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Safety Study of Transcranial Static Magnetic Field Stimulation (tSMS) of the Human Cortex

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ABSTRACT

Background: Transcranial static magnetic field stimulation (tSMS) in humans reduces cortical excitability.
Objective: The objective of this study was to determine if prolonged tSMS (2 h) could be delivered safely in humans. Safety limits for this technique have not been described.
Methods: tSMS was applied for 2 h with a cylindric magnet on the occiput of 17 healthy subjects. We assessed tSMS-related safety aspects at tissue level by measuring levels of neuron-specific enolase (NSE, a marker of neuronal damage) and S100 (a marker of glial reactivity and damage). We also included an evaluation of cognitive side effects by using a battery of visuomotor and cognitive tests.
Results: tSMS did not induce any significant increase in NSE or S100. No cognitive alteration was detected.
Conclusions: Our data indicate that the application of tSMS is safe in healthy human subjects, at least within these parameters.

Introduction

Non-invasive brain stimulation (NIBS) techniques have made an important contribution to cognitive neuroscience and have been proposed as a treatment for neuropsychiatric disorders [1]. Repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) are commonly used for NIBS in humans and animals. Recently we described that the application of transcranial static magnetic field stimulation (tSMS) in humans reduces the output of motor cortex – tested using TMS – for a few minutes after the end of stimulation [2]. Reduced motor output after tSMS can be explained by reduced motor cortex excitability. These results have been recently replicated by a different group [3]. tSMS using small magnets may thus be a promising tool to modulate cerebral excitability in a non-invasive, painless and reversible way.

Static magnetic fields, unlike time-varying magnetic fields, are not associated with induced electric currents and have been shown to influence a variety of biological systems [4]. A number of studies suggest that static magnetic fields act primarily at the synapse and alter the function of membrane ion channels [5], and the application of static magnetic fields to different animal preparations seem to have an effect that outlasts the time of stimulation [6]. When tSMS is applied in humans, the cortex is at least 2 cm away, so most of the strength of the magnetic field will not reach the target. The recommended limits by the World Health Organization (WHO) about safe exposure to static magnet fields are “time weighted average of 200 mT during the working day for occupational

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Conflict of interest: The authors A. Oliviero and G. Foffani declare that they are cofounders of the company Neurek SL, which is a spin-off of the Foundation of the Hospital Nacional de Parapléjicos. Moreover they are inventors in the patent P201030610.

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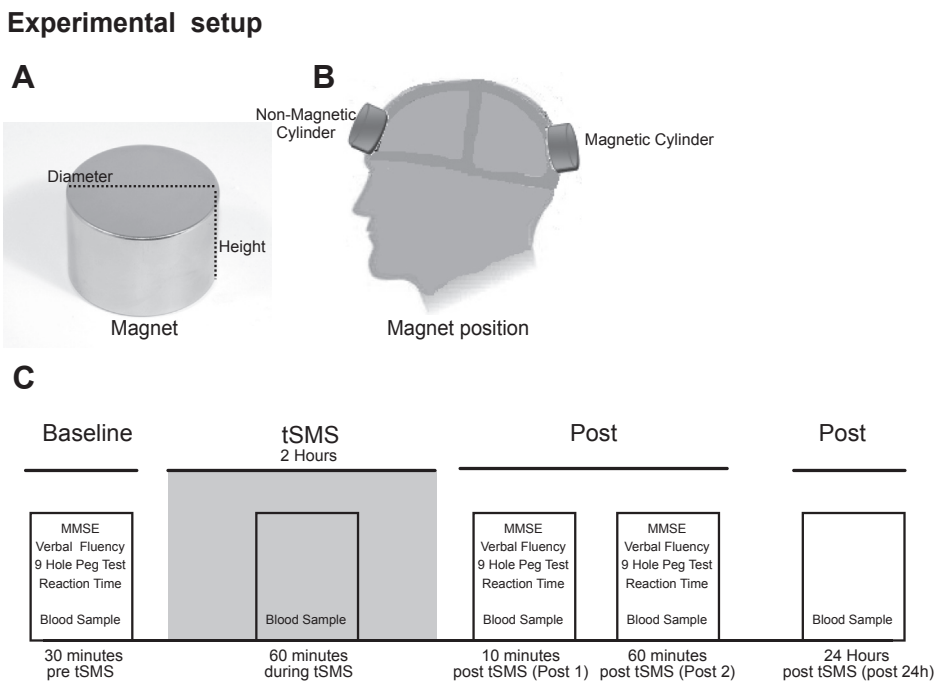

