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Neurostimulation

TITLE PAGE

i. Title

Neurostimulation in tactile perception

ii. Summary/abstract (1-2 paragraphs)

Neurostimulation techniques are used to study the healthy human central and peripheral nervous system non-invasively, by stimulating neural tissue magnetically or electrically. Such approaches have been successfully applied to study the motor system as well as several other brain systems. This chapter will focus on stimulation of the somatosensory system. Typically, neurostimulation is applied to a certain brain area by positioning a coil (e.g., in transcranial magnetic stimulation, TMS) or an electrode (e.g., transcranial electrical stimulation, TES) on the scalp location over the brain area of interest. When primary motor cortex (M1) is stimulated with TMS, motor-evoked potentials (MEPs) and twitches are observed in the targeted muscles of the body. However, unlike over M1, stimulation to somatosensory and other cortices does not produce immediately observable outputs. This introduces problems of localization and other challenges, such as the optimal experimental designs and behavioural tasks, when using neurostimulation to study tactile perception. This chapter will describe and evaluate these approaches. Practical and participant-specific difficulties will be noted. Neurostimulation methods offer relatively cheap and reliable means of modulating somatosensation, yet care is required to ensure that the experimental design is adequate, that the optimal location is stimulated, and that the data are able to answer your theoretical question.

iii. Keywords (5-10 keywords)

Transcranical Magnetic Stimulation, Transcranial Direct Current Stimulation, Transcranial Alternating Current Stimulation, Detection, Discrimination, Vibrotactile,

Fingers, Somatosensory Cortex, Localization, Neuronavigation

1. INTRODUCTION

1.1. A brief outline and history of brain stimulation

Non-invasive brain stimulation (NIBS) techniques can be used to study sensory, cognitive and motor processes in the brain and peripheral nervous system [1]. NIBS methods include primarily transcranial electrical stimulation (TES) and transcranial magnetic stimulation (TMS). These techniques are typically used to establish the excitability of a certain brain region and of corticocortical and cortico-spinal pathways. Moreover, by interference with ongoing processing it can be used to establish the role played by a brain region in a certain process [2, 3], and to monitor the magnitude and timing of physiological responses in healthy people and individuals with neurological disorders. Recently, such approaches have also proved useful as a treatment for patients suffering from neurological and psychiatric conditions. There is evidence that TES can be effective, for instance, in reducing impairment after stroke [4], improving symptoms of neglect [5] and reducing symptoms of depression [6]. What is considered the major advantage of these techniques, differently from other neuroimaging methods such as functional magnetic resonance (fMRI, see Chapter 18, this volume), electroencephalography (EEG, see Chapter 19, this volume) and magnetoencephalography (MEG), is the possibility to establish a **causal** role of a particular brain area in a certain sensory, motor or cognitive process. Therefore, these approaches are potentially very powerful. However, they also come with limitations and require a series of important precautions that must be taken for appropriate and effective use.

In this chapter, we will describe the most common neurostimulation protocols adopted in the context of stimulating the somatosensory system. We will discuss the strengths and limitations of these techniques and provide advice of good practice that may help to improve the reliability and effectiveness of studies in this domain. We will

focus on the practical use of TES and TMS techniques in studying the somatosensory system rather than discussing models and mechanisms that could explain the stimulation effects, a topic that is still unclear and a matter of debate [7, 8]. Although these techniques are considered safe, it is critical to follow some basic safety procedures for routine clinical and research applications, to reduce the risks of adverse effects [9–11]. Such procedures will be briefly detailed later in the chapter.

Historically, the first successful controlled direct electrical stimulation of the mammalian cerebral cortex can be traced back to the study performed by Fritsch & Hitzig in 1870 [12], in which they delivered galvanic current through bipolar electrodes to the anterior half of the dog's hemisphere. As a result of this stimulation, they found movements of muscle groups in the opposite half of the dog's body. The first human brain stimulation study, as credited by Beevor and Horsley (1890), was performed in 1874 by Roberts Bartholow, an American surgeon. Another surgeon, Harvey Cushing, stimulated the somatosensory cortex of an awake human patient in 1909 [13]. But the first systematic attempts to electrically stimulate the human somatosensory cortex was the pioneering work of Penfield and Boldrey [14], in which they mapped the somatosensory and motor cortices in humans using electrical stimulation. They described the functional anatomy of these brain areas in human, emphasizing the somatotopic organization of the hemibody [15, 16]. These pioneering works lead to the development of trans-cranial electrical stimulation (TES) methodology, whereby applying an electrical current at the scalp surface can directly affect brain activity. Originally, TES was applied with high intensity (i.e., 3-60mA), however, more recently lower intensities are most commonly used (i.e., 1-2mA) [17] (note that we will refer to the latest approach in all the subsequent parts of this chapter). Low intensity TES is typically applied using different approaches (e.g., transcranial direct current stimulation, TDCS; transcranial alternating current

stimulation, TACS; transcranial random noise stimulation, TRNS), which will be discussed later in relation to the somatosensory system. A comprehensive discussion on these different methods are beyond the scope of the present chapter (for a review on the topic see [18]).

The first attempt to apply magnetic stimulation to the head came a bit later, starting with the work of d'Arsonval in 1896 [19], in which the author applied an alternating current to a coil surrounding the head of an individual, successfully inducing phosphenes (i.e., luminous floating stars, zigzags, swirls, spirals and squiggles seen in the visual field). Years later, in 1959, Kolin and colleagues [20] for the first time applied magnetic stimulation to the sciatic nerve of a frog, inducing muscle contraction. Bickford and Freming extended this work in 1959 by stimulating peripheral nerves in animals and humans [21]. The birth of modern TMS methodology was 1985, with the work of Barker and colleagues [22] in which the motor cortex was stimulated using a coil placed over the scalp. One of the early attempts of stimulating primary somatosensory cortex to disrupt tactile perception in humans was provided by Cohen and colleagues in 1991 [23]. They reported that detection of electrical stimuli delivered on the index finger of a subject was attenuated or completely abolished when single pulse (sp) TMS was applied over contralateral sensorimotor cortex between 200 milliseconds (ms) before and 20 ms after the occurrence of the tactile stimulus. Figure 1 depicts a stimulation coil positioned to target the somatosensory cortex.

