Transcranial static magnetic field stimulation - new non-invasive brain stimulation tool

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Abstract Recent research has shown that the human motor cortex can be modulated by the application of static magnetic fields through the scalp. Transcranial static magnetic field stimulation (tSMS) has since received significant attention as a new non-invasive brain stimulation (NIBS) technique alongside conventional methods, such as repetitive transcranial magnetic stimulation and transcranial direct current stimulation. The advantages of the strong neodymium, iron and boron (NdFeB) magnet used in tSMS over other NIBS methods include the ease of use, absence of uncomfortable sensations for subjects, a lack of necessity for high operational skills and expensive devices, and conclusive sham stimulation allowing for controlled experiments and randomized controlled clinical trials. Hence, tSMS may be a new potential NIBS tool to modulate cerebral excitability.

Keywords: transcranial static magnetic field stimulation, somatosensory evoked potentials, motor evoked potentials

Introduction Non-invasive brain stimulation (NIBS), such as repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS), is an increasingly useful technique, not only to examine normal cortical function, but also to facilitate the treatment of various neurological disorders. Current research has reported that the human motor cortex can be modulated by the application of static magnetic fields (SMFs) through the scalp. Oliviero et al. showed that 10 min of transcranial static magnetic field stimulation (tSMS) using a powerful cylindrical neodymium, iron and boron (NdFeB or ‘neo’) magnet can reduce the amplitude of motor evoked potentials (MEPs) for a few minutes after magnet removal. In addition, they demonstrated that the polarity of the SMFs was not an important factor for neuromodulation, and that TSMS was not directly associated with induced electric currents. Since then, tSMS has received significant attention as a new NIBS technique alongside conventional methods, such as rTMS and tDCS. In recent tSMS over M1 studies, Silbert et al. showed that tSMS could reduce M1 excitability correlating to modulation of resting motor threshold of TMS, while Nojima et al. demonstrated enhanced short latency intracortical inhibition (SICI). In addition, we have previously reported that SMFs over the sensorimotor cortex (C3 of the international 10-20 system of electrode placement) reduced the amplitudes of the N20 component of somatosensory evoked potentials (SEPs). Moreover, tSMS over the visual cortex increases alpha oscillations and slows visual search abilities. These studies utilized the blocking and depressing effects of tSMS to create temporary cortical dysfunctions (‘virtual lesions’), which enabled a functional examination of the cortical regions.

Since the NdFeB magnet is an industrial product available on the market, tSMS does not require expensive devices or high operational skill compared to other NIBS methods. Furthermore, conventional NIBS techniques have some adverse effects such as itching, tingling, headache and discomfort which are not observed with tSMS. An additional advantage is the inability of subjects to distinguish between the NdFeB magnet (for tSMS) and a non-magnetic stainless cylinder (for sham stimulation) allowing for conclusive controlled sham tSMS stimulation experiments and randomized controlled clinical trials.

Mechanisms of tSMS Numerous cellular and animal studies have attempted to demonstrate SMFs altering central nervous function, and that moderate-intensity SMFs could induce magnetic reorientation of membrane phospholipids due to diamagnetic anisotropy effects. Of great interest to cerebral excitability are the results that SMFs are not associated with induced electric currents during activation, deactivation, or movement within the field. Furthermore, they alter the activation threshold velocity of voltage-gated...
sodium channels\textsuperscript{12,14,15,18} and voltage-gated calcium channels\textsuperscript{13,14,18}. Slow calcium influx and increased intracellular calcium ion stores caused by an impedance of calcium channels are thought to trigger long-term depression\textsuperscript{20,21}. This result, alongside previous cellular and animal studies\textsuperscript{10,12}, led to the inference that SMFs applied to the human cortex act primarily at the synapse and alter the membrane ion channels. However, it has also been postulated that tSMS reduces corticomotor excitability in association with modulation of the resting motor threshold, as with TMS\textsuperscript{4}. Hence, tSMS may not only alter the function of membrane ion channels, but also reduce membrane excitability, suggesting a possible role for non-synaptic (intrinsic) plasticity mechanisms.

