

TECHNICAL SPOTLIGHT

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Challenges of proper placebo control for non-invasive brain stimulation in clinical and experimental applications

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Abstract

A range of techniques are now available for modulating the activity of the brain in healthy people and people with neurological conditions. These techniques, including transcranial magnetic stimulation (TMS) and transcranial current stimulation (tCS, which includes direct and alternating current), create magnetic or electrical fields that cross the intact skull and affect neural processing in brain areas near to the scalp location where the stimulation is delivered. TMS and tCS have proved to be valuable tools in behavioural neuroscience laboratories, where causal involvement of specific brain areas in specific tasks can be shown. In clinical neuroscience, the techniques offer the promise of correcting abnormal activity, such as when a stroke leaves a brain area under-active. As the use of brain stimulation becomes more commonplace in laboratories and clinics, we discuss the safety and ethical issues inherent in using the techniques with human participants, and we suggest how to balance scientific integrity with the safety of the participant.

Introduction

In recent decades, the use of transcranial stimulation to explore and to improve brain function has become almost routine. Non-invasive brain stimulation is rapidly gaining credence as an effective treatment option for many neurological disorders, and is in common use in neuroscience laboratories. Two principal techniques are available. Transcranial magnetic stimulation (TMS) involves discharging brief magnetic pulses over the scalp, which induce electrical currents in underlying neural tissue. The second technique is transcranial current stimulation (tCS), which involves passing a small current between two electrodes placed on the scalp. In almost all published work, either direct current (tDCS) or alternating current (tACS) is used.

Non-invasive brain stimulation promises to be an important avenue for future clinical applications. TMS is currently approved in the USA only as a treatment for drug-resistant depression; however experimental and early clinical trials have suggested that the technique may be effective in managing a range of other disorders, including chronic pain, tinnitus, Alzheimer's disease and addiction

(Nitsche & Paulus, 2011). These early successes have led to it being used off-label to treat these and other disorders.

Here we discuss whether brain stimulation allows for a true placebo condition. We will also examine the technical and practical constraints on controlling experiments that use brain stimulation.

General principles of experimental control

Any scientific experiment must be accompanied by a proper control condition to ensure that any changes observed are genuinely due to the stimulation and not to incidental factors in the experimental environment or to variations in the participant's state. In testing other forms of intervention such as drug treatments it is common to give a group of participants an active dose of the drug and another group a placebo. Shapiro (1968) defined an experimental placebo thus: "A *placebo*, when used as a control in experimental studies, is defined as a substance or procedure that is without specific activity for the condition being evaluated". A good placebo would give the person taking it no clue as to whether the dose was active or not. A perfect placebo would mean that the researcher would not know unless told. Why deliver a placebo at all? Placebo-controlled trials allow for the specific effects of a treatment to be assessed, as distinct from the non-specific effects of the treatment environment. Applications that are efficacious and specific

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are the goal of experimental and clinical interventions (Chambless & Hollon, 1998).

While the technology for delivering non-invasive brain stimulation has been in development for several decades, addressing the ethical concerns related to the actual and potential uses of the techniques has lagged behind. Green *et al.* (1997) produced a set of guidelines for the conduct of research with (the then-new) repetitive TMS, and Rossi *et al.* (2009) developed clear and comprehensive guidelines for TMS usage, but since then little work has examined the ethical and governance issues raised by brain stimulation. Recent work has contemplated the implications of brain stimulation, such as its potential use in 'cosmetic' cognitive enhancement (Hamilton *et al.*, 2011; Cohen Kadosh *et al.*, 2012). These uses are of obvious future importance, and should be discussed in relation to other methods of cognitive enhancement (Heinz *et al.*, 2012).

The difficulty of placebo control in brain stimulation

In this section we examine how brain stimulation is usually controlled, and what are the barriers to true placebo control. Both TMS and tCS are associated with sensory phenomena that may make it possible for the participant to tell to which condition they have been assigned.

