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Direct current stimulation over the human sensorimotor cortex modulates the brain's hemodynamic response to tactile stimulation

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Abstract

Tactile stimuli produce afferent signals that activate specific regions of the cerebral cortex. Noninvasive transcranial direct current stimulation (tDCS) effectively modulates cortical excitability. We therefore hypothesised that a single session of tDCS targeting the sensory cortices would alter the cortical response to tactile stimuli. This hypothesis was tested with a block-design functional magnetic resonance imaging protocol designed to quantify the blood oxygen level-dependent response to controlled sinusoidal pressure stimulation applied to the right foot sole, as compared with rest, in 16 healthy young adults. Following sham tDCS, right foot sole stimulation was associated with activation bilaterally within the precentral cortex, postcentral cortex, middle and superior frontal gyri, temporal lobe (subgyral) and cingulate gyrus. Activation was also observed in the left insula, middle temporal lobe, superior parietal lobule, supramarginal gyrus and thalamus, as well as the right inferior parietal lobule and claustrum (false discovery rate corrected, $P < 0.05$). To explore the regional effects of tDCS, brain regions related to somatosensory processing, and cortical areas underneath each tDCS electrode, were chosen as regions of interest. Real tDCS, as compared with sham tDCS, increased the percent signal change associated with foot stimulation relative to rest in the left posterior paracentral lobule. These results indicate that tDCS acutely modulated the cortical responsiveness to controlled foot pressure stimuli in healthy adults. Further study is warranted, in both healthy individuals and patients with sensory impairments, to link tDCS-induced modulation of the cortical response to tactile stimuli with changes in somatosensory perception.

Introduction

Perceptible somatosensory stimuli are associated with a degree of cortical activation that is contingent upon the stimulus location, size and intensity (Fregni & Pascual-Leone, 2007). For a given stimulus, the degree of cortical activation is, in turn, dependent upon the integrity of peripheral, spinal and subcortical circuitry, as well as the excitability of involved cortical neurons (Maldjian *et al.*, 1999; Adolphs *et al.*, 2000; Beauchamp, 2005; Goldberg *et al.*, 2006). Strategies designed to facilitate or suppress the excitability of cortical neurons may thus enable modulation of somatosensation by increasing or decreasing the cortical response to a given stimulus. This might ultimately help to overcome deficits of sensation in patients with peripheral neuropathies. Foot sole somatosensory impairments in particular diminish balance and heighten the risk of suffering falls, which often result in injuries and long-term disability. Therefore, strategies to enhance somatosensation from the soles of the feet offer promise as valuable therapeutic interventions. As a preliminary exploration of this potential, the present study aimed to assess the ability of noninvasive brain stimulation to augment the cortical response [as indexed by functional magnetic resonance imaging (fMRI)] to a controlled mechanical stimulus to the soles of the feet.

Transcranial direct current stimulation (tDCS) is a noninvasive, safe and painless neurophysiologic intervention that alters cortical excitability by inducing low-amplitude current flow between two or more surface sponge electrodes (Schlaug & Renga, 2008). Depending upon the direction, duration and intensity of current flow, a single session of tDCS can facilitate or suppress cortical excitability in

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targeted brain regions for several hours following stimulation (Bindman *et al.*, 1964; Radman *et al.*, 2009). Recently, researchers have demonstrated that tDCS targeting the sensorimotor cortex is capable of modulating tactile acuity under certain situations (Matsunaga *et al.*, 2004; Rogalewski *et al.*, 2004; Ragert *et al.*, 2008; Mori *et al.*, 2013). However, the impact of tDCS on the underlying cortical response to a given stimulus has yet to be examined. We hypothesised that tDCS would modulate the excitability of the sensorimotor cortex and thus alter the degree of cortical activation induced by tactile stimuli. To test this hypothesis, we utilised fMRI to quantify the blood oxygen level-dependent (BOLD) response to a controlled pressure stimulus applied to the right foot sole, immediately following a single session of tDCS designed to facilitate left sensorimotor cortex excitability.

Materials and methods

Subjects

Sixteen young adults (mean ± SD age, 22.2 ± 2.1 years; 11 males) without any known neurological or other disorders were recruited for this double-blinded, sham-controlled study. All subjects were right-handed as determined by the Edinburgh Handedness Inventory (Oldfield, 1971). Subjects provided written informed consent for the protocol as approved by the Institutional Review Board of Peking University First Hospital, Beijing.

