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Regional Modulation of BOLD MRI Responses to Human Sensorimotor Activation by Transcranial Direct Current Stimulation

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Blood oxygenation level dependent (BOLD) MRI was used to monitor modulations of human sensorimotor activity by prior transcranial direct current stimulation (tDCS). Activation maps for a right hand sequential finger opposition task were obtained for six subjects before as well as 0–5 min and 15–20 min after a 5-min period of 1 mA cathodal and, in a separate session, anodal tDCS of the left-hemispheric motor cortex. Cathodal tDCS resulted in a global decrease of the mean number of activated pixels by 38% ($P < 0.01$) 0–5 min after stimulation, which reduced to 28% ($P < 0.05$) 15–20 min after stimulation. A region-of-interest analysis revealed a 57% decrease of activated pixels ($P < 0.001$) in the supplementary motor area, but no change in the hand area of the primary motor cortex. Anodal tDCS yielded a nonsignificant 5% increase of activated pixels with no regional differences. These findings support the view that reduced neuroaxonal excitability after cathodal tDCS causes reduced brain activity. However, rather than affecting the primary sensorimotor input of an active task, the process appears to dampen those responses that rely on cortico-cortical connections and related processing. Magn Reson Med 45: 196–201, 2001. © 2001 Wiley-Liss, Inc.

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Transcranial direct current stimulation (tDCS) of the human brain alters neuroaxonal excitability. In animals, the application of weak direct currents to the cortex has been demonstrated to result in hyperpolarization of cortical neurons for cathodal stimulation and depolarization for anodal stimulation (1). These modulations of membrane polarization were accompanied by decreased excitability and reduced spontaneous neuronal activity for cathodal tDCS, whereas opposite effects were induced by anodal tDCS (2–6). The safety of the procedures was supported by light and electron microscopy demonstrating that even prolonged (up to 3 hr) and repeated tDCS did not result in damage of neuronal tissue for all current strengths used (7,8). Epileptic activity was never elicited (9).

Human applications have shown that tDCS indeed leads to intracerebral current flow (10). However, the outcome variables measured so far mostly rely on indirect parameters such as clinical status of patients or performance in forced choice reaction time paradigms (11–13). A more recent study investigated the amplitude of motor-evoked potentials which were elicited by transcranial magnetic stimulation (TMS) of the motor cortex to characterize the influence of tDCS on cortical excitability during and after current flow (14). It was found that cathodal tDCS diminished motor cortical excitability by about 30%, whereas anodal tDCS increased it by about 40%. Because these changes sustained for up to 5 min after the end of stimulation, the induced effects were considered to reflect short-term depression and postexercise potentiation of brain activity (15).

The intensity and duration of the direct current used in these human tDCS applications were 1 mA and 5 min, i.e., within the safety range for electric stimulation (16) and below the values tested in animals. Skin temperature measurements under the electrodes indicated the absence of current-induced tissue heating and no participating subject developed clinical symptoms or behavioral changes. Because systematic studies are rare but needed for an extension of clinical trials, it is desirable to extend the tDCS assessment to noninvasive functional neuroimaging in order to broaden the basis for further physiologic insights as well as to provide detailed regional access and brain coverage.

Accordingly, this work represents the first attempt to detect tDCS-induced modulations of brain activity via changes of the blood oxygenation level dependent (BOLD) MRI response to a well-defined functional challenge such as sensorimotor activation. The approach tests the hypothesis that persistent differences in neuronal excitability after cathodal and anodal tDCS result in different degrees of cortical activity. It relies on the assumption that pertinent alterations translate into hemodynamically mediated differences in the BOLD MRI signal strength and/or the spatial extent of corresponding activations.

MATERIALS AND METHODS

MRI studies of six healthy subjects (four females, two males, age range 23–30 years) were performed at 2.0 T (Siemens Vision, Erlangen, Germany) with use of the standard head coil and gradients (25 mT m^{-1}). Written informed consent was obtained in all cases before the examinations. Neither cardiac gating nor special head restraints were applied. The experiments were approved by the local ethics committee in agreement with the standards set by the declaration of Helsinki.