[FIGURE 1 ABOUT HERE]

1.2. Stimulating the somatosensory system

The somatosensory system, and in particular the primary somatosensory cortex (S1),

which was central to the studies conducted by Penfield and colleagues, can be divided into four distinct cytoarchitectonic areas [24]. These areas are the Brodmann areas (BA) 3a, 3b, 1 and 2 [25] (see Chapters 16-18, this volume). S1 covers a large territory along the central sulcus and postcentral gyrus where there are several topographically organised maps of the body [26]. Although the precise location of each body part representation may vary between people, there is a within- and between-person consistency in the locations of different body part representations in S1. This allows neuroscientists to aggregate and map the results from different people in studies of cortical somatosensory functions [27]. For instance, the different fingers are organised (i.e., from little finger to the thumb) following a medio-to-lateral distribution symmetrically in the two hemispheres [26]. The anatomical location of S1, in the context of neurostimulation, has some advantages, for instance being very superficial – close to the scalp – and therefore easy to stimulate. However, there are also some disadvantages, for instance being anatomically adjacent to the primary motor cortex. The implications of these anatomical and other physiological characteristics of the somatosensory cortex will be discussed in detail later in the chapter.

When planning neurostimulation studies which aim to affect the somatosensory system while measuring participants' performance in a perceptual or cognitive task, the researcher must take several decisions. Such choices will later determine the quality of the data and in turn the reliability and effectiveness of the study. In subsequent sections we will first describe the materials that are typically necessary to perform TES and TMS studies (e.g., hardware, consumables and software). Then, we will review the most common parameters and protocols used to perform neurostimulation of the somatosensory system, primarily while participants perform a tactile task. We will continue by describing the different options available to identify

an optimal scalp location as a target site for stimulation. The main experimental designs, type of tasks and the dependent variables that can be measured will also be considered. In the last section we will provide a series of recommendations that can be useful to overcome some limitations common to neurostimulation of the somatosensory cortex.

2. MATERIALS

Here, we will describe some currently- available TES and TMS devices that can be used to stimulate the somatosensory system both at cortical and peripheral levels. Then, we will present current neuronavigation systems (NNS) devices, which are now considered key tools to allow precise stimulation of the brain area of interest during testing. This logic applies well beyond stimulation of the somatosensory cortex (i.e., any other brain area), with the exception of the primary motor cortex (M1), from which TMS provides direct readouts of changes in the cortical activity by means of the motor evoked potentials (MEP) response.

2.1. TES and TMS hardware

For both TES and TMS approaches, there are several available devices (Figure 2). Some examples of companies providing TES equipment are MagStim, NeuroConn and BrainStim. Such TES devices currently cost several thousand pounds, depending on the features and model, and are much less expensive than TMS devices.

[FIGURE 2 ABOUT HERE]

In terms of the available TMS devices, there are several options. The main manufacturers include, but are not limited to: Magstim, Mag&More, MagVenture,

Deymed, NeuroStart, Nexstim, Neurosoft and Neuronetics. Such devices cost perhaps ten times as much as TES systems, again depending on the features and model. They can be used both in research and clinical settings, although specific approvals may be required for clinical use. There is some debate about whether such devices provided by different manufacturers are equivalent in terms of their effectiveness. A few studies have directly compared them, though, in the clinical context [28] and in the research setting [29, 30]. Such comparisons show there may be slight differences in the strength and sound produced by different devices. It is therefore suggested that the intensity of TMS should be adjusted according to the individual participant's motor threshold to obtain comparable responses with different devices [29].

Establishing the resting (RMT) or active (AMT) motor threshold is an-almost universal standard practice to tailor the stimulation intensity of TMS to each participant. Such thresholds are usually defined according to Rossini et al [31], as the minimum stimulator intensity that produces MEPs with a peak-to-peak amplitude of 50 μV or higher on 5 or more out of 10 trials in which TMS is applied over M1 [31]. Even though this threshold is computed for M1 stimulation, the stimulator intensity defined is often used for stimulation of all other brain areas. This reference intensity is based only on the motor cortex. More recently, 10 out of 20 trials has been recommended [32], while more theoretically-motivated and potentially more efficient approaches have been developed, often called 'threshold-hunting', but involving parameter estimation by sequential testing (PEST or QUEST, see Chapter 1, this volume).

2.2. Neuronavigation systems

Neuronavigation systems in the context of TES and TMS are very valuable tools which allow more accurate stimulation of specific brain areas. Typically, a

neuronavigator system consists of a means of locating the participant's head (3D motion-capture) and a means of registering the subject's head to a 3D MRI scan. Anatomical and/or functional images from an fMRI scan can be imported into the neuronavigation software. If only anatomical images are available the locus of stimulation can be visualised and targeted using the subject space or in a normalised brain template space (e.g., MNI). If also functional images are available an fMRI contrast for the relevant condition can be used to visualise and target the functional activated brain area of interest [33]. Neuronavigation (Figure 3) is critical for accurately stimulating all brain regions with probably the only exception being M1, from which we have relatively direct readout of excitability from MEPs. The way in which the TMS coil is positioned on the scalp, in terms of location (2 or 3 degrees of freedom) and orientation (3 degrees of freedom), can significantly affect the brain's physiological response [34]. Critically, neuronavigation devices can effectively monitor these parameters when the coil is initially positioned, and later while TMS is delivered (online) during the experimental phase. Some neuronavigation systems are sold including both hardware and software components. One widely used system is Brainsight, which also provides MEP recording options. Similar systems are the Soterix, BrainVoyager or Brainlab. These systems may cost as much as the TMS system itself, currently more than £20k.

[FIGURE 3 ABOUT HERE]

An interesting freely-available neuronavigator software system is the InVesalius Navigator (IN) [35], which is an implementation of the InVesalius software program [36]. This system provides image-guided coil placement for TMS. It comes with software that can communicate with different motion tracking devices (i.e., MicronTracker, Patriot, Fasttrack and Isotrack II). Note that, differently from the

systems described above, in this case the researcher will need to have available such a motion tracking system to interface with the neuronavigation software. Likewise, this software will not provide MEP recordings, and this needs separate hardware and software.

The ‘gold standard’ for locating brain areas of interest is to have a well-calibrated neuronavigation system along with a recent functional and/or structural MRI scan for each participant. When this is not possible or available, several different methods are typically used to locate brain areas on the scalp based, primarily, on the 10-20 system for locating electroencephalography (EEG) electrodes. To facilitate measurement of participants’ heads, it is common practice to use a cap (e.g., swimming cap) on which researchers can mark anatomical landmarks such as the inion or vertex, or apply geometric grids of locations with the origin, for example, on the optimal location for eliciting MEPs from over M1. From these standard and relatively unambiguous landmarks, it is possible to move the TMS to different locations as a proxy for neuronavigation. In general, the further away from M1, the less precise the coil localisation. At least for the S1 hand area, with careful measurements of the head and M1 locations, we can now be quite confident about accurate coil positioning [27, 37].