Transcranial magnetic stimulation delivery is associated with a loud click due to heating of the stimulating coil as the current is driven through it. It may also be associated with significant (and sometimes painful) contraction of scalp, face or neck muscles. Recent developments of TMS have included temporally patterned bursts of stimulation, of which theta-burst stimulation (TBS) is currently the most widely used. Patterned stimulation such as TBS can be used to raise or lower excitability of a target brain area depending on the parameters used (Huang *et al.*, 2005). These temporally patterned regimes are typically more intense and less pleasant for the participant, but are of considerably shorter duration (< 1 min for TBS).

Transcranial current stimulation differs from TMS in that the delivery of stimulation is silent and does not cause muscle activation; however, at the start of stimulation, and throughout stimulation at higher stimulation intensities (above 1 mA), there may be a noticeable itchy sensation on the scalp under the electrodes. It is important to note that for the lower currents often used, there is only a cutaneous sensation during the ramping up and down of the current, so that during the period of constant stimulation there is typically no sensation (although detectability of stimulation may occur at 0.4 mA; Ambrus *et al.*, 2010). tACS induces weak cutaneous sensations which depend upon the stimulation frequency (Turi *et al.*, 2013), but subjects may experience visual disturbances during stimulation due to spreading of the current to the retina or visual brain areas.

In Table 1 we give examples of the difficulties of blinding or controlling each method of brain stimulation. We also give examples of clinical or experimental studies where these challenges have been met.

Technical options for sham

There are two common methods of controlling for the effects of brain stimulation in an experiment. The two methods differ in the amount of stimulation given to the participant. In the first type, which we call *sham control stimulation* (SCS), the participant receives a minimal amount or no stimulation, but the experimental experience is otherwise identical. In the second type, *off-target active stimulation* (OAS), a full dose of stimulation is delivered to

an area of the scalp where it is assumed to be unlikely to affect the process being studied.

Sham control stimulation would appear to be closer to Shapiro's definition of a placebo. In the case of TMS this may be arranged either by rotating the stimulating coil away from the head so that the magnetic field at the scalp is effectively zero, or by using a specially designed 'sham coil' that looks identical to a real coil, but which produces only an audible click and no magnetic pulse (Herwig *et al.*, 2010). tDCS sham delivery usually involves turning on the stimulator for a few seconds so the participant feels the itchy sensation at the electrodes, then covertly turning off the stimulator during the phase when the cutaneous sensations would normally be absent (Ambrus *et al.*, 2010, 2012). Neither of these options is perfect, and an experienced participant may be able to determine in which condition he or she finds herself. Even a naïve participant is likely to know that one session of stimulation feels different from another. In particular, it is often assumed that participants do not feel steady-state tDCS when delivered at a low current, although this depends greatly on the participant's cutaneous sensitivity, on the electrode montage used and on the impedance of the electrode-scalp contact. The cutaneous sensation of higher currents may be reduced through the use of topical anaesthetic (McFadden *et al.*, 2011), although in our experience the participants' reports of discomfort are helpful in establishing good electrode contact. Importantly for clinical applications of tDCS, while single-blinding of active versus sham conditions may be possible at low stimulation intensities, operator-blinding is more difficult, and participant-blinding becomes unreliable at higher levels (O'Connell *et al.*, 2012; Palm *et al.*, 2013).

In the case of OAS, the full amount of stimulation is delivered to the participant. It is typical to refer to a 'control site' in these experiments. Commonly, the vertex of the head is used as a control site in TMS experiments, and has been referred to as the 'Empty Quarter'. In tCS a montage may be used in which most of the current shunts between the electrodes rather than affecting the brain. Sham stimulation for tACS typically involves a 'control frequency', i.e. a frequency not thought to be involved in mediating the neural processing under study, and therefore is an active sham by our definition. It is our view that the use of OAS exposes the participant to additional and frequently unnecessary stimulation. While small amounts of TMS or tCS are thought to be safe and tolerable, we discuss in the next section the risks presented by brain stimulation.