Structural imaging comprised 3D T_1-weighted scans (FLASH, TR/TE = 15/4 ms, flip angle 20°, 4 mm thickness) to anatomically define the motor cortex hand area along the central sulcus as well as flow-sensitized acquisitions (TR/TE = 70/6 ms, flip angle 60°) delineating the macro-

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vasculature in pertinent sections. Dynamic functional acquisitions were based on T_2^*-weighted single-shot, blipped gradient-echo EPI (TR = 2000 ms, flip angle 70°, TE = 53 ms corresponding to zero phase-encoding and central *k*-space acquisition) at 2.0 × 2.0 mm^2 in-plane resolution and 4 mm section thickness (96 × 128 matrix, 192 × 256 mm^2 field-of-view, 10 sections).

Transcranial Direct Current Stimulation

Direct current was induced by a pair of square rubber electrodes (50 × 50 mm^2) connected to a specially developed battery-driven stimulator outside the magnet room. During MRI scanning the cables to the stimulator were disconnected. To properly position the electrodes on the subjects' head, the representational field of the right hand was determined using TMS (coil position with the maximum amplitude of motor evoked potential in the abductor digiti minimi). Before subjects entered the MR scanner the electrodes were placed atop the respective left-hemispheric hand area and above the contralateral right orbita using conventional electrode gel and elastics. For cathodal tDCS the cathode was placed above the motor cortex, for anodal tDCS the direction of the electric flux was reversed. For each subject cathodal and anodal tDCS experiments were performed in separate examinations at least 1 day apart (different order for different subjects). In either case a constant direct current of 1 mA strength was applied for 5 min. Subjects felt the current as an itching sensation at both electrodes.

Experimental Protocols

Functional neuroimaging of sensorimotor activation was performed before as well as 0–5 min and 15–20 min after DC stimulation. During the 5-min period of current application the subjects remained in the magnet without actual scanning. The requested motor performance was a cued sequential finger opposition task where subjects had to sequentially move all fingers to the thumb. A visually controlled frequency of 3 Hz was demanded by a flickering diagonal cross projected onto a transparent screen viewed by the subjects through oculars and a mirror arrangement atop the headcoil. Resting periods were indicated by the same flickering cross rotated by 45°. Paradigms followed a block design with 12-sec periods of finger-tapping and 18 sec of motor rest. The blocks were repeated 10 times yielding a total measuring time of 5 min.

Data Analysis

The dynamic MRI datasets were analyzed without spatial or temporal filtering. Functional responses to task-related changes in brain activity were identified by calculating correlation coefficients (17). The reference waveform representing the stimulus protocol was shifted by 6 sec (three images) with respect to stimulus onset to account for hemodynamic latencies. Quantitative maps of correlation coefficients were obtained by a fully automated and user-independent statistical analysis based on in-house software following the ideas outlined in Ref. (18). The approach estimates the individual noise distribution underlying the histogram of each correlation coefficient map and then rescales the correlation coefficients as percentile ranks of the noise distribution. In a first step, highly significant centers of activation are identified by automatically accepting all pixels above the 99.99% percentile rank of the individual noise distribution of correlation coefficients. This upper threshold corresponds to an error probability of $P \leq 0.0001$ or 1–2 false-positive pixels per map. Subsequently, a full delineation of coherently activated areas in the final activation map is achieved by iteratively accepting directly neighboring pixels as activated, provided their correlation coefficients exceed a lower threshold corresponding to the 95% percentile rank of the noise distribution, i.e., an error probability of $P \leq 0.05$.

The degree of activation was quantified in terms of numbers of activated pixels per experiment. These values were either determined as a global quantity including all sections acquired or derived from a region-of-interest (ROI) analysis which focused on the hand area of the primary motor cortex (M1) and the supplementary motor area (SMA). Alternatively, we evaluated putative changes of the BOLD MRI response strength ("functional contrast"), i.e., the percentage difference between the mean signal strength during rest and motor activity. The analysis involved either all activated pixels which ignores differences in pixel numbers and/or spatial extent before and after tDCS or was restricted to pixels that were activated both before and after tDCS. Statistical evaluations of group differences between the pre- and post-tDCS conditions were based on two-sided paired Student's *t*-tests with a significance level of $P \leq 0.05$.

