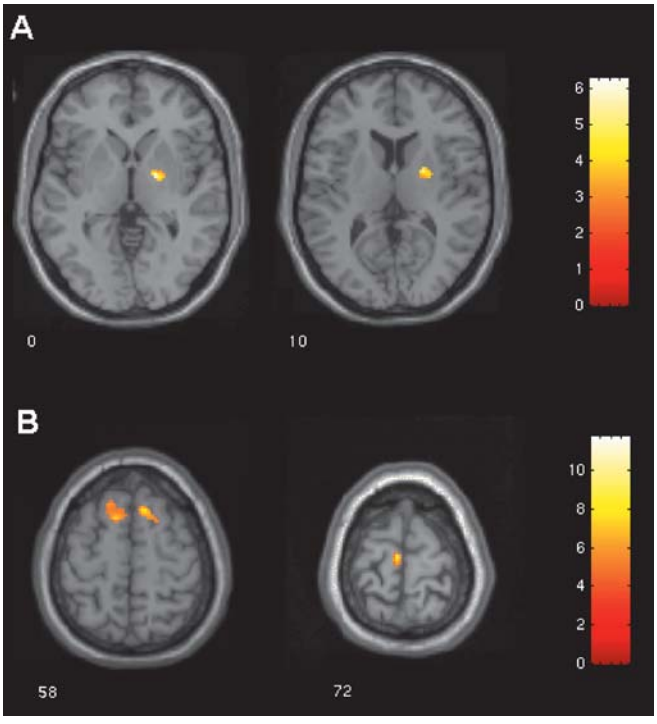

Fig. 3A, B Brain areas predicting the electrocortical responses (SCP changes in μV) during transfer trials in the dummy-fMRI sessions. **A** Activations during positivity in the pallidum (*left*) and the putamen (*right*). **B** Deactivations during positivity in the supplementary motor area (*left*) and at the vertex (*right*). The brain activations are overlaid on a normalized single-subject T 1 image from the MNI template (Montreal Neurological Institute). T-coordinates are depicted below each slice. The colour bar on the *right side* illustrates the t-value of the slope based on regression analyses

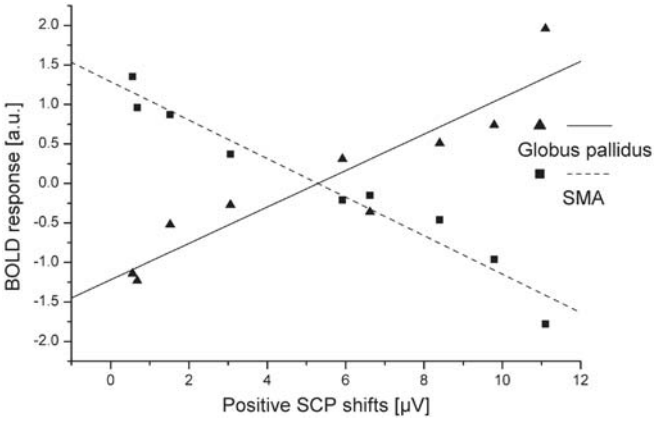

Fig. 4 The parameter estimates are the predicted BOLD responses (in standardized arbitrary units) in two voxels (pallidum: 19, –4, 0 mm, supplementary motor area: 2, 18, 58 mm) based on the SCP-amplitude during regulation of positive SCP shifts during the fMRI simulator session. Parameter estimates against SCP deflections in μV in the pallidum (*triangle*), the SMA (*rectangle*), their regression lines are depicted

humans. Surface negative SCPs reflect increased cortical activity, which coincides with a heightened BOLD response near the central position of the feedback electrode (pre- and postcentral gyrus, SMA), whereas decreased cortical activity reflected in surface positive SCPs resulted in an overall decrease of the BOLD signal (pre-frontal, parietal, temporal and somatosensory areas). The reported deactivations during required negativity may be related to the small negativities that were achieved (Fig. 1). Earlier work (Birbaumer et al. 1990) showed that the voluntary control of SCPs from a central electrode results in widespread changes of the SCPs (extending particularly into frontal and less so into parieto-occipital and temporal areas). The substantial reduction of the