The choice of SCS or OAS for a given experiment should be guided by two main factors. The safety of the participant should be paramount when using techniques that may have adverse effects. After this, the quality and reliability of the data should be the next consideration. In the following sections we deal with the potential safety issues in using TMS and tCS, and with the risks to data quality that result from SCS or OAS.

Safety issues

Brain stimulation exposes the participant to acute and longer-term risks. While the acute effects such as seizure might be the most easily detectable, there are also risks of build-up of effects from repeated stimulation (Monte-Silva *et al.*, 2010; Alonzo *et al.*, 2012). At present, the brain's response to repeated external challenges is not well known. These effects may be particularly difficult to detect or to manage when the spread of stimulation is more difficult to predict, as in tDCS (Miranda *et al.*, 2006). It is thought that adverse effects are already under-reported in the literature (Brunoni *et al.*, 2011). In Table 2 we suggest a set of exclusion criteria for

TABLE 1. Examples of clinical and experimental uses of transcranial brain stimulation, highlighting problems and solutions of controlling each method; examples are given of studies using each method, with an indication of how each problem was addressed

Technique	Problems	Solutions	Examples
TMS	Audible click	Sham coil	May <i>et al.</i> (2007) studied plasticity in the auditory cortex with 1 Hz rTMS. Participants were assigned to Active or Sham groups, who respectively received rTMS at 110% of motor threshold or clicks from a sham coil. After 1 week of treatment the Active group showed anatomical and functional changes in the target area
TBS	Audible click	Sham coil	Nyffeler <i>et al.</i> (2009) used TBS to improve neglect symptoms in people with right parietal stroke. Four experiments were run. In one experiment (2 × TBS) people received two applications of TBS over the intact parietal cortex separated by 15 min. In a second (Sham) the same protocol was used but with the use of a sham coil instead of a real TMS coil. In a third experiment (4 × TBS) an additional two TBS applications were delivered. A fourth experiment (Control) used the same timings as 2 × TBS and Sham, but without the stimulation phase. Amelioration of neglect symptoms was seen only in the real TBS sessions. A weakness of this study was that the four experimental groups consisted of different combinations of the same 11 patients, leading to imperfect blinding across conditions
tDCS	Cutaneous sensation	Reduce intensity or current density; increase ramping-up time	Ferrucci <i>et al.</i> (2008) investigated the use of tDCS in improving recognition memory in people with Alzheimer's disease (AD). A cohort of ten people with AD were given anodal, cathodal and sham stimulation over the temporoparietal area in separate sessions. Sham stimulation was arranged by running the stimulator at full current (1.5 mA) for 10 s then turning off the stimulator. Ferrucci <i>et al.</i> did not report whether the patients could distinguish the types of stimulation, although they did employ the useful tactic of keeping the experimenter who collected the data blind to the stimulation condition
tACS	Visual disturbances	Change montage to avoid ocular or occipital stimulation; reduce intensity; ramp in current	Kanai <i>et al.</i> (2008) used tACS to study the frequency-specificity of the excitability of the primary visual cortex. An electrode was placed over theinion and over the forehead, and a range of different stimulation frequencies (4–40 Hz) and intensities (0.25–1 mA) were applied between them. tACS was ramped up over 1 s in each trial. Participants rated the intensity of visual disturbances ('phosphenes') resulting from the stimulation, with eyes both open and closed. As this experiment requires conscious responses, the participants were asked to look for differences between frequency conditions; in fact they were asked to draw the phosphene patterns. However, the order of frequency conditions was randomized and was blind to the participant

TMS, transcranial magnetic stimulation; TBS, Theta-burst transcranial magnetic stimulation; tDCS, transcranial direct current stimulation; tACS, transcranial alternating current stimulation.