RESULTS

Figure 1 compares activation maps obtained for sequential finger opposition in five sections covering the primary motor cortex hand area before (left) and 0–5 min after (middle) cathodal tDCS of a single subject. The "binary difference" maps (right) reveal a significant reduction of the number of activated pixels as indicated by the prevalence of pixels coded in yellow. In contrast, reversing the polarity of the current in the same subject resulted in a different pattern. Figure 2 compares pertinent activation maps obtained before (left) and 0–5 min after (middle) anodal tDCS without a preferential change in the corresponding "binary difference" maps (right). Although these examples do not suffer from electrode-induced distortions, some cases exhibited a tolerable degree of signal loss mainly below the right-hemispheric frontal tDCS electrode and clearly outside the motor system.

The group responses of the six subjects are summarized in Table 1. The values represent the number of activated pixels averaged across subjects either in terms of a global response, i.e., for all sections acquired, or for a ROI analysis focusing on the motor cortex hand area and the SMA. Table 1 confirms the qualitative observations for a single subject (Fig. 1) by revealing a statistically significant 38% decrease of the total number of activated pixels immediately after cathodal tDCS. At 15–20 min after tDCS there was a weaker but still significant 28% decrease in the number of pixels. A more detailed ROI analysis resulted in marked regional differences. Most importantly, when exclusively analyzing the hand area as the central portion of