2.3. Vibrotactile devices & environmental conditions

Several types of tactile stimulation device can be used in behavioural and neuroimaging tactile tasks. A first main distinction can be made between electrical and mechanical tactile stimulators. The most commonly used electrical stimulator is the Digitimer, a constant current stimulator device. Bipolar or ring electrodes are used to stimulate certain body parts such as the fingers. In particular, bipolar adhesive electrodes can be placed on the distal and middle phalanges of one finger (e.g., left

index finger) with the anode approximately 2 cm proximal to the cathode [38]. Such stimulation is very effective and produces a good neural response that easily be recorded using EEG, and the peak somatosensory evoked potential (SEP) location and time used in subsequent neurostimulation experiments. However, the stimulation, despite being applied locally, tends to spread across nearby regions of the skin.

Mechanical stimulators may instead be better in terms of targeting a certain skin location and reducing the spread of the signal towards neighbouring skin regions. Some of these devices work better when the stimulation needs to be delivered at low frequencies (e.g., 0-40Hz) and others work better when the stimulation is delivered at higher frequencies (e.g., 100Hz and above). The former are the air-puff stimulators, pneumatic and/or hydraulic stimulators that are also typically used in a MEG and fMRI settings given their compatibility with these techniques (Chapter 18, this volume). Solenoids, loudspeakers and Oticon (i.e., bone conductor) stimulators are also widely used for higher frequency stimulation. Depending of the parameters set it is also possible to create a tapped or more a vibratory stimulation. MEG- and fMRI-compatible piezoelectric stimulators are also provided by Quaerosys and Dancer Design. These stimulators can consist of a matrix of 10 or more rods (1 mm in diameter), protruding from a flat surface of 4 × 8 mm. The rod can protrude and retract at 20 Hz for 1000 ms, producing clearly perceivable skin indentations [39]. If the matrix is large enough it is possible to create different spatial patterns of stimulation that can for instance resemble alphabet letters (Chapter 4, this volume).

Temperature and humidity are known to be important factors that can affect tactile performance (see Chapter 9, this volume). It is important that this parameters are monitored in the experiments [40]. This is critical when for instance a researcher

wants to perform a behavioural tactile study that has been previously done in a laboratory room (about 24 °C) or within the fMRI scanner room (18 °C) [41]. Remember, too, that electromagnetic interference between your TMS and your somatosensory hardware is always a strong possibility (Note 4.1.).

3. METHODS

In this section we will describe the typical experimental designs and protocols used to perform a neurostimulation study in the context of tactile perception. As a general remark, despite TES and TMS being brain stimulation techniques, the main outcomes of these experiments are typically behavioural data. The general rules that apply to this type of studies are therefore very similar to those used for behavioural experiments (see Chapter 1, this volume). We will discuss three main aspects: experimental design, type of neurostimulation to use, and how test and control sites for stimulation can be localised on the scalp.

3.1. Experimental design

There are different types of designs that are currently used to assess participants' performance in tactile perception tasks under neurostimulation (i.e., TES and TMS). Note that, as these are similar for tactile experiments not using neurostimulation, such designs won't be covered in detail, and extended description is provided in Chapter 1 of the present volume.

3.1.1 Single-interval designs

One type of design used for TES and TMS studies investigating tactile perception is a one-interval forced choice (1-IFC) design (i.e., also known as "Yes"/"No" task) [23, 42] in which participants have to report on each trial if a target stimulus (e.g., a tactile stimulus on a finger of a certain intensity or frequency) is present or not. Different

designs could also require a one-interval discrimination or classification (e.g., was it a strong or a weak stimulus?) The target stimulus in a detection task is typically delivered randomly in 50% of the trials. Depending on the study specific purpose, feedback can be provided to participants about their performance. One major advantage of single-interval designs is that the total amount of neurostimulation can be minimised. With only one interval, trials and blocks can be shorter, and if TMS is given on every interval, this halves the total number of TMS pulses given.

A limitation of the one interval design is that it can be affected by response bias – the tendency to respond more often with one option, such as ‘no’ or ‘weak’. Therefore, the outcome of participants’ performance may well reflect a combination of both perceptual sensitivity and the decision criteria used to respond. To overcome such a limitation, it is recommended to adopt an analytic approach that allows you to disentangle these two components. In this regard, the “d-prime” index can be used to estimate the perceptual component and “criterion” the decisional component of the task [33]. Indeed, in a 1IFC tactile detection task in which TMS was applied in three different conditions (on the S1 target site, on a parietal control site, supramarginal gyrus, SMG, and with no TMS), we found that participants adopted a more conservative criterion when TMS was delivered over both S1 and SMG compared to no TMS [33]. Therefore, when the TMS was present, participants were more likely to report that the stimulus was absent, even though their ability to detect the tactile stimulus was unaffected (comparison between S1 and SMG vs no TMS).

3.1.2. Multiple interval designs

A second type of approach is a 2 or 3-I/AFC design that, differently from the one just discussed, is a design that can be considered bias free or less prone to bias [43, 44]. In a typical experiment, participants are instructed to indicate in which of two

temporal intervals a tactile stimulus was delivered on the body, or when a certain body part (e.g., the index finger) was stimulated. Critically, in each trial the tactile stimulation is always present, though it is unknown to the participant in which of the two intervals (i.e., first or second). The occurrence of the tactile stimulus in the two intervals is randomly assigned. As for the 1-I/AFC design explained above, depending of the study purpose, feedback can be provided. We also used flashing light-emitting diodes (LED) to indicate to the participant the beginning of each interval and the potential imminent arrival of the tactile stimulus. We have found these indications are particularly useful when tactile threshold has to be established – the indicators allow participants to focus their attention in time and space to the potential arrival of the target. As mentioned elsewhere, these two types of design are not equivalent, even though they may look quite similar. One interval designs are known to have a greater memory component and also to be more prone to bias compared to two or three interval designs [45]. Designs with two or more intervals will take much longer to perform and require more neurostimulation.

In the case of an **on-line** neurostimulation protocol, participants should receive TES or TMS on every trial and during every interval, regardless of the presence of the tactile stimulus [80, 130–133]. Specifically, and against our expectations, we found subjectively that the cognitive demands of the task were greatly increased when TMS was delivered only on some trials – not knowing when a (distracting, slightly annoying) TMS pulse was going to be presented made it harder to focus attention on the target stimulus. When an **off-line** neurostimulation protocol is used, participants receive a period of TES or TMS before the behavioural task [134, 135]. In addition, there are also cases in which both online and offline neurostimulation (i.e., TES) is used as part of the same protocol [136].