Protocol

All subjects completed an fMRI protocol immediately following either real or sham (i.e. control) tDCS on 2 days separated by at least 1 week (Fig. 1). The anode was placed over the left sensorimotor cortex with the aim of increasing its excitability. The order of real and sham tDCS sessions was counterbalanced. The fMRI protocol was a block design comprising alternating blocks of foot sole pressure stimulation and rest (i.e. no stimulation). Each block was 30 s in duration and repeated three times (Hao *et al.*, 2012).

Transcranial direct current stimulation

The tDCS was delivered for 20 min up to a maximum current intensity of 2.0 mA by personnel uninvolved in any other study procedure. A battery-driven electrical stimulator (Chattanooga Ionto, USA) was connected to a pair of saline-soaked synthetic surface sponge electrodes (surface area, 35 cm^2 per electrode) placed on the scalp. The positive electrode was placed over C3 (according to the EEG international 10–20 system), which corresponds to the left sensorimotor cortex. The negative electrode was placed over the contralateral supraorbital region. At the beginning of each tDCS session, the stimulation intensity was increased manually from 0.1 to 2.0 mA in 0.1 mA increments. Subjects were instructed to notify study personnel if the stimulation became too uncomfortable or if they noticed continuous itching sensations. At this point, the current intensity was ramped down 0.1 mA and then fixed for 20 min. Across all subjects, real tDCS was applied at a mean ± SD intensity of 1.43 ± 0.39 mA (range 0.7–2.0 mA). The current was automatically ramped down over a 30 s period at the end of the session. During sham tDCS, the current was ramped up for the first 30 s of the session, but then ramped back down to 0 mA over the next 30 s. This procedure mimics the transient skin sensation of real tDCS that is typically felt at the beginning of stimulation, yet does not produce significant modulatory effects on the brain (Brunoni *et al.*, 2011). Impedance was continuously monitored throughout each session and never rose above 5 kΩ.

At the end of each study visit, subjects completed a short questionnaire surveying for potential adverse effects associated with tDCS (Brunoni *et al.*, 2011). In order to determine the effectiveness of blinding procedures, subjects were asked, "Do you believe that you received real stimulation during this session?" at the end of each session.

Foot sole tactile stimulation

A custom-built, magnetic resonance imaging-compatible tactile stimulation system was used to apply controlled mechanical pressures to the sole of the right foot (Fig. 1). Briefly, this system consisted of an air compressor and control unit located outside the scanner room, which was connected via plastic air tubes to a magnetic resonance imaging-compatible, aluminum pneumatic actuator attached to a support platform secured to the scanner bed (Hao *et al.*, 2012). The subject's right leg was secured to a plastic medical boot, which was modified and attached to the support platform. This setup enabled fixation of the ankle joint at 90° of dorsiflexion as well as adjustment of both knee and hip joint angles. Our previous work has demonstrated that this setup significantly reduces translational movements of the head and related magnetic resonance imaging motion artifacts (Hao *et al.*, 2012).

During each 30 s fMRI foot sole pressure stimulation block, continuous oscillatory pressure stimuli were applied to a circular area (4 cm in diameter) of the foot sole over the head of the first metatarsal of the right foot. The maximum force output of the actuator was set to 10% of the subject's body mass and was applied in a

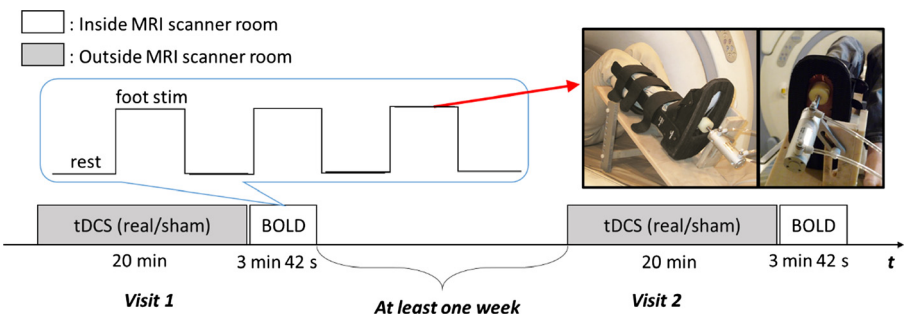

FIG. 1. Experimental design. tDCS was delivered outside the scanner room with the subject in a seated position. A block-designed BOLD fMRI protocol was then completed to quantify the cortical response to tactile stimulation of the right foot sole. Real and sham tDCS conditions were tested on separate days at least 1 week apart. tDCS condition was double-blinded and condition order was randomised. MRI, magnetic resonance imaging.