TABLE 2. Suggested set of exclusion criteria for participants in brain stimulation experiments

Exclusion criterion	Reason
Personal or family history of epilepsy	Brain stimulation alters regional excitability of the cortex, possibly putting the brain into a more seizure-prone state
History of skull trauma	Unfused fissures in the skull make prediction of peak currents at the brain surface difficult
Recently participated in brain stimulation	A sufficient wash-out period is required between sessions, to prevent build-up of effects and possible long-term depression or potentiation
Risk of metal fragments in the eyes or head	Metal fragments (such as from welding or metalworking) lead to unpredictable current flow and may move in a magnetic field
Use of neuro-active drugs	Some drugs are known to increase the risk of seizure, so modulating cortical excitability with brain stimulation is likely to add significantly to this risk
Possible pregnancy	While the fetus is unlikely to be affected directly by stimulation occurring some distance away, the secondary risks to the mother (such as from seizure induction) argue for exclusion

participants in brain stimulation. This list is not exhaustive, and each study should be reviewed for its potential interaction with the various risk factors. A recent list of drugs that may interact with TMS is given by Rossi *et al.* (2009), and it would be reasonable to conclude that the same drugs should be excludable in tCS studies.

Triggering a pulse of TMS over the scalp induces the electrical field near the coil to change rapidly both spatially and temporally. These changes cause action potentials in the neurones, followed by a longer refractory period as the cells recover. While the safety parameters of TMS are reasonably well explored, there remains a risk of seizure in people who may already be predisposed to epilepsy or who are taking certain medications (Tharayil *et al.*, 2005; Bae *et al.*, 2007).

Initial studies of tDCS in the 1960s reported some significant respiratory or circulatory side-effects (Lippold & Redfearn, 1964;

Redfearn *et al.*, 1964). In modern studies current levels are lower; nevertheless a potential side-effect of tDCS is burning of the skin due to heating (Frank *et al.*, 2010). It is now increasingly common to simulate the effect of tDCS on the brain by using finite element modelling (FEM) of the whole head; this allows the result of passing a current through tissues of different conductances to be determined prior to stimulation (Miranda *et al.*, 2006, 2009; Datta *et al.*, 2009; Salvador *et al.*, 2010). However, at present these models require certain assumptions: in particular it is important that the skull is intact, as the skull insulates the brain from peaks of current. FEM models typically use a single 'standard' head model (in fact, it is the 'Colin27' model created by the Montreal Neurological Institute, which is the brain model distributed with magnetic resonance imaging analysis packages such as SPM). Clearly, individual brains that differ significantly from this model will have different electric

field distributions at the brain surface. Some attempts have been made to use individualized head models to predict the effects of tDCS (Datta *et al.*, 2011). However, given the time and effort required in obtaining high-quality structural images and in the calculations required, we do not imagine that such a personalized approach will be widely adopted.

We also note the use of electrical stimulation for promoting bone repair after injury (Friedenberg *et al.*, 1971, 1974); although the currents used in tCS are comparable to or higher than those used for osteogenesis, the effect on the skull of repeated sessions of tCS is not known and has not been studied. Worryingly, these early studies also showed osteonecrosis at high currents or around the anode.

The greatest promise of brain stimulation for clinical applications appears to come when sessions of stimulation are delivered with a short inter-session interval. The exact parameters of stimulation that deliver a maximal effect are not known, and are likely to be person-specific. It is known that daily sessions of tDCS are more effective than sessions on alternate days (Alonzo *et al.*, 2012), but it is not necessarily the case that more frequent sessions are more beneficial. The mechanisms that underlie the longer-lasting effects of stimulation are complex and rely on processes with different time courses. It is known, for example, that the effects of rapid TMS protocols are sensitively dependent on the temporal parameters (Huang *et al.*, 2005; Hamada *et al.*, 2008), but larger time-scale effects have not been sufficiently explored.

