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Primer

Non-invasive Human Brain Stimulation in Cognitive Neuroscience: A Primer

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The use of non-invasive brain stimulation is widespread in studies of human cognitive neuroscience. This has led to some genuine advances in understanding perception and cognition, and has raised some hopes of applying the knowledge in clinical contexts. There are now several forms of stimulation, the ability to combine these with other methods, and ethical questions that are special to brain stimulation. In this Primer, we aim to give the users of these methods a starting point and perspective from which to view the key questions and usefulness of the different forms of non-invasive brain stimulation. We have done so by taking a critical view of recent highlights in the literature, selected case studies to illustrate the elements necessary and sufficient for good experiments, and pointed to questions and findings that can only be addressed using interference methods.

Introduction

Methods of non-invasive human brain stimulation are increasingly being used in the study of cognitive functions and promoted as a potential adjunct therapy in many psychological and neurological disorders. The volume of papers and the claims made in the realms of basic and applied research warrant close inspection of where the field stands, in terms of knowledge base, replication, physiological foundations, effect sizes, effect duration, experimental standards, applicability from the lab to clinical and other real world needs, ethics, and future possibilities. Several excellent primers exist on the basic physiology of human brain stimulation with reference to the motor system (Hallett, 2007), modeling (Bestmann, 2008), physiology and cognition (Dayan et al., 2013, Sandrini et al., 2011; Pasley et al., 2009), and safety (Rossini et al., 1994, 2015). This Primer will assume some familiarity with these papers to concentrate on questions specific to cognitive neuroscience. The first half of this Primer will deal with transcranial magnetic stimulation (TMS) and the second with the family of transcranial electrical stimulation methods (tES): transcranial direct and alternating current stimulation (tDCS and tACS), and transcranial random noise stimulation (tRNS). In this Primer, we have segregated these two classes of stimulation because of their different uses and effects; the first, in cognitive studies at least, being suprathreshold stimulation to disrupt ongoing activity, and the second mainly being neuromodulatory approaches to induce plasticity. TMS is used in both these approaches whereas tES is mainly limited to the second of these. Where TMS and tES are used in neuromodulatory approaches, the mechanisms and therefore results may be different. The Primer is not intended as a comprehensive survey, but as a guide to the important issues in current use. We have therefore tried to refer, wherever possible, but with inevitable, necessary exceptions to work published in the past 5–10 years.

Transcranial Magnetic Stimulation in Cognition

TMS in cognitive studies has several solid foundations. In the sensory domain, for example, the effects of V5/MT TMS on the perception of movement has received many between-laboratory replications (e.g., Ellison et al., 2007; Tadin et al., 2011; Wokke et al., 2014). The effects of TMS on language functions have also proved to be robust across laboratories and effects (e.g., Carreiras et al., 2012; Duncan et al., 2010; Papeo et al., 2015; Sliwinska et al., 2012, 2014, 2015), and the same applies in the study of the perception, preparation, and production of action (e.g., Buch et al., 2010; Catmur et al., 2011; Duque et al., 2013; Neubert et al., 2010; 2011). In the study of parietal cortex and frontal eye field function, the literature contains many highly replicable findings (Ellison et al., 2007; Ellison and Cowey, 2009; Hirnstein et al., 2011; Lane et al., 2011, 2012, 2013; Ronconi et al., 2014; Mahayana et al., 2014; Studer et al., 2014). Perhaps the most significant development in recent years is the successful migration of TMS into the ventral stream, exemplified by a series of studies on the roles of the fusiform and occipital face areas, the lateral occipital area, and the extrastriate body area in face and body perception. Here too, there has been a quick spread of reliability and replication (e.g., Urgesi et al., 2004, 2007; Dzhelyova et al., 2011; Pitcher, 2014; Pitcher et al., 2007, 2008, 2009, 2011a, 2011b, 2012; Mullin and Steeves, 2011; Silson et al., 2013). While there is little doubt that some major findings of TMS are on solid ground (some days we can even look M1 physiologists in the eye), in other areas, it is worth revisiting the fundamentals.

Stimulus Timing, Frequency, and Localization

The use of TMS in studies of cognition has reached a considerable level of stability and maturity. In deciding what stimulation to use, however, an appreciation of what the different forms of stimulation buy the experimenter may be useful. TMS in

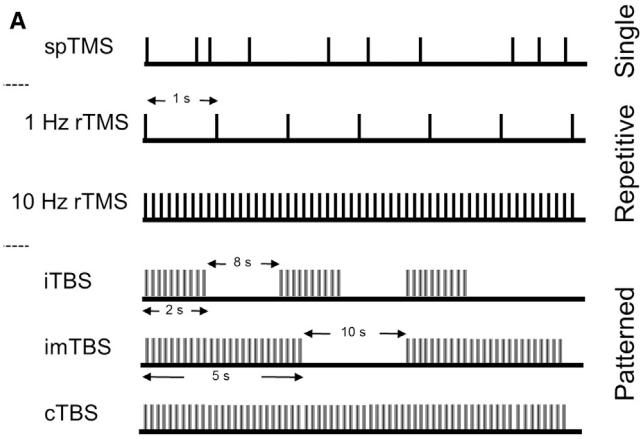

Figure 1. There Are Several Ways of Applying TMS in Cognitive Studies

TMS can be applied in single pulses (spTMS), multiple pulses, or repetitively (rTMS, applied in low or high frequencies). In theta-burst stimulation (TBS), there are three 50-Hz pulses applied at 5 Hz for 20–40 s (continuous TBS, cTBS) or each burst is applied for 2 s and repeated every 10 s for 190 s (intermittent TBS, iTBS). In a third variant, intermediate TBS (imTBS), 5 s burst trains are repeated every 15 s. These variants are guides rather than exhaustive, and not all possibilities are shown here. The choice of TMS application depends on the hypothesis and purpose of the experiment and knowledge of physiological responses. Figure from Dayan et al., 2013.

cognitive experiments can be delivered in single pulse, double pulse, on-line repetitive pulse, and off-line repetitive pulse. The latter has two main forms, theta burst and 1 Hz stimulation. Figure 1 shows these different forms. There are several important differences between these stimulation parameters. They do not have the same physiological effects, localization, behavioral effects, or safety profiles. The choice of which frequency to use depends on whether one wants to have excitatory or inhibitory effects and what kind of behavioral effects are being pursued. Single-pulse TMS has largely excitatory effects (but may interact with initial cortical state and task requirements to result in inhibition) (e.g., Waldvogel et al., 2000). Repetitive 1 Hz rTMS is widely used as an inhibitory intervention (Chen et al., 1997) and is classically associated with mimicking the effects of neuropsychological patients (e.g Guse et al., 2010). The use of higher frequencies, for example, 5 Hz and 10 Hz is widespread. The 10 Hz paradigm in particular is used in disruption studies (Walsh and Pascual-Leone, 2003), but it is not entirely clear whether the effect of frequencies of 5 and 10 Hz are predominantly excitatory or inhibitory. The effect partly depends on intensity, with low intensities tending to produce inhibition and higher intensities producing facilitation (Classen and Stefan, 2008). Theta burst paradigms are based on more solid physiological studies and continuous theta burst (see Figure 1) clearly has longer term inhibitory effects. Intermittent theta burst on the other hand tends to have excitatory effects (Huang et al., 2005). Theta burst paradigms have been used successfully in studying cognitive functions in a pure disruptive manner (e.g., Vallesi et al., 2007; Ko et al., 2008), but the specific use of the direction of the effects i.e., physiological excitation and inhibition, have rarely been exploited in a cognitive context (see Silvanto et al., 2007).