3.1.3. Detection and discrimination tasks

The two main experimental designs just described can be used with different tactile tasks. A very commonly used task in somatosensory neurostimulation is simple tactile detection, in which participants are instructed to report the presence of a stimulus (e.g., electrical, mechanical, or air puff) on the body [23, 33]. A more complex task is tactile localization, in which participants need to localise a tactile stimulus on their body, typically by naming the body part stimulated or by estimating the portion of the skin that received the stimulus [46]. Another level of complexity is provided by discrimination tasks [47], in which the participant has to establish whether a target tactile stimulus varies from a particular comparison stimulus, across different domains such as intensity [37], frequency [33, 48], spatial distribution [49, 50], temporal occurrence [51, 52], shape [53] or stimulus orientation [54, 55]. A widely used discrimination task is one that compares different frequencies of vibration. In a recent study, we adopted this paradigm in a 2-I/AFC design in which we applied single or double TMS pulses over the scalp in three separate conditions (i.e., TMS over S1, inferior parietal lobe, SMG, or with the active coil held away from the head) while asking participants to perform a tactile frequency discrimination task [33]. In this experiment, participants received a tactile stimulation on their index and middle fingers, one in the first interval and another in the second interval. The tactile stimulation delivered in the first interval was the standard (i.e., a vibrotactile stimulus delivered always at 200 Hz on the index finger), whereas the tactile stimulus delivered in the second interval on the middle finger was lower or higher in frequency than that in the first interval (i.e., the standard). Participants were asked to indicate whether the second stimulus was higher or lower in frequency compared to the first stimulus (Note 4.2.). Responses were given by lifting a pedal placed beneath the left or right foot. TMS was applied at 25 and 75 ms after stimulus onset in both of the intervals [33]. We found that TMS over S1 significantly disrupted tactile discrimination

performance, compared to when TMS was not present or was applied over the control site. The results of this experiment and one which involved a different type of tactile task is shown in Figure 4.

[FIGURE 4 ABOUT HERE]

3.1.4. Responses and measures

In terms of participants' responses, in tactile neurostimulation experiments, as in other cognitive studies, these can be given vocally, using the hands or feet. Vocal responses are useful when it is necessary to control for a lateralised response that is typically performed using hands or feet [56]. Vocal responses can be recorded using a microphone to allow off-line estimation of the participant's reaction times [57], particularly in the case in which speeded responses are required. When a hand or a foot is used for the response, inter-hemispheric interactions between sensory, motor and sensorimotor brain areas between the two hemispheres [58] should also be considered to avoid potential confounds [59]. This problem can be overcome by using different effectors, for example by using one finger for the stimulation, and a different finger for the response [39].

The outcomes of somatosensory TES and TMS experiments are primarily behavioural data, except for motor evoked potentials (MEP) when TMS is near motor cortex, or when neurostimulation is coupled with other neuroimaging techniques such as EEG, MEG, fMRI (discussed in Section 3.2.3 below). The dependent variables typically considered are of accuracy, reaction times, d-prime (i.e., sensitivity) or criterion (i.e., decision processes). We describe some of these measures here, but see Chapters 1-10, this volume, for a wide range of somatosensory variables). Here we just want to point out the critical role played by the decision criterion in tactile

neurostimulation experiments (this logic certainly applies beyond the tactile task context).

We have found that neurostimulation directly affects participants' responses, changing their decisional criterion. The mere presence of neurostimulation (e.g., TMS over the scalp, regardless of the site) increased participants' inclination to say that a tactile stimulus was not present. In theory, the decision criterion is independent from participants' sensitivity [33], although in practice they often co-vary. If signal detection theory (SDT) approaches are not adopted during certain tactile neurostimulation tasks, it would be very difficult to interpret the results where both the decisional and perceptual components are blended. Therefore, it would be a beneficial practice to include such measurements, whenever possible, in all relevant TES and TMS studies, particularly, when a one-interval design is used (Note 4.3.).

3.1.4. Output from motor cortex stimulation

Motor responses (MEPs) are very commonly recorded during TMS experiments when the motor cortex is stimulated. However, it is less common practice to record them when other brain areas, such as the somatosensory cortices, are stimulated. We argue that such measurements are very important in the context of somatosensory TMS, given the anatomical and physiological proximity of somatosensory and motor cortices, and the significant interactions between the two systems. Indeed, MEP recordings can be used as a tool to monitor online M1 activity while the somatosensory cortex is stimulated. This has two main advantages: first, it allows researchers to correlate these physiological data with behavioural performance in the tactile task, potentially on a trial-by-trial basis, to rule out possible confounds arising from accidental stimulation of M1 while targeting S1. Second, the presence of MEPs while stimulating S1 may provide an indirect indication of the

accuracy and sufficiency of the targeted S1 stimulation. Indeed, given that these two brain regions are very close anatomically, the lack of any MEP responses while stimulating S1 may suggest that the site selected may not be ideal (e.g., far from both M1 and S1), or that the TMS intensity is too low (Note 4.4.).

Several other methods can be used to generate and study the indirect effects of neurostimulation on somatosensation. Specifically, these approaches include short- (SAI) and long- (LAI) afferent inhibition. In a typical afferent inhibition (AI) protocol, a single [60] or multiple [38] cutaneous stimulation (typically electrical) is followed at a certain delay by TMS of the motor cortex. These cutaneous stimulation designs have been shown to modulate the amplitude of the MEPs evoked by TMS over M1 [61–65]. SAI and LAI are two dependent phases of inhibition that occur when there is a short or long interval between the afferent input and the TMS pulse. That is, activity of neurons in M1 changes in response to peripheral stimulation [66] with a decreased [67] corticospinal excitability in an interval included between about 20ms and 50ms (i.e., SAI) and 200ms and 1000ms (i.e., LAI) following median nerve (MN) or digit stimulation [68]. Note that the specific timing within these ranges at which the inhibition emerges and the magnitude of the response depends on the stimulated nerve or digit.

Somatosensory neurostimulation paradigms have been used as a tool to study sensorimotor control in healthy humans, and sensorimotor function in disease and following neurological injury. This is possible because specific sensory and motor pathways are involved in the generation of the phenomena (for a comprehensive review on the topic see [68]). The emergence of SAI and LAI is affected by factors such as the intensity of the cutaneous stimulation and the TMS, and the particular muscle recorded. A novel protocol called dual-site TMS (ds-TMS) has been

developed relatively recently. In this method, ds-TMS is used to investigate intra- [69] and inter-hemispheric [70, 71] interactions between the somatosensory areas and the primary motor cortex (M1). When designing this type of experiments is also recommended to possibly test participants at similar day time as circadian rhythms in hormones and neuromodulators can affect neuroplasticity [72].

3.1.5. Participant debriefing

It is always good and informative practice, after the testing phase, to debrief the participants. This is particularly critical in the context of neurostimulation, in at least three different respects. First, establishing whether the stimulation caused more than a reasonable temporary discomfort, if present. Second, it is beneficial to establish through a series of open questions about the participant's level of awareness of the target and control neurostimulation sites (i.e., for TMS studies) or montage condition (TES) during the experiment. Third, to assess whether there was a certain condition in which they experienced a greater discomfort or any general problems in paying attention [73] to the task compared to another condition or phase of the experiment. Ideally, the different neurostimulation conditions should be comparable in terms of their side effects, obviously excluding the no-TMS condition. Paying attention to what your participants experience is likely to improve recruitment and statistical power (Note 4.5.).