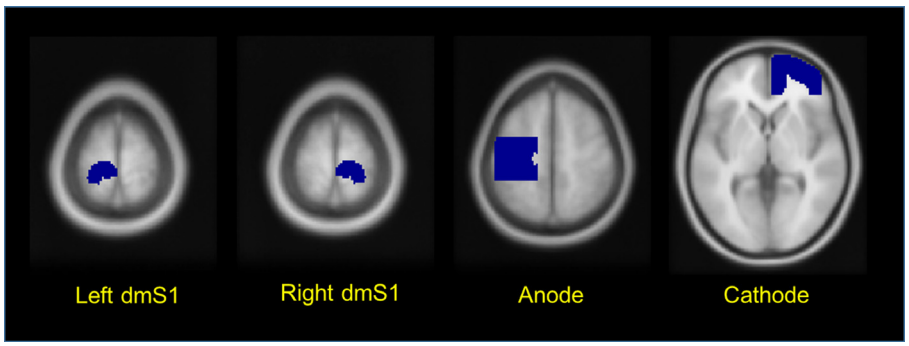

FIG. 2. The ROIs related to tDCS and somatosensory processing: left and right dmS1, left mid-lateral somatosensory cortex and the regions under the positive (Anode) and negative (Cathode) electrodes.

1 Hz sinusoidal waveform with a duty cycle of 80%. We have previous demonstrated that this paradigm induces a characteristic pattern of cortical activation but does not influence image quality or produce motion artifact with applied load (Hao *et al.*, 2012).

Magnetic resonance image acquisition

The MRIs were acquired at the Peking University First Hospital using a GE 3T (Signa Excite HD; GE Medical Systems, Milwaukee, WI, USA) whole-body scanner with an eight-channel receive-only head coil. BOLD data were acquired after tDCS using a standard echo-planar imaging sequence with the following parameters: repetition time/echo time, 2000/30 ms; flip angle, 90°; image matrix, 64 × 64; thickness/spacing, 4 mm/1 mm; field of view, 230 × 230 mm^2; 28 interleaved axial slices; and 30 repetition times. We acquired a total of 3300 BOLD images in each subject. The interval between the conclusion of tDCS and acquisition of the first BOLD image was < 10 min for all subjects. A high-resolution structural image was acquired prior to tDCS by using a three-dimensional fast spoiled gradient echo sequence for anatomical localisation (repetition time/echo time, 7.8/3.0 ms; flip angles, 20°; inversion time, 450 ms; field of view, 240 × 240 mm^2; slice thickness, 2.0 mm with 1.0 mm overlap; in-plane resolution, 1 × 1 mm^2).

Data and statistical analysis

Raw echo-planar imaging data were preprocessed with Statistical Parametric Mapping software (SPM8, Wellcome Department of Imaging Neuroscience, University College, London, UK). For each subject, images were realigned to the first scan to correct for potential head movement within scans, generating six-parameter head motion curves. Each time-series was corrected to compensate for delays associated with acquisition time differences across slices. Functional images were co-registered to the corresponding structural T1 image and normalised to a 2-mm isovoxel Montreal Neurological Institute template. Functional images in Montreal Neurological Institute space were then spatially smoothed using an 8 mm (full width/half maximum) Gaussian kernel and subjected to a high-pass temporal filter with a cutoff of 128 s. For each subject and tDCS condition, *foot stimulation* and *rest* blocks were modeled as a boxcar regressor (30 s on, 30 s off) convoluted with a double-gamma hemodynamic response function (see Fig. 1). These regressors were entered into a first-pass general linear model to generate parameter estimates for each condition (rest, foot stimulation). A subject-level contrast of parameter estimates, representing the percent signal change (PSC) of foot sole pressure stimulation as compared with rest, was generated separately for each tDCS condition using paired-sample *t*-tests. One-sample *t*-tests were utilised to generate a group-wise statistical map of each tDCS condition, using a false discovery rate corrected $P < 0.05$, with a threshold of at least 10 contiguous voxels. A paired-samples *t*-test was then used to analyse potential whole-brain differences between the real and sham conditions.