BOLD signal during cortical positivity is consistent with the postulated neurophysiological basis of SCPs (Birbaumer et al. 1990). An inhibitory or at least "disfacilitatory" function of surface-positive changes of the DC-potentials has been assumed. If SCPs are related to the summated activity of synchronized input of intracortical and thalamic fibres to the apical dendrites, our results are consistent with the animal data reported by Logothetis et al. (2001) who demonstrated a clear interdependence between local field potentials (LFP) generated by synaptic input to the dendritic tree and the BOLD response. Since the relationship of active inhibition and decreased neuronal activity as the neurophysiological basis of slow cortical positivities needs final neurophysiological confirmation, this interpretation is tentative. However, this speculation is strengthened by the fact that cortical positivity was highly correlated (r>0.88) with activity of primarily inhibitory structures of the basal ganglia such as putamen and pallidum and deactivation of pre-frontal areas devoted to motor preparation and attention. A comparable result was reported by Critchley et al. (2001) who trained subjects with electrodermal biofeedback. Profound relaxation induced by the training resulted in increased activity in the pallidum.

The extended reduction in haemodynamic flow during cortical positivity may also explain why operant training of voluntary production of positive SCPs leads to substantial reduction of seizures in intractable epilepsy (Kotchoubey et al. 2001), increased reaction time (Lutzenberger et al. 1979) and other forms of performance decrements (Birbaumer et al. 1990). One might speculate that patients learn to block the development of hyperexcitatory and paroxysmal activity by voluntarily "drying" up those cortical and subcortical regions involved in the generation of epileptic activity. Excitation thresholds of cortical assemblies reflected in amplitude changes of positive SCPs are increased through activity in a threshold-regulation-loop comprising the basal ganglia, thalamus and cortex (Braitenberg and Schütz 1991). The increased BOLD response in the basal ganglia during required positivity coincides with the reduction of cortical activation in premotor areas that are mainly active during negative SCPs. The basal ganglia play an important role in selective attention and in movement initiation as well as control and sequencing movement. The ventral lateral and ventral anterior thalamic nuclei project primarily to the SMA, which is in turn connected to the ventral lateral nucleus (Brunia 1999) via the striatum and pars interna of the pallidum. Heightened activation of the pallidum leading to inhibition is likely to increase thalamic activity. Again, the afferent pathways to the thalamus produce an inhibitory effect which in turn increases the excitation thresholds of the pathways to the cortex especially to the SMA and the DLPFC (Tamminga et al. 2001; Samuel et al. 2001). The activations in the globus pallidus and the deactivations in the SMA during positivity can be interpreted as efficient thalamo-cortical modulation of arousal in successful SCP-regulators via the globus pallidus. Deactivations in both task conditions were found in pre-frontal areas around the mid-sagittal line as well as bilaterally in temporo-parietal areas. In a meta-analysis by Shulman et al. (1997), comparable deactivations in a wide range of attention-demanding cognitive tasks were described (Raichle et al. 2000). The cognitive task used in this study was certainly attention-demanding and may explain these deactivations in both conditions, negativity and positivity.

In the present experiment it is impossible to separate changes in BOLD responses caused by the effort to self-regulate the SCPs from the achieved amplitude polarity changes (negativity or positivity). It is obvious that the chosen behavioral procedure to produce the required cortical differentiation is at least in part responsible for some of the observed BOLD effects. The same argument, however, may be applied to other experimental conditions used to induce SCP changes such as signalled preparation for movement as it is commonly employed for induction of cortical negativities. The following discussion of possible neural structures underlying the self-regulation task has to be treated with caution and is somewhat speculative. The situation may be in fact not as difficult as one might assume: The neural mechanisms behind successful SCP-regulation should be largely identical with those mechanisms used in different behavioural environments such as preparation for voluntary movement during cortical negativity and post-reinforcement satiation or thought-stopping for the induction of cortical positivity. To disentangle the effects of SCP-polarity changes from the effort to regulate them, a correlation analysis of the cognitive and behavioural strategies used by the subjects is necessary. The high intersubject variability, however, did prevent the appearance of significant correlations between BOLD response and different strategies used to bring the SCP-polarity under voluntary control.