Single- and double-pulse stimulation yield information about the timing of psychological processes. The original, classic example of Amassian et al. (1989, 1993) bears repetition. Figure 2 shows the essentials of these experiments. Their elegance has not been surpassed. A more recent paper (Pitcher et al., 2008) shows the progression of use from rTMS to double pulse and captures all the control elements required to make meaningful inferences from neural interference studies. To investigate the role of the right occipital face area (rOFA) and right somatosensory cortex (rSC) in the detection and embodiment of facial expressions, rTMS was applied to these regions during perceptual discrimination of facial expressions. Using rTMS, they established the task selectivity of stimulation (expression discrimination, but not identity matching, was impaired), and location specificity (there was no effect of stimulation to non-face regions of somatosensory cortex). Delivering double pulses of TMS at different times, they established a temporal hierarchy in which the rOFA was important between 60 and 100 ms and the rSC at 100–140 and 130–170 ms. The novelty of this work was in establishing a role for non-visual cortex in early face processing, but here we wish to draw attention to the methodological integrity of the experiment in covering the key bases of a cognitive TMS experiment: task, location, timing, and controls on all three variables.

These two experiments teach us another lesson, that of the necessity (or not) of cortical localization of TMS. In Amassian's experiment, the localization, using a round coil, was basically limited to left versus right hemisphere. Whereas in Pitcher's experiment, an individual subject's magnetic resonance imaging (MRI) structural scans were normalized against a standard template and mapped against the Talairach coordinates for rOFA and the face or finger regions of rSC. Therefore in one classic study, anatomical specificity was paramount, and in another a relative mystery. Perhaps the most common question still asked about TMS in cognition is how can one be sure about the anatomical specificity and how important is it. There is no absolute answer. It depends on the question being asked and the power required in the experiment. Sack et al., (2009) compared the four methods of TMS localization by examining the effect of TMS over the right intraparietal cortex (rIPC) on numerical processing. To look at the importance of localization, they ran the experiment with (1) individual functional MRI (fMRI)-guided TMS neuronavigation, (2) individual MRI-guided TMS neuronavigation, (3) group functional Talairach coordinates, and (4) the 10–20 EEG position P4. All the methods were valid and accurate; the difference was an issue of power. When the region of the rIPC was identified based on individual fMRI coordinates, five subjects were required to observe a significant effect of TMS. When the TMS was delivered based on individual MRI coordinates, nine subjects were required. Thirteen subjects were needed to observe effects using group coordinates and 47 were required for the use of the EEG 10–20 site P4.

State-Dependent TMS

The Amassian et al. (1989; 1993) and Pitcher et al. (2008) experiments already discussed exemplify the value of task and location specificity. Another heir to Amassian's approach in cognition comes from Silvanto's long line of studies in state-dependent TMS. In a TMS experiment on the motor system, the experimenter knows the level of excitability of the motor cortex from

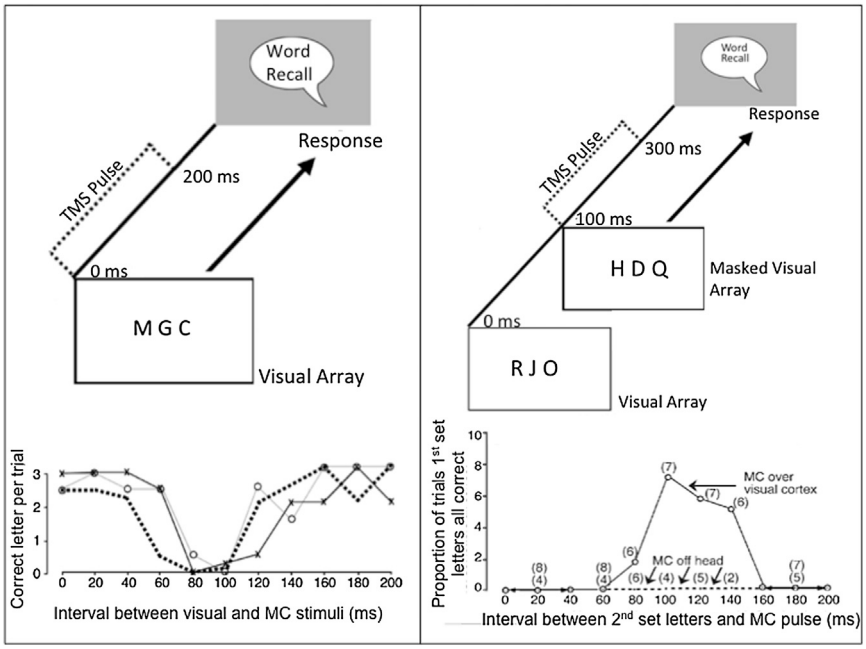

Figure 2. Amassian's Experiments
These experiments still stand as the classic example of an interference effect in TMS. Subjects were presented with trigrams and TMS was applied before or after onset of the visual stimuli. Masking of the first trigram produced by the presentation of a second trigram can be unmasked by TMS suppression of the second trigram. The proportion of trials in which the subjects correctly reported all the letters of the first trigram are presented as a function of the delay between the presentation of the second trigram and the TMS pulse. Numbers in parentheses are the number of trials with TMS and with SHAM TMS. MC, magnetic coil.