Using a standard approach (Weiskopf *et al.*, 2003; Goble *et al.*, 2011, 2012), we further examined the impact of tDCS on the cortical and subcortical response to foot sole pressure stimulation in specific regions of interest (ROIs). ROIs were selected *a priori* to include the left and right dorsomedial somatosensory cortices (dmS1) (Fig. 2). Using the coordinates (−13.2, −37.8, 70) of peak activation obtained from the same fMRI protocol in a prior study (Hao *et al.*, 2012), we created a surrounding sphere (radius 15 mm) and multiplied it by a mask of the paracentral lobule and postcentral gyri from the Automated Anatomical Labeling template (Tzourio-Mazoyer *et al.*, 2002). Anatomically, the dmS1 receives afferent signals from the contralateral foot and lower limbs. Functionally, the left dmS1 is activated by the same type of right foot sole pressure stimulation as applied in the current study (Hao *et al.*, 2012). As stimulation was applied only to the right foot, the ipsilateral dmS1 was included to provide a negative control ROI. In addition to these regions, we also included the cortical areas beneath each electrode. The positions of the anodal and cathodal ROIs were defined according to electroencephalographic positions C3 (anode) and Fp2 (cathode) of the international 10–20 electrode system. The size and depth of both anode and cathode ROIs was determined using previously-reported simulated and realistic models (Miranda *et al.*, 2009; Sadleir *et al.*, 2010).

The average PSC from rest to foot stimulation within each ROI was calculated for each subject following each tDCS condition using established methods within the SPM Marsbar toolbox (Brett *et al.*, 2002). The PSC value thus reflected the mean intensity of hemodynamic response within each ROI caused by foot sole pressure stimulation. The effects of *tDCS condition* (real, sham) on PSC values from each ROI were then analysed using two-tailed paired *t*-tests. The relationship between tDCS current intensity and the PSC value within each ROI was examined using Pearson's correlation coefficients.

Results

Fifteen of 16 subjects reported minimal itching sensations beneath the tDCS electrodes during stimulation. This discomfort was independent of the stimulation condition and current strength. No other discomfort or side-effects were observed or reported during the

study. The number of subjects who reported the correct tDCS condition (43.8%) was slightly less than that expected by chance, suggesting that subjects were adequately blinded to tDCS condition.

The whole-brain cortical response to right foot sole stimulation following real and sham tDCS is presented in Fig. 3, which portrays group-level BOLD activation maps for each condition. Following sham tDCS (i.e. the control condition), the contrast (foot stimulation > rest) yielded activation within the bilateral precentral cortex, postcentral cortex, middle and superior frontal gyri, temporal lobe (subgyral) and cingulate gyrus. Activation was also observed in the left insula, middle temporal lobe, superior parietal lobule, supramarginal gyrus and thalamus, as well as the right inferior parietal lobule and claustrum (false discovery rate corrected, $P < 0.05$). Following real tDCS, the same contrast yielded activation within each of the aforementioned regions, with the following exceptions: no significant activation was present in the thalamus and anterior cingulate cortex, whereas additional areas of activation were present in the left caudate nucleus and right insula. Group-wise analysis yielded no clusters with significant deactivation following either of the tDCS conditions.

Whole-brain group-level comparison revealed that, as compared with the sham tDCS condition, right foot stimulation following real tDCS was associated with greater activation within the left precentral gyrus, left middle frontal gyrus, left middle temporal gyrus and right postcentral gyrus (uncorrected, $P < 0.005$; cluster size > 10 voxels). In contrast, there were no clusters in which activation was less following real tDCS as compared with sham.

ROI analysis further revealed that right foot stimulation following real tDCS, as compared to sham, was associated with greater PSC in the left dmS1 ($P = 0.027$) (Fig. 4). There was also a trend towards greater PSC following real tDCS in the cortical area corresponding to the anodal electrode ($P = 0.052$). No effects of tDCS condition were observed for any of the other ROIs (all P-values > 0.1).