3.2. Neurostimulation type

3.2.1 Transcranial electrical stimulation (TES)

As mentioned above, there are three main types of low intensity TES: transcranial direct current (TDCS), alternating (TACS), and random noise stimulation (TRNS). In TCDS, a current is applied between two electrodes and has been argued to induce long-lasting changes in the brain. This technique may work by modulating brain

excitability via membrane polarization. In TACS, a current is applied across the scalp which reverses polarity, for example sinusoidally, at a certain frequency. TACS is supposed to interact with and affect ongoing electrical rhythms in the cortex. Finally, TRNS is an alternating current oscillating at random frequencies delivered through the scalp. For a comprehensive description of these methods see [74]. These techniques are capable of inducing changes in the electrical activity of neurons by altering their membrane potentials and in turn changing their synaptic efficiency [7, 75]. There are several standard protocols used to interfere with brain activity using TES, however, its effect is the result of different interacting factors that go beyond the protocol, for example the physiological status of the participant [76] and the type of task used. In general, and similar to TMS, there are two ways in which TES can be applied, before the participant performs the task (offline) or while the participant is performing the task (online). Several different protocols can be applied, and comprehensive guidelines, including safety and ethical considerations is provided by Antal and colleagues [77].

Several studies have used TES with the aim of modulating neural activity of the somatosensory system, and in turn participants' performance in tactile tasks [47, 78–82]. However, results regarding the effectiveness of such neurostimulation interventions on the somatosensory system are quite mixed. For instance, Saito and collaborators [47] compared the effects of TDCS, TACS and TRNS protocols on inhibitory circuit activity in the primary somatosensory cortex while participants performed tactile spatial discrimination tasks. They found that, with the neurostimulation parameters they used (e.g., stimulation frequency at 140Hz) anodal TDCS decreased the N20 component of the SEP and TRNS increased the N20 component. No effects were reported after TACS stimulation. More studies that systematically investigate the effect of these types of neurostimulation, using different

protocols and parameters, are needed to clarify the effectiveness of such techniques.

3.2.2. Transcranial magnetic stimulation (TMS)

Just as in TES, several different types of TMS protocols have been used to stimulate the somatosensory cortex [83]. Here, we will briefly describe the most popular ones. TMS can be applied with one pulse at a time, known as single-pulse TMS (spTMS); in pairs of pulses separated by a certain (short, e.g. 1-100ms) temporal interval, known as paired- or dual- pulse TMS (dTMS/pTMS) [33]; or in trains of three or more TMS pulses, known as repetitive TMS (rTMS). Repetitive TMS can be given at a constant frequency (e.g., 'slow' at 1Hz, 'rapid' at 10Hz), or in more complex temporal patterns, such as in theta-burst TMS [84].

TMS can also be applied either online or offline. In online protocols, TMS is applied while participants are performing the task, for example just before after stimulus presentation and/or during response generation [85], whereas offline TMS protocols apply TMS before, but not while, participants perform the task [86]. Typically, rTMS is used in offline protocols in which the effect caused by TMS is assumed to last after the end of stimulation, perhaps as long again as the duration of the TMS (e.g., TMS applied for 20 mins may have 20 mins after-effect). Such protocols are widely applied for studying the somatosensory system, however, a comprehensive list of available protocols can be found in the international TMS safety guidelines [32, 83]. The current developed and used protocols are considered both effective and safe in terms of the stimulation parameters, therefore, these guidelines should be carefully followed. In Figure 5 we depict some of the most common TMS protocols used to stimulate the somatosensory system.

[FIGURE 5 ABOUT HERE]

3.2.3. TES/TMS combined with other neuroimaging techniques

Neurostimulation of the somatosensory system has been used in combination with other neuroimaging techniques such as EEG, MEG and fMRI. Such neuroimaging techniques won't be discussed here in detail (see Chapters 17-19, this volume). A few studies have attempted the concurrent use of TMS and fMRI techniques [87], however, such approaches, probably due to technical challenges, are not widely used. More common is to use TMS offline (e.g., rTMS) before participants undergo fMRI scanning [88]. Such an approach allows researchers to estimate the effects of TMS on blood-oxygenation dependent (BOLD) signal changes across brain areas including and beyond the site(s) stimulated. Combining TMS with EEG is becoming more popular to evaluate the effects of TMS, and for studying the mechanisms behind the modulatory effects of TMS on cognitive and sensorimotor processing [89, 90]. These types of concurrent TMS-EEG studies have been also growing in the tactile domain, and it seems promising for understanding the effects of TMS on the somatosensory system [91, 92]. TES has also been used successfully in combination with EEG and MEG [93].

3.2.3 Peripheral nerve magnetic stimulation

The somatosensory system is different from all other sensory systems in that the afferent nerves are distributed throughout the peripheral nervous system and the body. This gives the somatosensory researcher unique access to the peripheral nerves, which is taken advantage of most spectacularly by microneurography (Chapter 15, this volume). While the peripheral nerves have very often been stimulated to study the responses in the brain (i.e., the somatosensory evoked potential, SEP, Chapter 19, this volume), the peripheral nervous system has not been much exploited as a site of electrical and magnetic interference with somatosensory

perception. It is remarkable that there are so many studies of the effects of brain stimulation on somatosensory perception [27], but only two that we know of using magnetic stimulation of peripheral nerves [33, 94]. Stimulation of the peripheral nerve provides several advantages over stimulation of the brain, which we describe here in the context of interfering with tactile perception on the fingertip.

First, between the index fingertip and the brain there are perhaps 100cm of peripheral nerves that can be targeted – along the arm, in the brachial plexus, even in the cervical spine and midbrain. Second, when the median nerve passes over the wrist and elbow joints it is pushed very close to the surface. This allows precise electrical and magnetic stimulation at the lowest-possible intensity to affect the nerves. Third, successful nerve stimulation can be reported directly on a trial-by-trial basis by the participant. Nerve stimulation even at low intensities evokes a prominent tingling sensation up and down the arm; at higher intensities, stimulation of motor nerves also evokes objective responses in the EMG as well as visible twitches. The tingling side-effect of stimulation can be used by the participant, inadvertently or on purpose, to monitor and control coil position. Fourth, and perhaps most importantly, stimulation of the peripheral nerve is, in our experience, much more tolerable than brain stimulation and poses fewer risks. Together, these advantages make peripheral nerve magnetic stimulation (PNMS) an ideal method for pilot-testing all potential brain stimulation studies of somatosensory perception.