**Measurement of magnetic field strength**

A recent study confirmed that the magnetic flux density ranged between 120 and 200 mT at 2-3 cm from the magnet surface with high reproducibility\textsuperscript{22}. This was sufficient to reach the majority of the cortical targets and alter biological functions\textsuperscript{14,18}. However, we used a different type of NdFeB magnet. These magnets are industrial products, and information on the consistency of the magnetic strength throughout the magnet, and from different production companies, is required. Therefore, we first assessed the strength of the NdFeB magnetic field.

The strength of the NdFeB magnet field was measured from the magnet surface to a depth of 8 cm, at intervals of 0.5 cm (Z-axis), directly through a human skull specimen (Fig. 1). We performed duplicate measurements at both the center and edge of the magnet surface using a Gaussmeter (FW BELL 5180, Pacific Scientific-OECO, Orlando, USA). The magnetic flux density was measured with an analog output with a 100 kHz sampling rate, ±0.75% accuracy, and DC-30 kHz bandwidth. Signals from each measurement were confirmed using an oscilloscope and subsequently digitized at a sampling frequency of 100 kHz using a 16-bit A/D converter (Power Lab; AD Instruments, New South Wales, Australia) and stored on a personal computer for later analysis. Each instrument was calibrated immediately before data collection\textsuperscript{23}.

Fig. 2A shows the association between the first and second magnetic field strength measurements. High reproducibility at both the center and edge of the NdFeB magnet confirmed the consistency of the field strength. Fig. 2B shows the association between the magnetic field strength and distance from the surface of the NdFeB magnet. In accordance with Coulomb’s law, decreases in magnetic field strength are inversely proportional to the square of the distance. We confirmed that at 2-3 cm from the magnet surface, the magnetic field strength ranged between 110 and 190 mT, sufficient to reach most cortical targets and alter biological functions, such as membrane ion channels\textsuperscript{14,18}, regardless of the presence or absence of the skull.

**Effect of tSMS over human sensorimotor cortex on somatosensory evoked potentials**

A number of NIBS studies using rTMS\textsuperscript{24-26}, theta-burst stimulation (TBS)\textsuperscript{27,28}, repeated trains of four monophasic TMS pulses (quadrupulse stimulation: QPS)\textsuperscript{29,30} and tDCS\textsuperscript{31-33} revealed that these techniques modulate the excitability of the primary somatosensory cortex (S1). However, the effect of tSMS on the excitability of S1 in humans has never been examined. With the aim of further investigation of the possibility of non-invasive modulation of primary somatosensory cortex excitability by the application of tSMS in healthy subjects, tSMS or sham stimulation over the sensorimotor cortex was applied to 10 subjects for either 10 or 15 min. For tSMS, a cylindrical neodymium magnet (NdFeB; diameter, 50 mm; height, 30 mm) with a maximum energy density of 41 MGOe and nominal strength of 735 N (75 kg) was used (Fig. 3A, B). Based on the accepted method for attaching scalp electrodes for experiments or EEG tests, the NdFeB magnet was centered over position C3 of the international 10-20 system to stimulate both primary motor and somatosensory cortices (Fig. 3C). In the first session, SEPs following right median nerve stimulation were recorded before, immediately after, 5 min, and 10 min after tSMS from F3 (frontal component) and C3’ (parietal component; 2.5 cm posterior to C3). In the second session, SEPs were recorded from six of the 10 subjects every 3 min during 15 min of tSMS stimulation of the peripheral nerve. Fig. 4 shows the grand average waveforms.
Fig. 2  A: The association between first and second magnetic field strength measurements. High reproducibility at both the center and edge of the NdFeB magnet showed the consistency of the field strength in this study. B: The association between magnetic field strength and distance from surface of the NdFeB magnet. We confirmed that at 2-3 cm from the magnet surface, the magnetic field strength ranged between 110 and 190 mT, strong enough to reach most cortical targets, and alter biological functions, such as membrane ion channels, regardless of the presence or absence of the skull.