the motor-evoked potential (MEP). This is important because both between and within individuals, the effects of TMS will differ according to the state of excitation of the brain tissue being stimulated. In cognitive experiments, however, we have no measure of the state of excitation of the PPC, FEF, DLPC, OFA, angular gyrus, and all our other favorite sites. There have been attempts to define stimulation levels by measuring the thickness of the skull and the distance between the coil and the cortex and then stimulating at a percentage of motor threshold (Stokes et al., 2007), but distance is no guide to state and there is no way of calibrating other areas of the cortex with the state of M1 (e.g., Stewart et al., 2001). Silvanto's paradigm uses adaptation to influence the initial state of the region being stimulated. In his first study (Silvanto et al., 2007) subjects were adapted to color/orientation combinations for 30 s and subsequently asked to report the color of test stimuli (see Figure 3). TMS was delivered during the presentation of some of these test stimuli. Without the application of TMS, subjects reported test stimuli biased toward the complementary color of the adaptation, but with TMS over the visual cortex, subjects' reports were biased toward the original, adapting stimulus color. Thus, Silvanto was able to selectively excite and suppress anatomically overlapping populations of neurons outside the motor cortex based on the differential effects of TMS as a function of initial state. Subsequent uses of the state-dependent paradigm have proven its utility in several domains. Cattaneo et al., (2012) showed that adapting a region of the visual field led to impairments in mental imagery in that region of space and that this inhibition was unmasked by the application of TMS to occipital visual cortex. Moving up the processing hierarchy, Silvanto and Soto (2012) used state dependency to show that TMS facilitated performance on a visual short-term memory task. This is an important experiment because it provides a physiological rationale for an enhancement effect in a TMS experiment. The literature abounds with claims of enhancements, but few have any grounding in physiology (an issue to which we will return in the second part of this Primer when we discuss transcranial direct and alternating current studies). State dependency also applies to memory states as well as perceptual states. Soto et al., (2012) had subjects search for a target preceded by a color cue that had to be either remembered (memory condition) or attended to (priming condition). When TMS was applied during the memory state, performance was enhanced, and when TMS was applied during the priming state, performance was inhibited.

It is often assumed that state-dependent TMS is limited to the sensory domain because that is where adaptation is most commonly studied (Cattaneo, 2010; Cattaneo et al., 2008, 2009, 2010a), but it is worth examining one more example of state dependency at a higher level of psychological processing to complete the methodological picture. Cattaneo et al. (2010b) investigated category-specific neuronal representations in the encoding of tool words in the left ventral premotor cortex (PMv). Subjects were primed with a category name ("tool" or "animal") to adapt the PMv to one or other category of objects. TMS was then applied at the onset of a target word that was either congruent or incongruent with the primed category. As in the previous three examples, TMS interacted with the previous stimulus exposure and abolished the priming effect of the semantic category of tool.

Taking these and other state-dependent experiments together, one can see that state dependence is an important methodological factor in cognitive experiments. It is one area where TMS experiments could be improved if these adaptation paradigms were used more often because state dependency is the only physiologically generalizable explanation of TMS effects that can be tested in studies of cognition.

The mechanisms of state-dependent effects are currently understood as an interaction between the induced level of activity by the adapting stimuli and the electrical stimulus delivered by TMS. The best available explanation offered by Dayan et al. (2013) and Silvanto et al. (2008) is that TMS affects excitatory and inhibitory populations differently and that the effects of adaptation operate mainly on changing the suppressive effect of inhibitory populations. Furthermore, Pasley et al. (2009) have measured spike and field potential activity as a function of

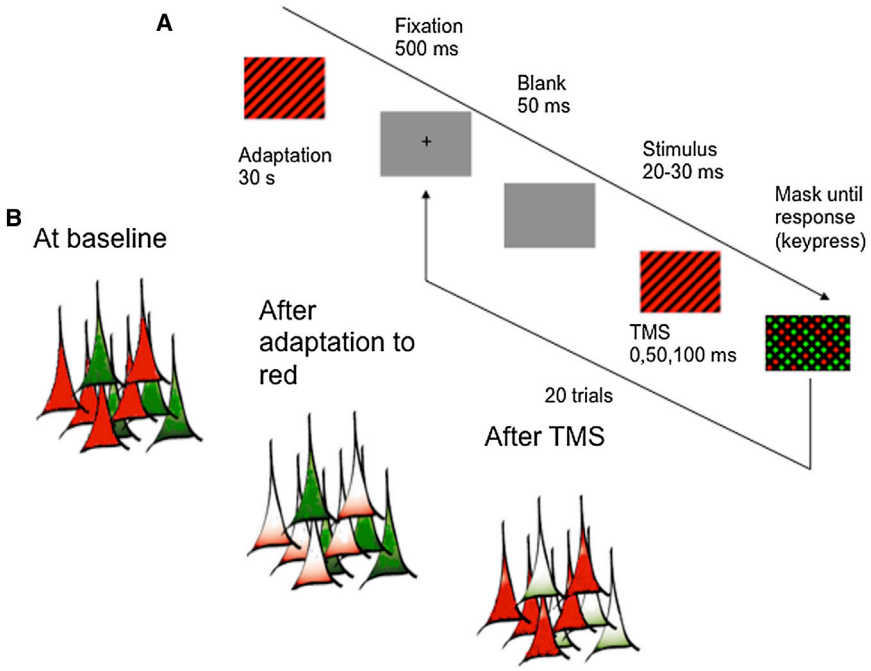

Figure 3. TMS Adaptation

(A) The TMS-adaptation paradigm. In this paradigm, visual adaptation is used to systematically manipulate the activation states of functionally distinct neural populations before application of TMS. In this study, subjects adapted to a combination of color and orientation. The adaptation period of 30 s was followed by 20 experimental trials in which subjects were asked to report the color of the test stimulus. Three TMS pulses were administered on each trial at stimulation onset asynchronies of 0, 50, and 100 ms after stimulus onset. (B) A schematic representation shows activation states of neurons tuned to green and red at various stages of the TMS- adaptation paradigm. At baseline, before adaptation, both neural populations are at their baseline level of activity. After adaptation to red, neurons tuned to green are more excitable than neurons tuned to red. This outcome of adaptation is reversed with TMS: facilitation of the adapted attribute is enhanced whereas detection of the unadapted attributes is suppressed. Taken from Silvanto et al., 2008.

spontaneous discharge rates. The variability and response is partly explained as state-dependent effects. More precisely, they conclude that higher activity before TMS predicts greater responses to the stimulation.

TMS Intensity

The choice of intensity in a cognitive experiment is not a simple matter. One has three options: to stimulate all subjects at the same absolute intensity, to stimulate all subjects at the same intensity relative to motor threshold, or to stimulate at an intensity modified by calculating the distance between the coil and cortex. The latter seems the most principled and quantitative, but following from our discussion of state dependency, we see that the extra precision is illusory. The extra work in obtaining an MRI of all subjects, recording MEPs, measuring the coil-cortex distance, and then calculating the ''correct'' value falls at the hurdle of verifying that cortical state in the motor strip means anything elsewhere in the brain (e.g., Stewart et al., 2001). Therefore, the choice is between an absolute or a relative value.