As the intensity of applied tDCS current varied across subjects, we also examined the relationship between tDCS intensity and the PSC induced by foot stimulation within each ROI. Pearson's correlation analysis revealed that PSC values within the anode and cathode ROIs were larger in those subjects who received tDCS current at greater intensities (Fig. 5). However, the observed PSC within both the left and right dmS1 was not correlated with the intensity of tDCS.

Discussion

In the control condition (i.e. following sham tDCS), sinusoidal pressure stimuli applied to the right foot sole induced a distributed pattern of cortical activation within numerous brain regions linked to an array of sensorimotor and cognitive functions. Activation within these regions was expected and consistent with our previous study employing the same fMRI-compatible tactile stimulation system (Hao *et al.*, 2012). In addition to the primary and secondary somatosensory cortex, activation was observed within multiple regions linked to somatosensory processing: the insula has been associated with the perception of light touch (Yoo *et al.*, 2003; Nagai *et al.*, 2007), the superior parietal lobule and supramarginal gyrus are involved in the discrimination of multiple somatosensory stimuli and their integration with other perceptual modalities (Wolpert *et al.*, 1998; Bohlhalter *et al.*, 2002), the middle temporal lobe participates in tactile-motor processing (Hagen *et al.*, 2002), the frontal gyrus has been implicated in tactile imagery (Yoo *et al.*, 2003) and the claustrum is an important node in cross-modal matching (Hadjikhani & Roland, 1998). Moreover, foot pressure stimulation induced activation within the cingulate gyrus, which is believed to be closely involved in the regulation of attention to sensory stimuli (Baleydier & Mauguiere, 1980). Although outside the scope of the present study, future research employing resting-state fMRI and/or arterial spin labeling may shed light on the functional connectivity between these regions. Moreover, studies including block designs that alter the magnitude of foot pressure, as well as attentional focus, may help to delineate the specific role of each of the above regions in the processing of this type of somatosensory feedback.

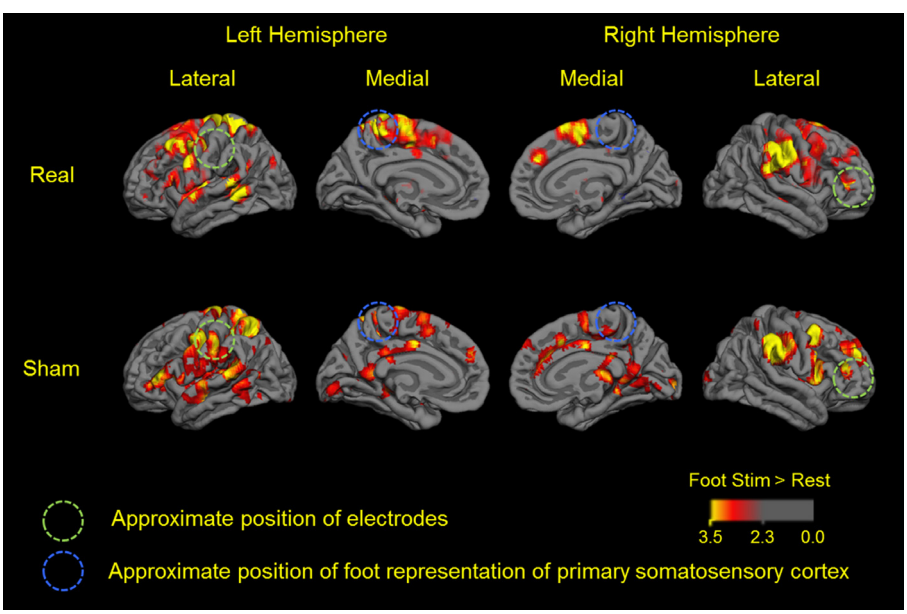

FIG. 3. Activation associated with right foot sole pressure stimulation following a single 20 min session of real or sham tDCS targeting the left sensorimotor cortex. Statistical parametric maps representing the group average of both stimulation conditions were false discovery rate corrected ($P < 0.05$) and overlaid on the pial surface.