More than being just better in principle or in participant comfort and safety, PNMS works extremely well. Unlike several of our attempts at interfering with tactile perception using TMS, every experiment we've done with PNMS has worked as expected – stimulation over the median nerve impairs all aspects of task performance for tactile stimuli presented at the fingertip [33]. Stimulation impairs performance on

tactile detection and discrimination, in both one- and two-interval experimental designs, and with both single and double-pulses of TMS. Increasing stimulation intensity worsens tactile detection thresholds in a predictable manner. Stimulation during presentation of the tactile stimulus has a greater effect on perceptual thresholds than stimulation before or after stimulus presentation. Stimulation of the median nerve has a greater effect on index finger perception than stimulation of the ulnar nerve, despite similar side-effects. These results will be reported elsewhere. Based on our experience of PNMS, we strongly encourage and advise all somatosensory brain stimulation researchers to test and develop their protocols first on the peripheral nervous system – if you can't make your protocol work well there, what hope do you have when stimulating the brain?

3.3. Scalp test and control site localization

Here, we will discuss how to localise the test site and an appropriate control site, with a focus on stimulation of the somatosensory cortex. Several approaches have been used to identify the location on the scalp to target a specific brain area both for TES and TMS. When the location is an area beyond M1, including for S1, the task is quite complex because of the lack of direct and objective consequences of S1 stimulation on a trial-by-trial basis. However, although some studies have reported that TMS over S1 may elicit sensations, such phenomena have not received systematic investigation [49, 95–98]. It is therefore difficult for the researcher to establish whether the coil is correctly positioned to appropriately affect S1 activity as desired. Identifying the correct site of stimulation on the scalp is a fundamental prerequisite that will affect all subsequent steps of the experimental procedure. We will briefly describe the three most common approaches used to overcome this problem and identify S1 on the scalp (for a systematic review on this topic see [27]).

A widely used approach to target the hand area of S1 is a heuristic that consists in finding the location of a particular representation in M1 (estimated through MEP responses in a hand muscle) and then moving the coil posteriorly by about 2cm (i.e., in a range between 1 and 4cm) and/or until a motor response (i.e., MEP) is no longer detected [27]. This strategy is problematic for several reasons. First, given that S1 and M1 are anatomically contiguous in the brain, moving away from M1 implies that researchers are likely also moving away from S1. That said, it is generally very difficult to stimulate S1 and M1 independently. Activity of S1 directly affects M1 and vice versa [38, 68] given that the two systems communicate via a network of extensive connections [99–104], and motor cortex cells respond directly to sensory stimuli [105–108] as sensory cortex cells can control motor behaviour [109]. In order to mitigate such circumstances it may be beneficial to monitor the MEP responses and to test whether it correlates with the effects of TMS on tactile perception [33]. You may also be able to use different coil orientations to stimulate S1 as compared to M1 [110, 111]. Indeed, avoiding M1 stimulation may significantly reduce the probability of directly stimulating S1. Second, and critically, the hand area of S1 is not posterior to the hand area of M1, it is approximately 2cm lateral [27] [33,37].

A second localization approach, especially in the earliest TMS studies that stimulated S1, consists in positioning the coil over the C3/C4 electrode in the 10:20 system coordinates [23, 112–114], or moving posteriorly halfway between C3/C4 and P3/P4, to CP3/CP4, or moving ~2cm posterior to C3'/C4'. The rationale behind this specific positioning can be traced back to earlier evidence suggesting that the C3/C4 location lay approximately over the central sulcus, or slightly posteriorly [112, 115]. However, different studies have attributed a different anatomical location to the C3/C4 position, either that of the S1 or M1 hand area [42, 95, 116, 117]. Holmes and Tamè [27] systematically reviewed this literature and it seems that there was no general

agreement among researchers regarding the actual location of S1 and M1 hand area relative to the C3/C4 electrodes on the scalp. Therefore, this strategy also seems not to be an optimal approach to correctly identify S1 at the scalp level. Systematic review and meta-analysis of all the available brain imaging and neuronavigation evidence, however, is much less ambiguous [37].

A third strategy that can be used to localize S1 is to take advantage of anatomical and functional data coming from structural and functional magnetic resonance (fMRI) imaging. In particular, some studies have used a single, standard head and brain template scan and registered each participant's head to the template [118]. Others have used structural scans of each participant (this reduces the risk of misplacing the coil due to inter-subject variability) [119], and yet other studies used individual structural scans in combination with individual functional MRI data [33, 120]. This last approach arguably provides the best estimation of the S1 location (see Figure 6). Overall, we strongly recommend using - and reporting - all available sources of evidence to target the S1 location optimally: accurate head and scalp measurements to find the vertex and C3/C4 locations; functional localisers using TMS to locate the optimal M1-hand area; MRI data where available, ideally both individual functional and anatomical scans. If neuronavigation is available, then a carefully-coregistered scan of a head template may be sufficient. At the very least, the C3/C4 electrode location is, on average, very close to the representation of the index finger in S1 [27, 37].

[FIGURE 6 ABOUT HERE]

Once the target brain area has been established, the next important step is to identify a control area to stimulate which is not involved in the processes we are aiming to

study, yet at the same time is comparable in terms of the peripheral auditory, cutaneous, and deep sensations and movements induced by the stimulation (TMS or TES). Ideally, the participant will not be able to discriminate the different stimulation sites by how they feel on the head. For an appropriate choice, there are a few critical aspects that should be considered. We will start by discussing this in the context of TMS.

First, despite the fact that newer TMS devices are becoming more and more precise in terms of localization and capability to selectively stimulate a certain brain area [32], TMS procedures can still be quite uncomfortable and even painful. Importantly, the level of annoyance and/or discomfort is not the same across different locations on the scalp. Instead, it varies strongly and systematically as a function of scalp location [121], as well as the intensity [122] and type of protocol with which TMS is applied. Typically, superior and posterior scalp locations are not associated with significant discomfort, whereas, frontal and temporal locations can cause moderate to high discomfort and pain [123]. It has been shown that the TMS side effects affect some aspects of task performance such as participants' accuracy at the task [124] as well as their reaction times [123]. When selecting a control site, it is therefore critical to find a location that, in addition to being suitable for the process that is studied, is also comparable in terms of side effects with the target site (Note 4.6.). In particular, when participants are performing a tactile task, it is critical to monitor and balance the tactile sensations generated by the TMS or TES on the scalp surface of different sites (Note 4.7).