The problem here is that it is not obvious which method is optimal. We simply do not know what a given level of stimulation means in terms of cortical disruption. Models of TMS induction have not addressed state (but see Pasley et al., 2009). Using TMS alone, we cannot measure the initial state of cortex, although this has been achieved in studies that have combined EEG and TMS (e.g.: Taylor et al., 2010; Taylor and Thut, 2012, Romei et al., 2008a, 2008b). On this simple question—how much stimulation to deliver—rests a lesson about all TMS disruption experiments. The lesson is this: the value of the inferences made in any TMS disruption experiment is a function of the controls within that experiment. Within a given experiment, one needs to ensure that the level of stimulation given to the site of interest is the same as the level given to the control site. This means that a negative result may always be due to failure to excite the relevant neural population, but this is a welcome constraint on the degrees of freedom in an experiment. The TMS community can hide behind apparent specificity, but the fact is that stimulation intensity in the literature is largely a historical accident following from the use of a fixed stimulation level by a few laboratories and others using 120% of motor threshold (on the assumption that this relates to the safety guidelines published based on MEPs; Rossini et al., 1994, 2015).

The Choice of Control Site

Following from the points on stimulus intensity, the value of inferences made in TMS experiments is also affected by the quality of the control site. The traditional all-purpose control site is the vertex, but this is a control for noise, twitches, and some cortical activity. Better inferences about location specificity can be made if a control site is active, that is, part of the circuitry being tested. There are three main reasons for this. First, stimulating part of the same circuitry may reveal inter-aerial or inter-hemispheric interactions (Battelli et al., 2008; Plow et al., 2014; Duecker et al., 2013). Second, a control in the same circuit is often nearby on the cortex and is therefore a good control for scalp sensations and noise (Tadin et al., 2011). Third, it provides the most stringent test of claims of localization of function (Vangeneugden et al., 2014).

Combining TMS with Other Methods

The combination of TMS with other methods has remained the specialized pursuit of only a few laboratories, but gains have been made using TMS with both EEG and fMRI.

TMS and EEG

The combination of TMS and EEG has proved to be particularly useful in studies of vision and attention. TMS-EEG has been used to examine the effects of TMS on subsequent physiological activity and interactions between task-relevant brain areas, as well as to study the importance of pre-stimulus activity on perception of real stimuli or TMS-induced phosphenes. Since

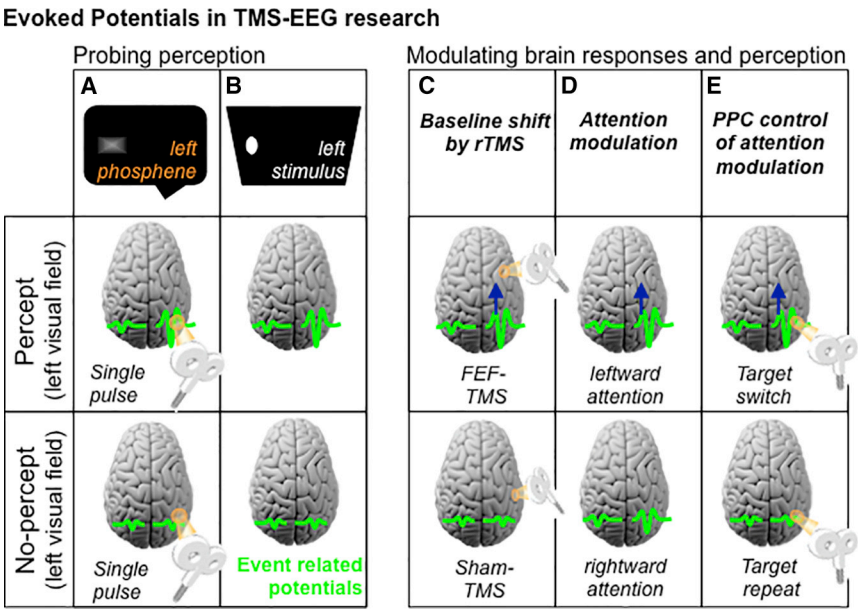

Figure 4. EEG and TMS

Evoked potentials triggered by visual stimuli or TMS pulses and their modulation by perception and attention.

(A and B) Probing Perception: the evoked potential elicited by (A) a TMS pulse or (B) a visual stimulus presented at detection threshold is modulated by perception (here examples are provided for left visual field stimuli only).

(C and D) Modulating Brain Responses and Perception: visual-evoked potentials can be modulated by (C) TMS over the frontal fields during covert leftward attentional shifts, producing a baseline shift in early visual activity, and by (D) the direction of covert attention.

(E) Right posterior parietal TMS in-between trials disrupts the visual-evoked potentials evoked by visual search arrays, but only when the attentional system needs to be updated due to a switch in target feature, again with corresponding behavioral effects. Figure from Taylor and Thut (2012).

Ilmoniemi et al., (1997) first established reliable TMS-EEG, the challenges have been conceptual more than technical, but progress has been made in several fields. Ilmoniemi et al., (1997) were able to measure the spatial and temporal spread of TMS-induced activity in task-free experiments. In cognitive experiments, there are now a number of high-quality studies using TMS-EEG to understand perceptual and task-dependent processes. Romei et al. (2008a) used TMS-EEG to demonstrate a causal relationship between cortical state prior to stimulus presentation and sensitivity to occipital cortex TMS that may induce phosphene perception. Subjects in a low alpha state were more likely to report phosphenes than those in a high alpha state before TMS was delivered. Other work has shown that pre-event cortical state is an important predictor of perception and other cognitive functions (cf Kounios and Beeman, 2009). Romei's work is one of the early papers in what has become an important stream of work (Hanslmayr et al., 2007; van Dijk et al., 2008; Romei et al., 2008b; Mathewson et al., 2011; Dugué et al., 2011). Given that the technical challenges are now routine, this is one area of TMS research that is ripe for many valuable new studies. Because of the temporal resolution of TMS and EEG, it is hard to think of any other way in which pre-stimulus state effects can be studied with more effectiveness.

TMS-EGG can also be used to measure the physiological effects of TMS-induced perception. Taylor et al. (2010) applied TMS to the occipital cortex and required subjects to report the presence or absence of phosphenes. The difference between post-TMS electrophysiological activity in visual cortex was seen only 160 ms (and later at 280 ms) after TMS (Figures 4A and 4B). This is important because it shows that the effects of TMS emerge earlier than comparable effects with real visual stimuli. In understanding the effects of TMS and using it to probe vision, studies like this, which allow us to account for the differences between the circuitries being stimulated by TMS and real visual stimuli, are essential.

There have been many other uses of TMS-EEG. The most important for our purposes is the use of TMS in its disruptive mode to record the subsequent effects on both behavior and electrophysiological activity. A good example of this is Sadeh et al. (2011), who presented face or body part stimuli to subjects and applied TMS pulses to the OFA or the extrastriate body area (EBA) in double pulse pairs at 60 and 100 ms post face/body onset. The authors obtained a double dissociation between these parameters: OFA TMS changed the N1 component for face but not body stimuli, and EBA TMS changed the N1 component for body but not face stimulation. We have selected this last example as a lead in to the next section on TMS and fMRI because it provides a beautiful example of how thinking through the temporal and spatial aspects of a problem in cognitive neuroscience can produce a body of replicable work, across different laboratories, which cannot be achieved with any single method.