Fig. 3  Experimental setup for tSMS over the sensorimotor cortex. A: The NdFeB magnet and non-magnetic stainless steel were settled on the scalp by using an adjustable-arm lightning stand. B: For tSMS, the cylindrical NdFeB magnet (diameter, 50 mm; height, 30 mm) was used with a maximum energy density of 49 MGOe and a nominal strength of 862 N. For sham stimulation, a non-magnetic stainless steel cylinder of the same size, weight and appearance was used. C: The NdFeB magnet for tSMS and the non-magnetic stainless steel cylinder for the sham stimulation were centered over position C3 of the international 10-20 system for electrode placement, using an adjustable arm light stand. SEPs were recorded from the C3’ (parietal component; 2.5 cm posterior to C3) and F3 areas (frontal component) as outlined in Brain Stimul 2014 7(6): 836-840.
of SEPs recorded from the F3 region. The amplitudes of N18 (frontal component) and N20 (parietal component) significantly decreased immediately after both 10 and 15 min of tSMS, and returned to baseline within 5 min following the intervention. No effect was observed while recording SEPs every 3 min during sham stimulation. Our results suggest that tSMS over the sensorimotor cortex transiently reduces the excitability of the somatosensory cortex. tSMS was able to modulate human cortical somatosensory processing, and hence, might be a useful tool for inducing plasticity in cortical sensory processing. The lack of change in the amplitude of SEPs with tSMS implies that the use of peripheral nerve stimulation to cause SEPs antagonizes diamagnetic ion movements (e.g. Na⁺, K⁺, Ca²⁺, Mg²⁺)¹³,¹⁵,¹⁸) and distorts ion channels during exposure to SMFs.

Modulation of SEPs by the application of tSMS over the primary and supplemental motor cortices

In rTMS and tDCS studies, M1 is considered an important target with proven efficacy in chronic pain treatment. On the other hand, although the supplementary motor area (SMA) is thought to be a generator of SEPs, the effect of tSMS on the excitability of SMA has never been examined. Therefore, we investigated whether tSMS over the M1 or SMA modifies the excitability of S1. tSMS and sham stimulation over the M1 or SMA were applied to 14 subjects for periods of 15 min. SEPs following right median nerve stimulation were recorded before, immediately after, 5 min, and 10 min after tSMS from the C3’ and F3 sites (Fig. 5). Immediately after 15 in of tSMS over M1, amplitudes of the N33 component of SEPs at C3’ significantly decreased by up to 20%, returning to baseline within 10 min following the intervention (Fig. 6). However, tSMS over the SMA did not influence any components of SEP amplitude. Our results suggest that different components of SEPs are reduced according to the tSMS stimulation site. As shown previously, tSMS over C3 modulates the N20 component of SEPs, while the amplitude of N33 is affected by tSMS over M1. This result showing that tSMS over M1 can reduce the N33 component of SEPs at C3’ is consistent with low-frequency repeated TMS and cathodal tDCS studies. Therefore, tSMS could be a useful tool for modulating cortical somatosensory processing. SMA is likely to be a more difficult area to target with tSMS as it is located in the interhemispheric fissure, which would result in attenuation of the magnetic field strength.

Conclusions

SMFs, unlike time-varying magnetic fields, are not associated with induced electric currents, and have been shown to influence a variety of biological functions. SMFs have been suggested to act primarily at the synapse, and it has been proposed that these fields alter the function of membrane ion channels. The advantages of using a strong NdFeB magnet in tSMS compared to other NIBS methods include ease of use, absence of uncomfortable sensations for subjects, a lack of necessity for high operational skills or expensive devices, and conclusive
sham stimulation, which allows for controlled experiments and randomized controlled clinical trials. In this study, we have demonstrated that tSMS was able to modulate human cortical somatosensory processing, and that different components of SEPs were reduced according to the tSMS stimulation sites. Hence, tSMS has the potential for becoming a new NIBS tool to modulate cerebral excitability.

Fig. 5 Experimental setup for tSMS over M1 and SMA. The NdFeB magnet was centered over the representational field of the right abductor pollicis brevis (APB) muscle, as determined by a single-pulse TMS for M1 stimulation. For SMA stimulation, the NdFeB magnet was centered 3 cm anterior to the Cz of the international 10-20 system for electrode placement. SEPs were recorded from the C3’ (parietal component; 2.5 cm posterior to C3) and F3 areas (frontal component).

Fig. 6 Grand average SEP waveforms recorded from C3’ after right median nerve stimulation immediately following tSMS over M1 showing attenuation of the P25 and N33 component of SEP amplitudes at C3’.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this article.

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