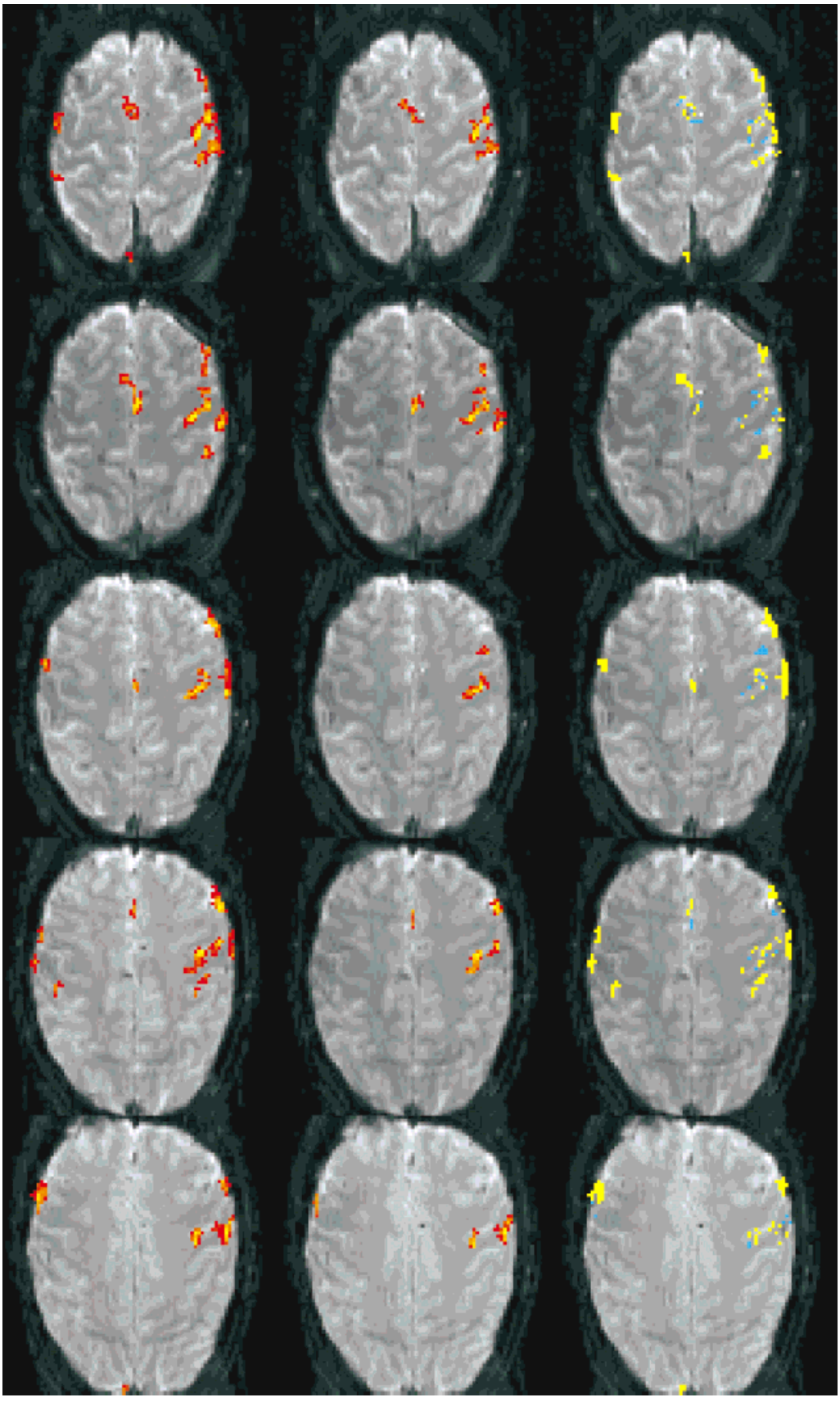

FIG. 1. Activation maps for sequential finger opposition before (left) and 0–5 min after (middle) cathodal tDCS for five contiguous sections covering the sensorimotor area of a single subject. (Right) "Binary difference" maps with pixels solely activated before (coded in yellow) or after (coded in blue) tDCS. The dominance of yellow pixels refers to a decrease of the overall number of activated pixels after cathodal tDCS.