TMS and fMRI

The combined use of TMS and fMRI comes in three main forms. TMS can be applied inside the scanner or TMS can be applied immediately before the subject is placed in the scanner. The two applications have been driven by different goals. Stimulation in the scanner is a technical and logistical challenge and these factors have tended to take precedence over the cognitive gains. To date, the experiments using TMS inside the scanner have either confirmed previous findings or reported activations distal from the site of stimulation (Bestmann et al., 2003; Baudewig et al., 2001; Bestmann and Feredoes, 2013; Sandrini et al., 2011; Sack, 2010). For example, Sack et al., (2007) applied TMS to the right parietal cortex while subjects were carrying out visuospatial tasks in the fMRI scanner. The work showed a clear right hemisphere frontoparietal network of areas associated with visuospatial functions. The corroborative, but valuable nature of simultaneous TMS-fMRI has been noted by Sack (2010) whose critique is particularly helpful in the context of cognitive neuroscience. The value of simultaneous TMS-fMRI rests on two main features: distal effects of the stimulation that may implicate effects caused by changes induced elsewhere

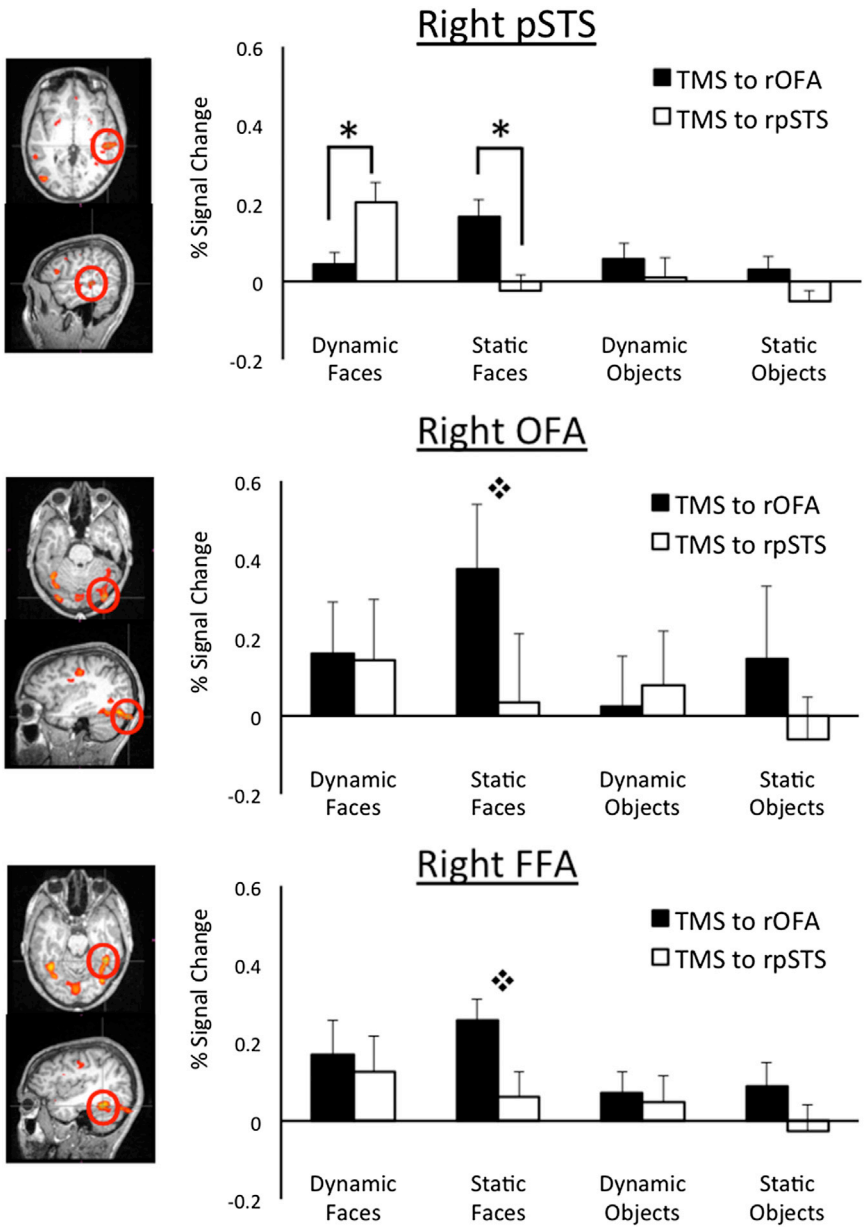

Figure 5. FMRI and TMS
The size of the TBS disruptive effect for all stimulus categories in the three face-selective regions of interest: rOFA, rFFA, and rpSTS. The TBS disruptive effect was calculated by subtracting the percentage signal change for each stimulus category after TMS stimulation of the rOFA and rpSTS from the pre-TMS baseline. Hence, a positive score denotes aTBS-induced reduction in the region of interest. In the rpSTS, TBS to rOFA reduced the response to static but not dynamic faces and TBS to the rpSTS itself reduced the response to dynamic but not static faces (asterisk denotes a significant difference in Bonferroni corrected tests). TBS delivered over the rOFA reduced the response to static faces in the rOFA and in the rFFA (diamond denotes a significant difference in Bonferroni corrected tests). Error bars represent SE. Figure from Pitcher et al., 2014.

of the ventral visual cortex that represent invariant dynamic information about faces. Pitcher's approach was to disrupt processing in the rOFA and right posterior superior temporal sulcus (rpSTS) using theta burst TMS prior to subjects being presented with dynamic or static faces. Theta burst stimulation of the rOFA reduced the neural response to both static and dynamic faces in the downstream face-selective region of the fusiform gyrus. However, theta burst stimulation of the rOFA diminished the activity in response to static but not dynamic faces, while stimulation of the rpSTS reduced the response to dynamic but not static faces. This dissociation showed that dynamic and static facial information relies on separate anatomical pathways. The value of this finding is that it is not confirmatory, but challenges current views of face perception, which suggest that all face information is relayed via the OFA. This study shows that some dynamic facial information indeed bypasses the OFA (Figure 5).

than the target site of stimulation, and state dependence (Bestmann and Feredoes, 2013). The latter is an important consideration (see section above) and has been well established in combined TMS-fMRI experiments. All the major issues in concurrent TMS-fMRI have been addressed in Siebner et al. (2009), a comprehensive consensus paper, and Bestmann and Feredoes (2013).