The described physiological effects are compatible with an interpretation that successful self-regulation of slow cortical potentials and correlated changes in BOLD signal reflect changes in attentional demands of the two tasks required: While cortical negativity is achieved primarily by allocation of preparatory attentional resources to sensorimotor and frontal brain regions, cortical positivities are achieved by a reduction of attentional resource allocation or even on active inhibitory process blocking the described neuronal structures responsible for selective attention. Neurovascular changes as detected by fMRI are highly sensitive to attentional demand characteristics, which make our speculation plausible.

To achieve satisfactory differentiation of the required electrocortical changes, areas responsible for executive control and memory retrieval (parahippocampal and dorsolateral pre-frontal area) have to be activated, probably indicating retrieval of differential cognitive strategies such as various types of imagery and motor preparation (Roberts et al. 1989). The variable activation patterns observed in individual subjects may reflect different mental strategies to successfully generate reliable SCP-shifts. For example, four subjects reported

motor imagery (e.g. walking with the dog), two used language-related strategies (e.g. imagery of phrases from bible sections), other subjects used emotional strategies or more abstract mental images. Simple (kinesthetic) motor imagery (Porro et al. 2000) leads to activation in the posterior part of the precentral gyrus and SMA. A magnetoencephalographic study (Ogiso et al. 2000) found activation in the precuneate and SMA during imagery of hurdling in self-centred space. Decety et al. (1996) reported activation in the DLPFC, the anterior cingulate, premotor cortex, the SMA, and the basal ganglia during imagery of writing similar to our study. The inferior and superior parietal cortex were also activated during imagination of joystick movement (Stephan et al. 1995; Samuel 2001). The more complex the imagery, the more widespread cortical areas are activated.

The SMA, a structure involved in motor preparation and response selection, seems to be activated in all studies using motor imagery and also in most of our subjects prompted to produce differential SCP shifts. Retrieval of imagined motor and visual objects or scenes reported by our subjects involved the dorsolateral pre-frontal cortex, anterior insula, inferior parietal cortex and precuneus. Exactly these regions were also found activated during physiological self-regulation in our study. Language processing areas were activated during trials of required negativity and positivity possibly reflecting the fact that the discriminative stimuli presented carried linguistic significance.

All participants in this study were well trained and a high consistency in the production of SCP-shifts between the fMRI simulator and the actual fMRI session can be assumed. Indeed, we found that successful SCP differentiation was predicted by the activation of a basal ganglia-thalamo-cortical network. It is, however, possible that there was not a complete concordance between the dummy and the actual fMRI session. The consistency of the reported results and the results of the study by Kotchoubey (1997) mentioned above, favour the generalization of the achieved physiological regulation in these well-trained subjects. A plausible assumption that performance declined during the session of actual fMRI measurement implies that the real covariation between the task and BOLD response is even stronger. To obtain single trial correlations of SCPs with the BOLD response, recordings of the electrocortical activity in the low frequency domain simultaneously with fMRI would be necessary. However, the continuous image acquisition during task performance used in this study leads to large scanning artefacts of the RF pulses of the gradient coils in the EEG signal. The removal of these artefacts is difficult and existing correction algorithms in non-invasive experiments with humans (Allen et al. 1998; Bonmassar et al. 2001) have not yet been tested for the slow-wave range . An alternative approach in the future could be the intermittent acquisition of SCPs and fMRI with an inevitable loss of information.

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