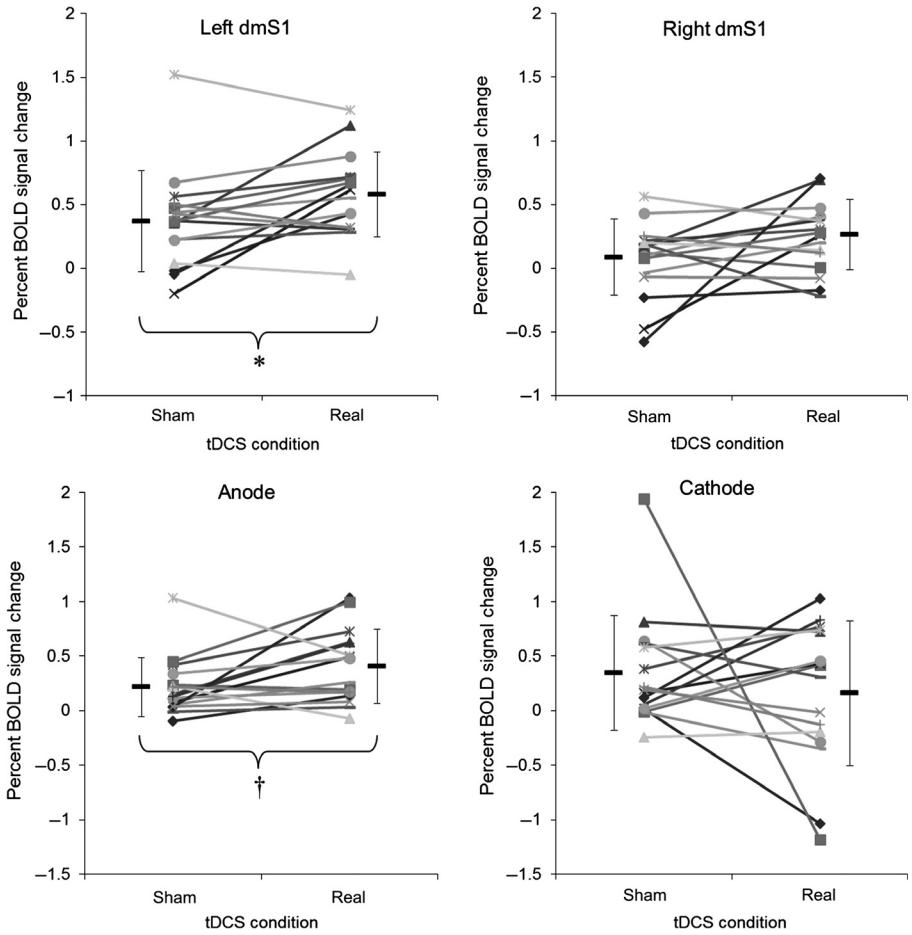

FIG. 4. The effects of real and sham tDCS on the cortical response to foot sole pressure stimulation within preselected brain ROIs. For each ROI, the PSC (foot stimulation > rest) within each condition has been provided for each subject. Group means and SDs are shown on either side of the individual data. The PSC was significantly greater following real than sham tDCS in the left dmS1 [*P = 0.027; 95% confidence interval (CI) = 0.16–0.58 for sham and 0.40–0.75 for real, Cohen's d = 0.59], and there was a trend towards higher PSC under the anode site (†P = 0.052; 95% CI = 0.07–0.35 for sham and 0.22–0.58 for real, Cohen's d = 0.65). By comparison, neither the right dmS1 (95% CI = −0.09–0.23 for sham and 0.10–0.39 for real, Cohen's d = 0.63), nor the cathode (95% CI = 0.07–0.62 for sham and −0.19–0.50 for real, Cohen's d = −0.33) ROIs were significantly different between tDCS conditions (both P-values > 0.05).