The second form of TMS and imaging is "off-line," in which the TMS is typically delivered before the subject enters the scanner. Because this method is released from the technical challenges of simultaneous TMS-fMRI, it has been more amenable to use with more complex cognitive designs and hypotheses. A recent example is that of Pitcher et al., (2014). This study addressed the issue of functional interactions between regions

The third form of integrating TMS and imaging is the use of TMS and ligand binding studies using positron emission tomography (PET). Strafella and colleagues have investigated anatomical connectivity and distal effects of TMS in ligand-binding PET studies. These studies have been able to show detailed cortical to subcortical distal effects. For example, stimulation of the dorsolateral prefrontal cortex (DLPFC) produced changes in dopamine release in the caudate nucleus or in the putamen after stimulation of the motor cortex (Strafella et al., 2001; 2003). In related studies, changes in subcortical activity, induced by motor cortex stimulation, have been shown to be different from changes produced by stimulation of the dorsal premotor cortex (PMd) (Bestmann et al., 2004; 2005).

Inducing Plasticity

The attraction of using TMS to induce cortical plasticity is that it both allows one to study behavioral change and to induce change that may have clinical value. Ridding and Ziemann (2010) have identified all the major factors in this field and rightly state that "even in neurologically normal subjects the variability in the neurophysiological and behavioural response to such brain stimulation techniques is high." Anyone proposing to induce plasticity using TMS or tES (see below for the tES section to this Primer) should begin with Ridding and Ziemann's survey. There are many factors that interact with brain stimulation including age, attention, sex, physiological state, genetics, and time of day. There are, however, some cognitive studies that are good examples of inducing plasticity. Following on from the Battelli et al. (2008) study of extinction in a normal population, Agosta et al. (2014) successfully alleviated visual extinction in a group of patients with chronic stroke by applying low-frequency TMS (assumed to be inhibitory) over the left, intact parietal cortex. The idea, using a "push-pull" model of inter-hemispheric interactions, is that by inhibiting the intact parietal lobe, the damaged hemisphere would suffer less from the inhibitory competition of the intact hemisphere.

Transcranial Electrical Stimulation in Cognitive Neuroscience

From our discussion of TMS, it is quite clear that the use of the methodology has reached a level of maturity signaled by standard procedures, replication, integration with other techniques and constraints on explanations of data. With transcranial direct and alternating current stimulation and transcranial random noise stimulation, the same claim cannot be made. There are three goals of using tES in cognitive studies: one is to explore the contributions of the areas to a function, the second is to understand the physiological mechanisms of these effects, and the third is to enhance cognitive function. The third of these has dominated the literature and the apparent simplicity of using tDCS, tACS, and tRNS has led to a large number of papers that make claims to enhance cognitive functions. An incomplete list of these enhancements includes mathematical cognition, reading, memory, mood, learning, sleep, perception, decision making, pain, motor skills, Parkinson's disease, autism, creativity, anxiety, dyslexia, migraine, motivation, cognitive decline, moral reasoning, etc. (Cappelletti et al., 2013; Flöel 2014; Brunoni et al., 2012, 2014; Dmochowski et al., 2013; Kuo et al., 2014; Cohen Kadosh et al., 2010; Snowball et al., 2013; Meinzer et al., 2013; Moreno-Duarte et al., 2014; Vicario and Nitsche, 2013; Zaghi et al., 2011; Shiozawa et al., 2014; Zhu et al., 2015; Horvath et al., 2015b). This may be a good time to remember Carl Sagan's warning that "Extraordinary claims require extraordinary evidence." Such a diverse range of claims certainly raises questions about the assumptions, measures, and quality of work in this field. In this Primer, we discuss tES as an umbrella term, but it is important to distinguish three types; tDCS, tACS, and tRNS. tDCS is mainly used to modulate excitation and/or inhibition, and to improve and in some ways alter cognitive functioning. tACS, on the other hand, is mainly used with the goal of changing oscillatory brain states. tRNS is used to induce excitation and resulting plasticity (Chaieb et al., 2011; Terney et al., 2008). We grouped them in this Primer for three reasons: the first is that the same equipment is used for all three forms of modulation and the understanding of the induced current changes is similar given that the delivery is by the same electrodes. The second is that while the literature in tDCS is large and growing, the literature is tACS and tRNS is limited. The third is that the range of cognitive functions and the approaches to these functions for which people use these three methods are similar.

The need for modeling of current density and distribution in tES is appreciated and sound attempts are being made to make links between the effects of tES in humans to in vitro and in vivo experiments in animals (Datta et al., 2011; Dmochowski et al., 2011; Bikson and Rahman, 2013; Edwards et al., 2013). These models have not yet begun to influence practice in studies of cognition; thus, we do not have a firm basis on which to interpret the physiology of experimental effects.

There are a number of simple questions that need to be asked in assessing papers using these techniques: what is an adequate control stimulation condition? What are the effects of the intensity of stimulation? What are the effects of montage placement? For simplicity, when making statements that refer to all three methods in this section, we will use the term "transcranial electrical stimulation" (tES).

Control Conditions in tDCS, tACS, and tRNS

The Four Cornerstones of Assumption: Polarity, Intensity, Duration, Montage

The Effects of tDCS Polarity. One of the features of the literature in tDCS cognitive studies is the implicit assumption that anodal stimulation is always excitatory and cathodal stimulation is always inhibitory (see Horvath et al., 2015a). Bestmann et al. (2015) have given a detailed account of why this cannot be the case. It is broadly true that polarity-dependent tDCS changes are directional; however, the effects are not uniform under the electrodes (Batsikadze et al., 2013) and interactions with different cell morphologies and cortical surface shapes create inhomogeneities that in turn change the net effects of stimulation (Bestmann et al., 2015). This is one reason to approach the link between assumed physiology and behavioral effects with caution. It is an important message of this Primer that the field needs to stop making naive one-to-one links between polarity and behavior.

The Effects of tES Intensity and Duration. Intensity and duration of stimulation are two further reasons to be less confident that tES is operating mechanistically in a push-pull way between excitation and inhibition. In cognitive tES studies, the modus operandi is to take the findings from MEP studies and assume that they transfer to regions outside the motor cortex, but there is a tendency to only take the findings that are easy to deal with. For example, if we consider stimulation intensity, many studies assume a linearity of stimulation effects from 1 to 1.5 to 2 mA. The simple fact is that this is not true. Batsikadze et al. (2013) have shown in the motor cortex that when stimulation intensity is increased from 1 mA to 2 mA, direct current loses its opposing polarities, which results in cathodal stimulation inducing excitatory effects (Figure 6). This is a very basic constraint because anodal effects in cognitive studies are routinely interpreted as

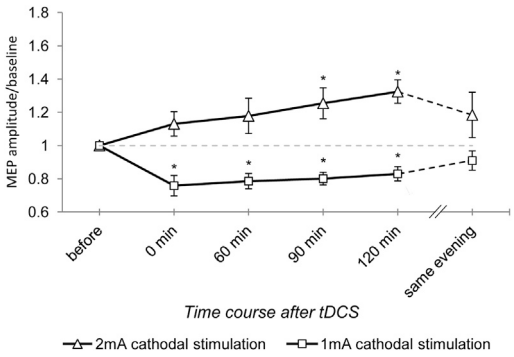

Figure 6. Effect of tDCS Current on Single-Pulse MEP Amplitudes
This figure taken from Batsikadze et al. (2013) shows that the "classic" inhibitory profile of 1 mA of cathodal DC stimulation is reversed when intensity is increased to 2 mA.

being due to excitation and cathodal effects due to inhibition (Boggio et al., 2010; Chi et al., 2010; Fecteau et al., 2007; Hecht et al., 2010). A further connection between the physiology and cognition here lies in the time course of the effects of the stimulation. The effects of 2 mA emerge after only 90 min and it is reasonable to ask, following the comments of a referee, how many times effects have been missed in cognitive studies (cf. Agosta et al., 2014) by not continuing to measure effects for longer periods.