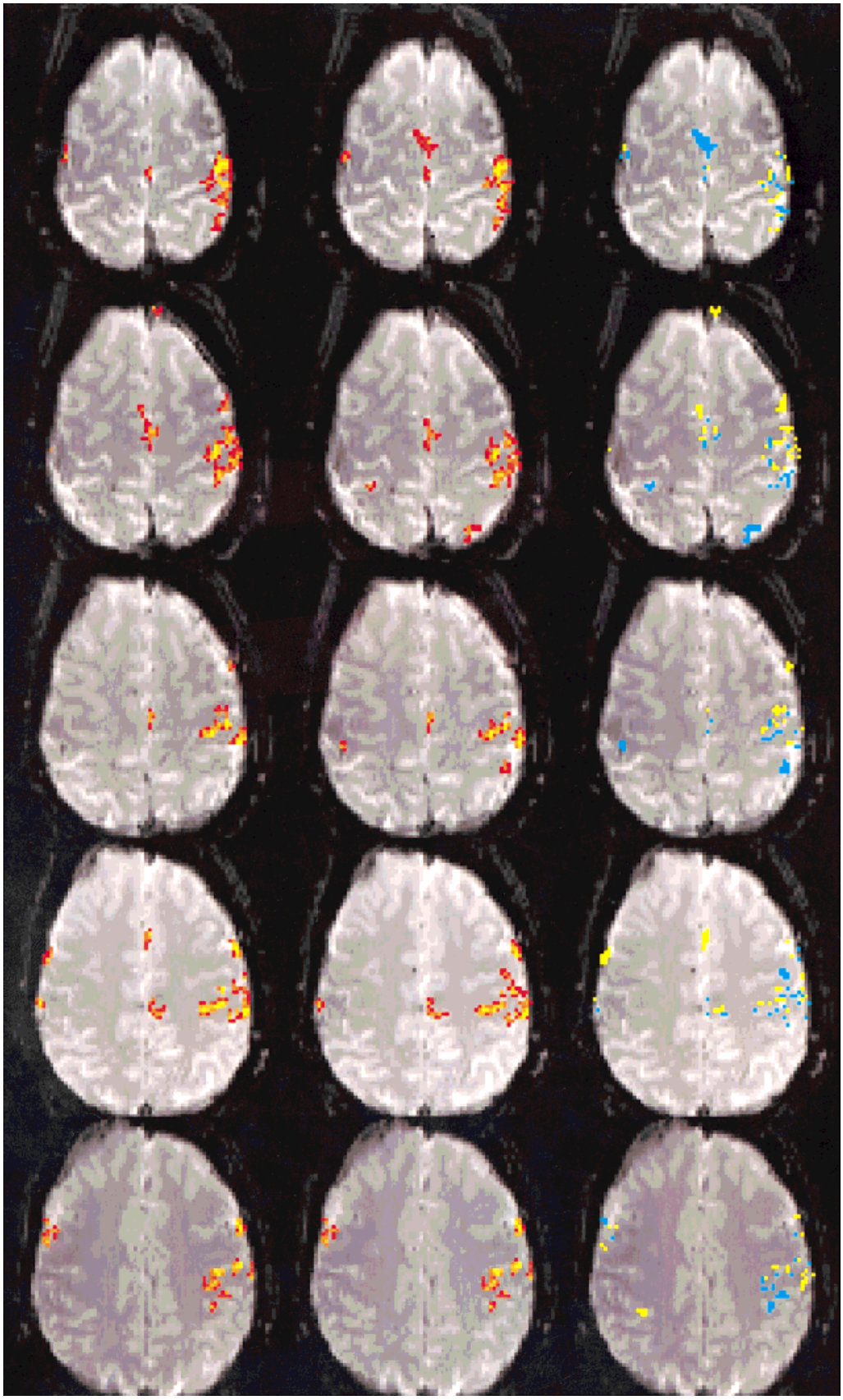

FIG. 2. Activation maps for sequential finger opposition before (left) and 0–5 min after (middle) anodal tDCS for the same subject as in Fig. 1. (Right) "Binary difference" maps with pixels solely activated before (coded in yellow) or after (coded in blue) tDCS suggest no preferential change in the overall number of activated pixels.

Table 1
Number of Activated Pixels (mean ± SD, $n = 6$) for a Sequential Finger Opposition Task Before and After Transcranial Direct Current Stimulation (tDCS)

tDCS	ROI	Before tDCS	0–5 min after tDCS	15–20 min after tDCS
Cathodal	Global	1133 ± 425	701 ± 308**	818 ± 248*
	M1	77 ± 18	73 ± 9	78 ± 27
	SMA	87 ± 36	37 ± 29***	61 ± 29
Anodal	Global	788 ± 295	829 ± 547	895 ± 341
	M1	66 ± 32	73 ± 32	55 ± 39
	SMA	87 ± 61	83 ± 77	68 ± 67

*$P < 0.05$, **$P < 0.01$, and ***$P < 0.001$ (two-sided paired t-test relative to basal activations). The pixel size corresponds to a volume of $2 \times 2 \times 4$ mm^3. Global = all activated pixels in all 10 sections, M1 = hand area of the primary motor cortex, SMA = supplementary motor area.

M1 (e.g., compare respective areas in the three central sections shown in Fig. 1), no changes between conditions were found. In contrast, most pronounced alterations were observed in the SMA in which cathodal tDCS resulted in a highly significant 57% decrease of the number of activated pixels. The absence of a major change for anodal tDCS as suggested by Fig. 2 is also borne out by the quantitative data given in Table 1. The mild tendency for a nonsignificant 5% increase in the number of pixels presented without indication for regional differences.

In general, i.e., both for cathodal and anodal tDCS, the BOLD MRI signal increase in the activated pixels of all acquired sections remained unchanged from 3.5–3.8% before to 3.5–3.6% after stimulation. This also holds true regionally for the M1 hand area (3.1–3.3% before vs 2.9–3.0% after tDCS) and the SMA (2.4–2.5% before vs 2.4–2.5% after tDCS). The slightly smaller BOLD MRI responses in M1 and SMA may be ascribed to an even better reduction of vascular contributions than found when averaging across activations in all 10 sections. This similarity of response strengths emerges from the use of similar selection criteria (thresholds) in the automated analysis, so that putative responses at lower amplitudes escape acceptance. In fact, when restricting the analysis to only those pixels that were commonly activated both before and after tDCS, the corresponding results confirm the findings for the number of activated pixels: cathodal tDCS significantly decreased the BOLD contrast from 4.8% before stimulation to 4.1% afterwards (all sections, $P = 0.02$). The ROI analysis again yielded no changes in M1 but resulted in a significant reduction of the BOLD contrast in the SMA from 3.0% before to 2.7% after cathodal tDCS ($P = 0.03$). Anodal tDCS revealed no significant changes in BOLD contrast either globally or regionally.