The major novel finding of the present study was that, following real tDCS as compared with sham, right foot sole stimulation was associated with greater PSC of the BOLD signal within the left posterior paracentral lobule (i.e. the dmS1). These results suggest that a single session of tDCS effectively modulates the cortical response to controlled foot pressure stimuli in healthy adults. The dmS1 contains representations of the feet and lower limbs (Hari & Forss, 1999). Importantly, these effects were selective to the left dmS1 and not the right dmS1. tDCS is believed to modulate cortical excitability by altering the relative concentration of freely moving anions and cations in the extracellular milieu (Bikson *et al.*, 2004), which in turn raises or lowers neuronal resting membrane potentials (Bindman *et al.*, 1962; Purpura & McMurtry, 1965). Thus, the most likely interpretation of our findings is that increased BOLD activity following anodal tDCS results from an increase in the sensitivity of the cortex to afferent signals. BOLD fMRI is limited, however, in that the nature of the activity (excitatory vs. inhibitory) cannot be ascertained. Nor is it possible to completely separate changes in cortical excitability or metabolism from changes in neurovascular coupling. Nevertheless, administering tDCS with the anode over the sensory cortex has been reported to increase both the magnitude of somatosensory evoked potentials and cerebral blood flow within brain regions involved in sensory processing (Matsunaga *et al.*, 2004; Zheng *et al.*, 2011). As the cortical components of the somatosensory evoked potential are due to the summation of synchronous synaptic activity, increased somatosensory evoked potentials after real tDCS may be due to an increase in efficacy of synaptic transmission or increased phase coupling in these pathways. Alternatively, if the neurons involved in processing the signal were more excitable, they would then be more easily discharged and produce a larger synaptic input in cortical processing (Matsunaga *et al.*, 2004). The increased hemodynamic response induced by tDCS expressed an increase of oxygen and glucose availability of nervous tissue, which can also reflect stronger cortical excitability. Future studies are therefore warranted to concurrently quantify the effects of tDCS on (i) the BOLD and perfusion (e.g. using arterial spin labeling) responses to foot sole stimulation, and (ii) direct measures of somatosensory cortical excitability as quantified by noninvasive neurophysiological techniques, in older adults both with and without peripheral somatosensory impairments.

Several behavioral studies have demonstrated that tDCS designed to facilitate neuronal excitability within the sensorimotor cortices alters the ability to perceive somatosensory stimuli (Rogalewski *et al.*, 2004; Ragert *et al.*, 2008; Mori *et al.*, 2013). For example, Ragert *et al.* (2008) reported that a single, 20 min session of tDCS targeting the left primary sensory cortex with a cur-

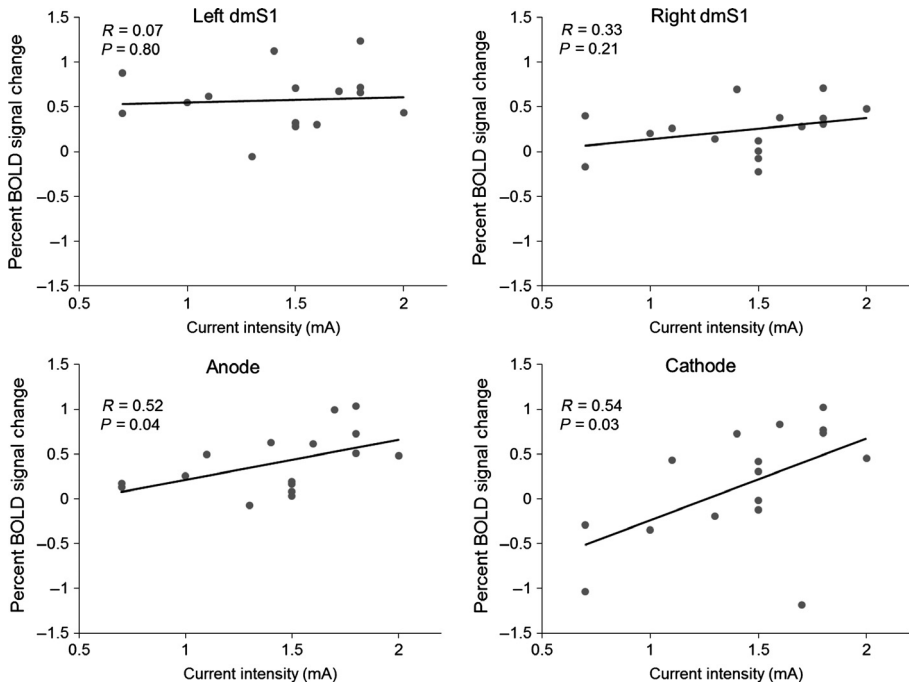

FIG. 5. The relationship between tDCS current intensity and the BOLD PSC induced by right foot sole stimulation within four ROIs. Although a target intensity of 2.0 mA was chosen, tDCS was administered at different intensities across subjects to ensure comfort. Although real tDCS current intensity was correlated with the PSC under the electrodes [95% confidence interval (CI) = 0.03–0.81 for anode and 0.06–0.82 for cathode], it was not correlated with the PSC within the left or right dmS1 (95% CI = −0.44–0.55 for left dmS1 and −0.19–0.71 for right dmS1). R-values reflect the strength of the Pearson correlation.