Choosing an appropriate method of control

We have discussed a number of issues that arise in the use of brain stimulation. We have suggested that there are two separate types of control condition that are appropriate for such experiments. How should one choose an appropriate method for a given experiment? Two factors influence this decision: the safety of the participant, and the desire to maintain the scientific integrity of the data.

We suggest that where possible sham conditions should employ inactive sham stimulation to minimize the stimulation dose per participant. However, we acknowledge that this may not always be practicable as the active stimulation condition may produce perceptible effects that would make the two conditions distinguishable. Although this problem may be lessened through the use of between-participant experimental designs, these designs typically entail lower statistical power and are less attractive to the experimenter. SCS is consistent with Shapiro's (1968) definition of a placebo, in that the participant does not know which treatment is being applied, and the treatment probably has no effect on the person. While there may be quibbles over specific deliveries of TMS or tCS (such as clicking from the coil, or itching at the scalp), SCS could fairly be called a placebo, especially if these factors were identical in active and sham sessions.

But what about OAS? The key is the word 'specific': if the stimulation is delivered to a brain area that is known (inasmuch as this is possible) not to be involved in a task, the stimulation might indeed be considered a placebo. However, ACS differs markedly from the usual medical idea of a placebo, in that the stimulation is being delivered somewhere. While the task-related brain area may be unaffected in the OAS condition, nevertheless the person's brain tissue is being affected in some way. While the stimulation levels used in most experimental settings are well within physiologically 'safe' limits (Jahanshahi *et al.*, 1997; Bikson *et al.*, 2009; Datta *et al.*, 2009), it is still possible that small changes in neural excitability could induce deleterious effects.

There are some cases in which an active control is necessary. For example, high-intensity tACS around the frontal or occipital areas is likely to cause visual disturbances due to stimulation of the retina or visual cortex (Kanai *et al.*, 2008; Schutter & Hortensius, 2010). In this case the participant is always aware of the stimulated conditions. It would therefore be sensible to choose two separate electrode montages, with one over the target brain area and the other over a neutral location that would produce the same visual sensations. However, stimulating one area of the scalp is likely to feel very different from stimulating another: even a naïve participant will realize that TMS over dorsolateral prefrontal cortex has different sensory consequences from vertex stimulation. A primary purpose of a control condition in an experiment or trial is to show the specificity of the effect to the primary condition; therefore, the control must replicate as closely as possible the 'active' condition but the hypothesized brain area should not be stimulated. In this view, OAS gives the fairest comparison of active with sham conditions, as the only difference between the conditions is the position of the electrodes or stimulating coil.

We recommend that active control brain stimulation be used as a last resort, and that appropriate safety checks are employed. First, the impact of the control stimulation on the brain should be understood, ideally through current density modelling or through relating the planned stimulation parameters to known physiological measures. Second, the experimental design should include tests for change of function in areas near to where the stimulation is to be delivered. For example, sham TMS is often delivered to the vertex of the head, or electrode position Cz. The closest brain region to Cz is the precentral gyrus (Koessler *et al.*, 2009), so an experiment that uses Cz as a location for OAS should include a test for motor function.

Conclusions

In this article we have discussed two different common ways to control for the effect of stimulation delivery in experiments or clinical trials. While these controls are often generally called 'sham stimulation', we have identified two separate types of sham, which we call active and inactive sham stimulation. All brain stimulation experiments carry some risk to the participant. It is the ethical responsibility of the researcher to minimize these risks for any individual participant, while at the same time maximizing the scientific utility of each experiment. In this article we have argued that active control brain stimulation carries greater risks than inactive control, and should be avoided where possible.

Conflict of interest

The authors declare no conflicts of interest.

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Abbreviations

FEM, finite element modelling; OAS, off-target active stimulation; SCS, sham control stimulation; TBS, theta-burst transcranial magnetic stimulation; tCS, transcranial current stimulation; TMS, transcranial magnetic stimulation.

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