DISCUSSION

This work for the first time demonstrates that BOLD MRI is capable of detecting modulations of neuronal activity exerted by prior transcranial stimulation with a weak direct current. The observed reduction of activation after cathodal tDCS is in agreement with basic neurophysiologic data reporting diminished excitability of the motor cortex (2–6). However, rather than reducing brain activity to a functional challenge in general, the direct representations of an active sensorimotor task were found to be unaffected, whereas related cortical processing appears to be strongly dampened.

In fact, as a second important finding, the present results suggest a hitherto unknown spatial heterogeneity of cathodal tDCS modulations which probably indicates a task-related specificity in the extent of tDCS-induced alterations. In particular, the dampening of cortical activity after cathodal tDCS does not seem to apply to brain regions that directly encode for the active performance of a task. In other words, the execution of a sequential finger opposition involves neural finger representations within the M1 hand area which cause identical BOLD MRI responses independent of the presence or absence of preceding tDCS. Thus, the tDCS-related reduction of activation spares the finger representations in M1, but affects other regions including premotor areas, SMA, and ipsilateral motor cortex. Because the resulting maps (i.e., middle column of Fig. 1) mainly consist of representations of the actual task in contralateral sensorimotor cortex, they appear "cleaner" than those obtained without tDCS (i.e., left column of Fig. 1). Whereas activations in premotor areas and ipsilateral motor cortex are almost completely eliminated, the number of pixels activated in the SMA is reduced by 57%. It may be hypothesized that the mechanisms underlying cathodal tDCS effectively remove activations from associated processing that emerge via cortico-cortical connections, but are unable to suppress the representations of direct sensorimotor input.

A third important observation is the fact that the modulations of the BOLD MRI responses to sensorimotor activation lasted for at least 20 min after cathodal tDCS, provided the application of the current is sufficiently long (5 min) and strong (1 mA). These prolonged effects exceed those found by TMS for similar conditions (14). Although they cannot be explained by simple shifts of membrane potentials, since a complete cancellation of electrical brain activity by hypothermia (19,20) has been unable to abolish comparable after-effects in animals, it still remains an open question whether long-term depression may serve as a likely candidate for this phenomenon (21–23). Nevertheless, if weak cathodal tDCS through the intact skull provokes depression-like phenomena in humans, the method opens new therapeutic possibilities in a variety of clinical conditions.

In contrast to early electrophysiologic studies (2,5), no significant changes were found for anodal tDCS of the motor cortex. This may be explained by the finger task used as well as by the specific nature of the BOLD MRI contrast. For example, various functional neuroimaging studies have demonstrated that movements of a single finger activate the complete hand area in the anterior wall of the central sulcus (24,25). Because this situation may demand a maximum supply of oxyhemoglobin by elevated blood flow, any further increase of neuronal excitability will not lead to a further upregulation of blood flow and a corresponding decrease of the intravascular deoxyhemoglobin level determining the MRI-detectable BOLD contrast. Such a "ceiling effect" has also been observed under pharmacologic challenge using a vasodilating agent (26) as well as in asymptomatic patients

with carotid occlusive disease causing an exhausted reserve capacity (27). Moreover, the quantitatively not yet fully understood relationship between the degree of neuronal activity and the hemodynamic response strength prohibits an unambiguous interpretation of the BOLD contrast in terms of cortical involvement.

CONCLUSION

Assuming a correspondence between the degree of neuroaxonal excitability and BOLD MRI responsiveness, the present findings suggest that weak cathodal tDCS generally reduces the degree of cortical activation apart from areas containing direct representations of an active task performance. Extending electrophysiologic data, the present observations of regionally specific modulations of sensorimotor activations in the intact human brain render cathodal tDCS a means to selectively reduce cerebral excitability and, equally important, to prolong the effects for several minutes after the end of stimulation.

With functional MRI as a suitable tool for an assessment of tDCS modulations of brain activity, it becomes possible to monitor current-induced effects in much greater detail in humans and to elucidate their potential for enhancing neuroplasticity in foreseeable clinical applications such as epilepsy and depression. Whether the cathodal tDCS method may be exploited as a neuroscientific tool to distinguish between primary sensory input and higher order processing, or even to separate bottom-up from top-down processes, remains to be seen in future studies involving more sophisticated functional challenges.

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