rent intensity of 1.0 mA enhanced tactile spatial acuity in the contralateral hand, as compared with sham tDCS. Mori *et al.* (2013) demonstrated longer-lasting effects of tDCS on tactile sensation in patients with multiple sclerosis. Specifically, five daily sessions of tDCS over C3 or C4 (on the 10–20 EEG electrode placement system) at a target current intensity of 2.0 mA improved spatial discrimination thresholds on the hypoesthetic hand for at least 2 weeks after the last tDCS session. For a given individual, the BOLD response to a tactile stimulus is dependent upon the stimulus intensity (Jousmäki & Forss, 1998; Arthurs *et al.*, 2000; Backes *et al.*, 2000; Nelson *et al.*, 2004). For example, Nelson *et al.* (2004) employed a magnetic resonance imaging-compatible magnetomechanical device to deliver controlled vibrations to the right hand of healthy young adults. They observed that the degree of activation within the primary somatosensory cortex increased in accordance with both the amplitude and frequency of vibration. A similar stimulus–response relationship has also been observed by electrically stimulating the median nerve at the wrist (Jousmäki & Forss, 1998; Arthurs *et al.*, 2000; Backes *et al.*, 2000). These studies therefore suggest that the magnitude of the PSC achieved by fMRI (or somatosensory-evoked magnetic fields recorded by magnetoencephalography) becomes greater as the intensity of the applied stimulus increases. The results of the present study are, to our knowledge, the first to show a tDCS-induced augmentation of the somatosensory cortical response to a controlled tactile stimuli, provide further support for this model and offer a mechanistic explanation for previous reports of the tDCS-mediated enhancement of somatosensation. As somatosensation is critical to understanding and interacting with the world around us, future studies that apply sensory stimuli at intensities both above and below an individual's threshold of perception are warranted in order to determine if tDCS increases the cortical response, and therefore perception, across all stimuli.

It is important to note that the effects of real tDCS on foot sole sensory performance are also dependent upon factors other than the cortical response as measured by BOLD fMRI in the present study. Behavioral experiments are thus still needed to examine the capacity of tDCS to alter the perception of foot sole tactile stimuli. Additionally, in the current study, functional magnetic resonance images were only conducted following the administration of tDCS. As such, the magnitude of the tDCS-induced change from 'baseline' cannot be compared across conditions. The acquisition of functional brain images both immediately before and after both real and sham tDCS would have strengthened our results by enabling further comparison to pre-tDCS 'baseline' conditions. Nevertheless, our finding of an increase above sham supports our hypothesis that anodal tDCS is capable of modulating the cortical response to foot stimulation.

Somatosensory impairments are common in aging and disease, and often lead to functional decline and falls (Allison *et al.*, 1984; Woollacott *et al.*, 1986; Van Deursen & Simoneau, 1999; Horak *et al.*, 2002; Quai *et al.*, 2005; Shaffer & Harrison, 2007). In our study, we show that real tDCS, relative to sham, modulates the cortical response to peripheral stimulation in regions linked to somatosensory integration and interpretation. We suggest that enhanced cortical excitability might be the neural substrate for previously-reported effects of tDCS on somatosensory perception (Jousmäki & Forss, 1998; Arthurs *et al.*, 2000; Backes *et al.*, 2000; Nelson *et al.*, 2004). As foot-sole somatosensation is critical to gait and balance, we further contend that tDCS may be a valuable new method of improving gait and balance (Zhou *et al.*, 2014). Future studies combining the current approach with tests of tactile perception and balance in older adults and those with somatosensory impairments are therefore encouraged.

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Abbreviations

BOLD, blood oxygen level-dependent; dmS1, dorsomedial somatosensory cortex; fMRI, functional magnetic resonance imaging; PSC, percent signal change; ROI, region of interest; tDCS, transcranial direct current stimulation.

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