Figure 1. Schematic representation of experimental set up. A. Magnet (MAG60r, Neurek SL, Toledo, Spain). B. Magnet location over the occipital cortex (Oz location of the 10-20 EEG international system), and an additional non-magnetic cylinder over the frontal cortex (Fpz location of the 10-20 EEG international system) to counterbalance the weight of the occipital magnet. C. Time course of the experiment. The experimental protocol is divided in five time points: baseline, during tSMS, post1, post2 and 24 h.

exposure" (i.e. 8 h/day, 5 days/week) (http://www.who.int/peh-emf/publications/facts/fs299/en/index.html). With the magnets we normally use in our lab (MAG45r and MAG60r; Neurek SL, Toledo, Spain), at 2 cm from the axis (the approximate distance from the scull to the cortex) the magnetic field is around 150–200 mT [7], so within the safe limit proposed by the WHO. Moreover, many studies about safety of magnetic resonance imaging (MRI) techniques consider safe an exposure to magnetic fields >8T for experimental sessions that can last hours [8]. On the other hand, it cannot be excluded that the different gradient shape and/or the different magnetic field orientation may have different safety profiles.

The purpose of this study was to test the safety of prolonged tSMS (2 h) of the occipital cortex in healthy volunteers to establish safety guidelines for future tSMS experiments and therapeutic trials. We tested the effects of tSMS on a cellular level, by measuring serum levels of neuron-specific enolase (NSE) and protein S-100 [9] – sensitive markers for neural or glial brain damage – in healthy volunteers before, during and after tSMS. In order to provide further evidence for the safety of tSMS, a battery of neuropsychological tests were performed to exclude cognitive adverse effects. Specifically, we chose the Mini Mental State Exam (MMSE) as an evaluation of global cognitive state [10], the Nine-Hole peg test (NHPT) to evaluate a fine motor task and visuomotor coordination, a two-choice reaction time test to assay attentional levels (and again visuomotor coordination). Verbal fluency, a cognitive process considered to be primarily frontal lobe-dependent, was tested to determine cognitive function associated to a brain location distant from the stimulated area [11].

Methods

Subjects

Seventeen healthy volunteers participated in this study (10 males; mean age 34.4 ± 7.3 years; age range 24–45 years). Exclusion criteria were significant medical or psychiatric illness, pregnancy and concurrent use of neuroactive drugs. We also excluded individuals with pacemakers, brain stimulators, medication pumps or any type of metal object in the head including eyes – except for dental appliances or fillings – which might pose a physical hazard during tSMS. All subjects but one were right handed according to the Edinburgh handedness inventory [12]. The study was approved by the local ethical committee. Informed consent was obtained from all subjects.

Experimental set-up

Experimental set-up is shown schematically in Fig. 1.

tSMS procedures

To deliver tSMS we used a cylindrical Nickel-plated (Ni–Cu–Ni) NdFeB magnet of 60 mm diameter, 30 mm of thickness and a weight of 370 g (MAG60r, Neurek SL, Toledo, Spain). North magnetic field polarity was used (i.e. north pole was placed over the scalp). During the experiment, all subjects had tSMS over the occipital cortex (Oz location of the 10-20 EEG international system), and an additional non-magnetic cylinder was located over the frontal cortex (Fpz location of the 10-20 EEG international system) and remained fixed during the whole experiment to counterbalance the weight of the occipital cylinder. The non-magnetic cylinder was a steel nickel-coated cylinder, had the same size, a weight of 368 g similar to the MAG60r (MAG60s, Neurek SL, Toledo, Spain). The cylinders were held in place with a leather strapping system (MAGlet60+, Neurek SL, Toledo, Spain). The tSMS was applied for 2 h.

Blood samples for determining NSE and S-100

We measured serum concentrations of NSE and S100, as sensitive markers of neuronal damage and glial activation, respectively. Blood samples were taken in EDTA-free tubes from each subject at