Recently, Meteyard and Holmes [121] developed a 'scalp mapping of annoyance ratings and twitches' caused by TMS in humans (TMS-SMART, [121]). They systematically mapped the degree of disturbance caused by TMS at 43 locations

across the scalp. Participants were asked to perform a choice reaction time task while TMS was applied on different locations. After each five trials of the task per TMS coil location and orientation, they provided ratings of annoyance, pain and muscle twitches. The resulting maps can be a very useful tool to assess the best matching location of a control site for any given target site in a study. The authors provided the data as an online resource that can be freely accessed and used (https://tms-smart.info). To ensure that the experimental results derive from modulation in the brain active caused by the TMS or TES, and not simply because of peripheral side-effects [3, 125, 126], additional types of control are also available. For instance, the stimulation location could stay the same, but additional behavioural tasks and conditions can provide a task-based control. The least useful or powerful control condition is one in which TMS is either not present, or a 'sham' form of TMS is given. Such sham TMS needs to be proven to be effective on a location-by-location basis before it can be taken as a strong control condition. TMS over the vertex is commonly used, but this can only be a good control for other midline coil locations that have almost no side-effects (i.e., for very few locations).

One final factor that should be considered when stimulating the somatosensory cortex with TMS or TES is the feasibility of reaching the desired body part's representation in the somatosensory cortex. As we have seen from the mapping studies described in the first section of this chapter, the representation of body parts in the homunculus follows a topographic distribution over primary somatosensory cortex. Such organization makes some body parts easily accessible in terms of the capability of TMS to interfere with the relevant cortical activity, and some others more difficult to access. For instance, body parts such as the genitals, feet and toes, at least according to the traditional homunculus, may almost be out of reach, at least with the current TMS devices due to their anatomical location in S1. Moreover, other

sensory areas such the secondary somatosensory cortex (S2), may also not be easy to stimulate, though there are some examples in the literature in which stimulation of this area has been done [85, 127–129].

4. NOTES

In this section we will describe some methodological advice that can be useful to refer when conducting somatosensory TES and TMS experiments.

4.1. Interactions between neurostimulators and tactile stimulators

Neurostimulation devices produce large transient electromagnetic impulses (TMS) or constant or time-varying electrical currents (TES). These electromagnetic disturbances can travel relatively unimpeded around the lab. Just this week we set up a MagStim BiStim TMS system about 30cm from a National Instruments Card which was passing an analogue signal to an Oticon virbotactile stimulator, via a small car stereo amplifier. Two TMS pulses were presented on every trial of the experiment, along with a vibrotactile target in half of the trials. The participant (NH) could not feel any of the target stimuli, and instead only felt the vibrator click with every TMS pulse (confirmed by holding the vibrator to his ear). The solution was to move the TMS system to the other side of the laboratory (~2m away), away from whichever sensitive electrical point of our setup (likely in the NI Card connector interface) was generating the artefact.

We strongly advise researchers to assume that nothing in your setup works correctly until you can prove it! Critically, comparing a vibrotactile task with TMS or TES to a task that has no TMS or TES (or when the neurostimulation system is away from the body and less likely to produce electrical artefacts on the body) is a very poor way to ensure that your experiment is working correctly. Make sure to rule out all potential

artefacts as explanations for any apparent interference in tactile perception. It is not your reviewers' or readers' responsibility to control your experiments – it is yours.

4.2. Choosing a tactile task

In the experiment referred to, we deliberately made the task complex – the standard frequency was 200Hz and presented on the index finger, the comparison was higher or lower and presented on the middle finger. This task required participants to attend to two fingers, in sequence, and to focus on vibration frequency differences. We chose a complex design because two earlier experiments in this series, both using a two-interval task, had failed to find any effects of TMS over S1 on tactile detection. By adding both frequency and location components to the discrimination task, we hoped that S1 would be more involved in the task, and that TMS would then be effective. This hope was successful, although we do not know which task component was critical. In our experience, neurostimulation studies need to be designed to be as powerful as possible on the first attempt (e.g., high intensity TMS, difficult task, strong control conditions, accurate neuronavigation). First, because neurostimulation can be uncomfortable and comes with some risk for our participants – it is our duty to make the experiments as good as they can be. Second, because neurostimulation studies often just don't work. By attempting to maximise the involvement of a brain area, and by stimulating that brain area precisely, both in location, and at the time it is likely to be involved in the task, we can improve our chances of learning something – anything – from the study.

4.3. Neurostimulation likely changes participants' decision criterion

When estimating the effect of the TMS applied on the somatosensory cortex the main measure is participants' task performance and possibly reaction times. When participants undergo neurostimulation, in addition to the well-known perceptual

changes that the intervention can generate, there may be also changes in the criterion used to respond. Indeed, it may be that the simple presence on the scalp of the TMS or TES is altering the decisional criterion that participants decide to adopt in responding to the task – e.g., becoming more conservative or liberal in deciding whether a stimulus has been felt or not. Therefore, the outcome of participants' performance may well reflect a combination of both their perceptual sensitivity and their decision criteria used to respond. To overcome this limitation, we suggest whenever possible, to adopt an approach that consider such events. A useful approach is to apply the signal detection theory to analyse the data that allows an estimation of both potential changes in perceptual sensitivity and decisional criterion.

4.4. Neurostimulation in relation with motor evoked responses

Determining the motor threshold is an important component in any TMS experiment, as this parameter is often used to determine the intensity of the neurostimulation. Therefore, care should be taken to assess threshold in an efficient and effective manner. The excitability of the corticospinal tract is often taken as an index of the excitability also for stimulating other brain areas and pathways. This is a sensible thing to do, and a universally accepted protocol, however, excitability of other brain areas may not be the same as the motor cortex. At least, it may provide a good general estimate of scalp-to-brain distance for your participant. Such an approach is probably primarily dictated by the fact that the motor cortex is the only brain region in which it is possible to have a direct and relatively simple physiological read out of excitability in the MEP.

As specified elsewhere in the chapter, when stimulating S1 it is recommended to monitor the output from motor cortex responses during TMS sessions, as S1 stimulation can cause direct and/or indirect changes in the motor excitability. This is

particularly critical when a brain region away from S1 and/or M1 is used as a control site (e.g., SMG), as such regions will likely affect motor cortex excitability to a lesser extent. MEP variability should also be monitored across sessions if the experiment is performed in several sessions across days, weeks or months. When stimulating M1, it is generally recommended to orient the TMS coil so that the induced current runs posterior-to-anterior at about 45 degrees to the midline (i.e., perpendicular to the central sulcus). However, for S1 stimulation of the fingers (i.e., index and middle fingers) we found that an orientation of **90 degrees** seems to be better in terms of producing fewer MEPs and fewer side effects (e.g., jaw twitching) whilst also being effective in interfering with task performance, and by inference, S1 activity. Not that this orientation (90 degree) differs from what is standardly recommended for the stimulation of other locations (brain areas) on the scalp.