The Effects of tES Montage Placement. Polarity, intensity, and duration are three of the four cornerstones of assumption. The fourth, and most important, is the electrode montage. Almost everything that is assumed in cognitive studies is based on the effects of MEPs measured using one electrode over M1 and either a frontopolar or shoulder electrode (Nitsche and Paulus, 2001; Nitsche et al., 2003; Stagg et al., 2011). In cognitive studies, however, the two most common electrode montages are a bilateral, homotopic arrangement or a reference over the frontopolar cortex. There are two immediate concerns. The first is of course whether regions stimulated in each hemisphere, say left and right PPC or left and right PFC, will interact. The second is that the frontopolar cortex is not a dormant site in cognitive terms. Nonetheless, a remarkable number of studies interpret their findings as if the effects are due to pure excitation/inhibition under the electrodes, and without any interaction between the two sites. We need to be conservative here in the absence of evidence, but a simple question for studies using bilateral DLPFC or PPC electrodes is what is the possibility of interactions between these areas?

The Four Cornerstones of Assumption Revisited

The use of tES in cognitive studies is clearly not as intellectually or methodologically mature as the field of TMS. Our survey of the uses of tES in cognitive studies shows that we have imported a set of assumptions from the physiological sciences without testing their validity. What we also find is that none of the four cornerstones survives even the briefest inspection. This provides us with both an opportunity and an imperative. The opportunity is to prescribe some conditions for assessment of tES experiments. The imperative is that we consider the strength of the claims made in enhancement studies and the effects they may have on the public perception and use of our findings.

Minimum Conditions for Execution and Interpretation for a tES Experiment

Control Sites. Our first recommendation concerns control conditions. There are many tES experiments in which stimulation of a site is compared with sham stimulation and the conclusion is that a particular area is important for a function. We would suggest that stimulation versus no stimulation is the weakest form of stimulation conditions and suggest that all experiments include a control site. Control polarity may be sufficient here, as it would allow experimenters to claim site specificity. However, there may also be interactions between polarity and task characteristics (e.g., Antal et al., 2004).

Control Task. As with TMS experiments, every tES experiment requires a control task as well as a control stimulation condition. Just as one needs a control site to make claims about the effects of stimulating a specific brain region, so too there is a need to show that effects are specific to tasks or task components. As an example, consider that there are effects of tDCS on, say, decision making following stimulation of the DLPFC. The DLPFC is involved in several functions, including working memory. As a minimum case, then, one would need to establish that the effects on decision making are separate from any possible effects on working memory, and to do this would require a working memory control task. It is surprising how often task controls are either non-existent or functionally irrelevant.

Site and task are components of experimental design with few degrees of freedom, but the remaining recommendations concern interpretation. There are too many degrees of freedom in the choice of some of these variables to prescribe how the experimenter chooses them, but there are good constraints we can put on how these are used.

Intensity. The current state of the field provides no guidelines for stimulation levels based on safety studies in M1. The assumption that intensity simply summates is clearly not tenable. We would therefore suggest that if experimenters wish to be able to make statements about excitatory or inhibitory effects, they limit their stimulation levels to those with known effects in the motor cortex.

Duration. As with intensity, the effects in M1 do not simply summate with increasing duration. The case for matching effects with known motor effects is the same here as for intensity, but the major caution is that even in making comparisons with M1, one cannot justify the assumption that cortex outside M1 will respond in the same way to changes in intensity or duration. This awaits testing in combined tES/imaging experiments.

Montage. Perhaps this is the greatest minefield because the effects of montages other than the M1 montages can only be indirectly inferred. There are many reasons to try new electrode sizes, numbers, and montages, but until we know something about the effects of these variables, it is important to interpret the physiology conservatively or not at all as a causal factor in behavioral effects.

Polarity. The polarity of stimulation can only be inferred where the montage conforms to parameters established in studies of M1 excitability. Jacobson et al. (2012) carried out a meta-analysis of the literature and observed that while the effects of anodal

stimulation in cognitive studies are often facilitatory, there is no reliability in the symmetry of polarity and cathodal stimulation.

Effect Robustness. There is a clear distinction to be made concerning whether effects are scientifically interesting or of clinical value – the two goals are different. If a small effect is obtained during the course of an experiment, then that is scientifically interesting. To begin to have clinical relevance, however, the effect must be robust over hours, days, weeks, or months. As we discuss in Public Communication of Results, making claims about utility based on results that last a few trials or minutes is unwarranted and potentially harmful.

TES Application to Addictive Behavior

We have presented a critical case of tES thus far to put the new user in the strongest position possible to enter the field knowing its challenges. However, there are positive signs and here we suggest addiction as a case study of an area where tDCS may develop some utility. There is a lack of effective pharmacological interventions in most forms of drug addiction, especially addiction to psychostimulants (Phillips et al., 2014) and the nature of the disorder puts addicts at higher risk of abuse and suicide when treated with medications. The potential of brain stimulation interventions has become an attractive option because they are cheap, tractable, and deliverable in low socioeconomic and noncompliant populations (Ekhtiari and Bashir, 2010). Preliminary studies with tDCS in nicotine (Boggio et al., 2009; Fecteau et al., 2014; Fregni et al., 2008; Meng et al., 2014; Pripfl and Lamm, 2015; Xu et al., 2013), alcohol (Boggio et al., 2008; da Silva et al., 2013; Pedron et al., 2014; Klauss et al., 2014; Nakamura-Palacios et al., 2012), cocaine (Conti et al., 2014; Conti and Nakamura-Palacios, 2014; Gorini, et al., 2014), and methamphetamine (Shahbabaie et al., 2014) dependents have yielded some interesting results, but there are clear hurdles that remain. The first hurdle of course is that of replicability, and the second is that of establishing appropriate cognitive and neural targets for tES for which there is no shortage of candidates. The list of cognitive candidates includes appetitive or impulsive motivational states (such as subjective craving or objective cognitive bias) and/or withdrawal-driven or compulsive motivational states, risky decision making, executive control, self-regulation, affective processing, memory reconsolidation for drug-related cues and outcomes, complications associated with addictions such as fatigue or psychosis, and cognitive deficits associated with addictions. All of these targets are subject to the constraints we discussed surrounding tES in general including robustness, replicability, longevity of effects, and physiological understanding. A third hurdle is to understand tES-induced neuroplasticity with patients under the influence of drugs. Neuroplasticity changes during tES will of course be affected by the type of drug of abuse, level of dependence, and duration of abstinence (Grundey et al., 2012). This will make generalization of outcomes very hard in different classes of drugs, different experimental settings, and different groups of patients.