4.5. Neurostimulation and the participant sample size

Similar to other psychophysical experiments, it is critical to have a comparable number of participants tested for the control and experimental group/conditions, also enough to get good counter-balancing, but we have found that sometimes more is worse. As participants are recruited for neurostimulation studies, we find – anecdotally – that well-motivated, or ‘good’ participants often turn up early during recruitment. As the study continues, and the recruitment pool of participants willing to undergo neurostimulation decreases, it becomes harder to find experienced, motivated participants who are comfortable with neurostimulation techniques. There may be, therefore, a trade-off between sample size and data quality – uncomfortable participants do not perform somatosensory tasks well. In theory, statistical power increases proportional to the square-root of the sample size (i.e., to double power, you need to quadruple the sample). We suspect that this theoretical law of diminishing returns is even worse in practice, because better participants tend to be

recruited earlier. In general, we recommend improving the statistical power of your study by focussing on increasing the effect size – more trials, better controls, stronger stimulation – than on the sample size. Of course, you won't know if this strategy has worked until you run a well-powered replication of any of the effects that you find!

Counterbalancing is particularly important for short experiments, or those with small sample sizes. It is also a good practice to always consider the participants' perspective on the task. Indeed, we should be aware that they can be anxious, and not familiar with neuroscience methods, and that we are stimulating their brains directly. We have found several participants arriving at the experiment not having read the Information Sheet, seeming surprised that their brains will be stimulated. These participants did not complete the study. Particular care must be taken in making participants comfortable before, during and after neurostimulation. This can be done by describing to them the different phases of the experiment as well as the potential sensations/discomfort that these techniques may cause in a calm and sensible manner. The experimenter may need to stop an experiment for 'technical reasons' when their participant is clearly not comfortable with the procedures, even if they state verbally that they are happy to continue.

4.6. Neurostimulation control locations for somatosensory stimulation

A great challenge to apply neurostimulation on the somatosensory cortex (e.g., S1 and S2) is to correctly identify the target site (e.g., S1) and a comparable control site on another region of the brain. The target location is challenging as there is no direct physiological read out when stimulating the somatosensory cortex. The best practice is to use a neuronavigation device that can provide anatomical and possibly functional information of the correct location to reduce the probability of site errors [137]. As a control site, an area that is not involved in the perceptual and/or cognitive

process under study should be identified also assuring a similar grade of side effects for the target and control site [121]. The vertex should be avoided as a potential control site given the absence of major side effects/cutaneous sensations that such location when neurostimulated is generating. Remember that neuronavigation is only as good as the images and human operators that are used with it. We find that the only way to minimise error in coil positioning is to take multiple head measurements, to record everything, and always to be wary of human error. Measure twice, stimulate once!

4.7. Neurostimulation as a somatosensory stimulus

Remember that TES and TMS are themselves multisensory stimuli – the electrical and magnetic field can induce current in muscles, nerves and receptors [138]. They may contract muscles, stimulate free nerve endings and peripheral nerves, contract blood vessels. TMS also creates a loud sound. When close to the eyes, retinal stimulation may directly produce flashes of light; when close to the ears, muscular contractions may move the eardrums and the eustachian tube (personal experience!). If all of these side-effects are matched by location- or task-based control conditions, a clean and simple experimental design may be possible. But, specifically in somatosensation, the peripheral side-effects of stimulation may act as masking stimuli, interfering with touch perception not due to stimulation of the brain, but to stimulation of the skin, nerves, and muscles. Note that there have been attempts to reduce scalp discomfort and tactile sensations by treating the locus of stimulation, before the TMS was applied, using topical lidocaine/prilocaine cream [10], though this is not a common practice. Did TMS interfere with somatosensory perception only because of its effect on S1, or also due to its effect on the scalp? It is each researcher’s task to answer this question and rule out trivial confounds.

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FIGURE CAPTIONS

FIGURE 1. A figure-of-8 coil (black) positioned over the primary somatosensory cortex (orange) in the left hemisphere. Note that in the image the scalp has been removed to better appreciate the TMS coil location relative to the brain area.

FIGURE 2. Neurostimulation hardware. (A) Magstim BiStim system, with two Magstim-200 magnetic stimulators. (B) MagVenture system, with one Butterfly figure-eight coil.

(C) NeuroConn tES device with a pair of rubber electrodes and sponge pads applied on a mannequin’s head using elastic rubber straps. (D) BrainStim tES device with a pair of rubber electrodes and sponge pads.

FIGURE 3. Typical neuronavigation system used to assist with TMS positioning. The subject is sitting down, wearing a cap to flatten hair and allow easy access to and marking on the head (A). The experimenter holds a TMS coil (B) in the left hand, and supports the subject’s head in the right hand. Behind the experimenter is a Polaris infrared camera which monitors the locations of reflective markers placed

on the subject's head and the TMS coil (C). On the right is a workstation (D) incorporating the TMS hardware (bottom) and the neuronavigation computer monitor (top). As the experimenter moves the TMS coil around on the subject's head, the MRI scan of the subject's brain is rotated accordingly, showing the intended target and/or trajectory of the TMS pulse (E). See also Note 4.6.

FIGURE 4. TMS over primary somatosensory cortex affects tactile detection in a task-dependent manner. A. Effect of S1 TMS on tactile detection in a one-interval forced choice ('yes'/'no') design, expressed in d-prime. B. Tactile detection thresholds from a two-interval forced-choice design, expressed in arbitrary units. Both experiments were done with dual-pulse (dp) TMS over SI and SMG. Results are redrawn from Tamè and Holmes 2016, Experiments 1 and 2, respectively [33]. TMS over S1 was effective only in the one-interval design, implicating different task demands.

FIGURE 5. Some commonly used TMS protocols while stimulating the somatosensory system with TMS. SAI, short afferent inhibition; LAI, long afferent inhibition. Single pulse TMS typically requires 5-10s intervals between stimulation. Dual pulse TMS may increase the effectiveness of TMS; the pulses could be 1ms to 1s apart (e.g., using the MagStim BiStim system). Repetitive TMS can be done 'offline' at low frequencies (1Hz) for up to 30 minutes before performing a task or with high-frequency patterned TMS, or 'online', with higher frequency (say, 5-20Hz) trains of pulses during task performance. TMS over the motor cortex can be combined with prior somatosensory stimulation in the short- and long-latency afferent inhibition methods (SAI, LAI) – prior tactile stimulation inhibits the subsequent output from motor cortex TMS.

FIGURE 6. Mean scalp locations for M1-FDI (red) and S1-index (magenta) locations, as used by Tamè, Holmes, and colleagues [23,33,37]. Also shown are scalp landmarks used in the 10:20 electrode positioning system. White circle: vertex, Cz; green circles: other scalp landmarks and electrode positions, including C3', often positioned as indicated, at 2 cm posterior to C3, although C3’ is also often described as halfway between C3 and P3, which is likely ~3.6 cm posterior to C3.