In making the step from cognitive neuroscience laboratory to the clinic, we also need to be aware that optimal parameters in the lab may not be the parameters optimized for clinical treatment. The problem here is the size of the parameter space we face in choosing protocols: when one multiplies intensity, duration, montage, sham, control site, tES-type, task, number of treatments, and outcome measures into the consideration of a protocol (Rostami et al., 2013), the size of the task can appear daunting. Cognitive interventions are judged by how they help individuals and here we face another hurdle—that of inter-individual differences. There are wide ranges of neurocognitive variances within drug-dependent populations compared with laboratory populations, and there is a need for physiological studies that can help address these differences. The field currently has no taxonomy with which to address these differences. To rectify this, the field needs to examine the predictive role of interindividual differences in the tES outcomes with clinical typology (a simple sentence masking a complex and difficult task). The final challenge is to produce clinical applications with meaningful effects. How successfully this is done (if it can be done) depends on solving all the criticisms we address in other sections of this Primer. Durability, cumulative effects, feasibility, patient compliance, and tolerability for long-term multisession tES interventions are just some of the challenges we face.

Public Communication of Results

This is not a section that would find a place in many neuroscience Primers. The vast majority of neuroscience is basic science that does not have any direct implications for the public, nor does it use equipment that can easily be obtained or used outside the laboratory. However, things are different with tES. The equipment is relatively cheap, easily obtainable, and simple to use. There is a need to constrain the claims based on tES experiments that is not required of any other claims in cognitive neuroscience. Headline-making claims that we can read minds, have discovered the seat of consciousness, or can show that some brain activity is correlated with thinking about love rather than lettuce will hardly change behavior. Even truly exciting findings such as the advances in neuroprosthesis (Donoghue, 2002), the discovery of grid cells (Moser et al., 2008; 2014), or new manipulations in optogenetics (Packer et al., 2013) will not have people demanding or trying to implant themselves with brain computer interfaces, neural GPS systems, or lasers. The difference with tES is that overblown and unreplicated claims that tES can improve memory, attention-deficit hyperactivity disorder, mathematical skills, general intelligence, learning, decision making, and language skills has the consequence of people either demanding tES or trying it out for themselves. The responsibility here lies entirely with the scientists. It is we, not the journalists who speak of ''brain boosting.'' It is we, the scientists, who say things like ''all these machines are is a 9 V battery in a box.'' In addition, it is we who hype our results and cross the line between what is scientifically interesting and clinically or recreationally possible. Ethics, like charity, begins at home. When a journal of the standing of *Nature* carries a headline ''Shocks to the brain improve mathematical abilities'' (Callaway, 2013) concerning two studies, we have to ask how this will be perceived. It is doubtful that the non-scientific reader will note that the studies have not been independently replicated, that only one of them tested mathematics, that the gains are as small as being milliseconds faster at some simple sums, and that only six people were tested in follow-up. When it is claimed that tDCS can improve problem-solving abilities (Chi and Snyder, 2012), the casual reader will not notice that

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only one-third of subjects improved, that there is no evidence that effects are sustained beyond 3 min, that there was no active control stimulation, and that there was no control for order effects.

If irresponsible claims based on what has been done is insufficient reason to look at how we communicate, then perhaps speculations based on what has not been done will give us pause. Given the lack of convincing demonstrations that tES can be applied in real-world settings, putting claims out in the press that the methods have "unlimited potential" are unrealistic. Two particular examples betraying poor judgment of how things may be viewed by non-experts and also of the exigencies of making muddy effects work in the field are the suggestions that tDCS may have uses in the military (Levasseur-Moreau et al., 2013) or in sport (Davis, 2013). There is to date no evidence that tDCS can even produce its classic excitatory or inhibitory effects in M1 in subjects who are moving during the application of the stimulation, nor that in any significant, replicated effect, the stimulation can benefit subjects beyond a few minutes.

There are several voices of reason out there, but they need to be louder. Sehm and Ragert (2013) have articulated very well the limitations of tES in the military: third party effects, unknown long-term dangers, the problems of transferring effects to the real world, and the specificity of modulation. Their analysis could be applied to many of the claims to enhancement effects. Davis (2014) also makes a strong case for caution. He focuses on the unknown effects of stimulation, the unknown side effects of stimulation (an important distinction from the first), the lack of clear dosing guidelines, and the lack of translational studies from adults to children. The extension to children is disturbing. On the positive side, some groups are beginning with modeling studies of the effects of tDCS in the developing brain (Minhas et al., 2012; see also Moliadze et al., 2015), but some studies (e.g., Andrade et al., 2013) have stimulated children as young as 5 years old before any significant modeling data or even safety predictions are available. In such cases, the minimum requirement in reporting needs to be an account of the clinical cost-benefits analysis to prevent such studies being taken as precedents for safety.

Competing accounts of the need for regulation of tES have appeared recently. Santarnecchi et al. (2013) have argued for the need to regulate the use of devices. In a counter, Walsh (2013) has noted that regulation of such simple devices in this technological age is next to impossible, and that if the brain stimulation scientists can instead regulate their language and hype, this may not even be necessary. The additional damage of overstating the "boosting" effects of tES is that some of the hyped findings may be scientifically interesting and this can be lost in the heat. Perhaps the field should step back from applications, address fundamentals, and remind itself that the brain is interesting enough for its own sake.

Conclusions

In this Primer, we surveyed two sides of the human brain stimulation coin. On one side, is a mature field of TMS that over 25 years has improved standards, has many important between laboratory replications, enhanced the understanding of its basic mechanisms, filtered the few areas where it may have clinical impact from the many that have been probed, and integrated with other techniques in cognitive neuroscience. The other side that everyone is currently noticing, tES, is still in its infancy with respect to serious cognitive neuroscience. We could be polite and concentrate on the positives of this shiny side, but the field is not short of reviews that do not critically assess what has been done and what cannot be done with tES. If this Primer is to serve a serious purpose, it is to alert the new user to ensure that minimum standards are met in the design, execution, interpretation, and delivery of experimental findings to ensure that the signal-to-noise ratio in the tES literature is increased.

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