State-dependency in brain stimulation studies of perception and cognition

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We address the importance of understanding initial states of neuronal populations and of state-dependent responses in cognitive neuroscience experiments with special emphasis on brain stimulation studies of perception and cognition. The approach we present is based on evidence that behavioural and perceptual effects of transcranial magnetic stimulation (TMS) are determined by initial neural activation state; by systematically manipulating neural activation states before application of TMS, one can selectively target specific, even spatially overlapping neural populations within the affected region. This approach is potentially of great benefit to cognitive neuroscience and remediation programmes as it combines high spatial and functional resolution with the ability to assess causality.

Introduction

'Excitation and inhibition are both present from the very stimulus out-set and are pitted against one another. The central circumstances may favour one at one time, the other at another.' Sherrington, Nobel Prize lecture 1932.

Sherrington’s words might seem like a statement of the obvious, but it is a simple truth ignored in many cognitive neuroscience experiments. To respond to demands made by changes in the environment, the sensory, motor and cognitive systems of the brain need to be able to adapt over varying time scales, to alterations in rewards, visual input, response requirements, experience and to injury. Studies using methods of brain stimulation and recording of sensory and cognitive functions, however, often take no account of the initial state of the subject and there are several important consequences of this. Ignoring initial state limits the generality of conclusions about the properties of neurons and networks. It can mask the dynamics of interactions between neurons with different response properties within brain areas. It can also lead to suboptimal interventions in rehabilitation. Perhaps most importantly, it enables one to forget that many findings about neuronal properties or the functions of brain regions are only valid for the specific conditions in which the data were obtained.

Here, we address the importance of state-dependence in the context of perceptual and cognitive experiments that use transcranial magnetic stimulation (TMS) (see Glossary) or direct current stimulation (DC). State-dependence is, of course, not new and it can mean many things: different levels of fatigue, sleep or wakefulness, drug free or dosed, novice or expert or primed or unprimed. All these conditions may be associated with different brain states and have been studied in many experiments, and in TMS studies of the physiology of the motor system state they are well accounted for (e.g. Refs [1–5]). Cognitive sciences lag behind, however, partly because it is more difficult to make a direct link between brain state, in terms of excitation and inhibition than it is between physiological measures such as the motor evoked potentials (MEPs) and neural states of excitation or inhibition. Indeed, in cognitive experiments, the baseline assumption still seems to be that TMS indiscriminately affects all types of neurons in the targeted region independent of state (the belief is still founded, see ‘State-dependency and brain stimulation: segregating overlapping populations’ later). The goal of this article, then, is to introduce a new method of assessing the effects of magnetic stimulation, applicable to perceptual and cognitive studies, which enables one to make inferences about initial state as strong as those that can be made in studies measuring MEPs. If we pose the question, for any brain stimulation or recording experiment, ‘do the findings generalize to other tasks and response conditions’? The answer seems obvious — no, the results of imaging and stimulation experiments are very sensitive to experimental conditions. Nevertheless, some conditions are favoured over others, partly out of ease of replicability, partly out of historical accident but also because they fit with current orthodoxies. For example, in research on the parietal

Glossary

\textbf{Adaptation}: reduction of response to a sensory stimulus induced by repeated presentation of that stimulus.

\textbf{Electroencephalography (EEG)}: the measurement of electrical activity produced by the brain as recorded from electrodes placed on the scalp.

\textbf{Offline TMS}: in offline paradigms, a longer lasting (up to an hour) suppression of neural activity is induced with tTMS before subjects perform a behavioural task.

\textbf{Online TMS}: single pulse (or brief pulse trains of) TMS applied during a behavioural task.

\textbf{Phosphenes}: subjective experience of flashes of light that can be induced by application of TMS over the visual cortex.

\textbf{Transcranial direct current stimulation (tDCS)}: the application of weak electrical currents (1–2 mA) to modulate the activity of neurons in the brain.

\textbf{Transcranial magnetic stimulation (TMS)}: non-invasive method for modulating neural activity by weak electric currents induced by rapidly changing magnetic fields.
Box 1. Receptive fields are state-dependent

The response properties of single units often provide the basis for imaging, lesion, stimulation and simulation experiments but they are state-dependent. Neurons in the lateral geniculate nucleus (LGN), for example, exhibit different spatial and temporal properties as a function of global synchronization. When the EEG is synchronized in the α–δ range LGN neurons fire in short bursts [48,49]; when the EEG is desynchronized, LGN neurons exhibit more sustained firing patterns [50,51]. Furthermore, the shape and size of the receptive fields of LGN neurons change as a function of brain synchrony. The shapes of receptive fields in the cat striate cortex are also correlated with the general state of the brain as assessed by EEG:

Figure I. Changing shape of cortical receptive fields during different EEG states. The impulse rate of a single subfield is colour-coded according to the scales shown (maximum scaling) and the complete receptive field is outlined in white. Parts (5 s) from the corresponding EEG traces are shown. Receptive fields are wider during synchronized EEG and the subfield overlap increases. (a) Endstopped simple cell 'Off' response, (b) End-stopped simple cell 'On' response, (c) Simple cell 'Off' response, (d) Simple cell 'On' response. [47]

Figure II. Effect of selective attention on the responses of a neuron in prestriate area V4. (a) Responses when the monkey attended to one location inside the receptive field (RF) and ignored another. At the attended location (circled), two stimuli (sample and test) were presented sequentially and the monkey responded differently depending on whether they were the same or different. Irrelevant stimuli were presented simultaneously with the sample and test but at a separate location in the RF. In the initial mapping of the RF, the cell responded well to horizontal and vertical grey bars placed anywhere in the receptive field but not at all to white bars of any orientation. Horizontal or vertical grey bars (effective sensory stimuli) were then placed at one location in the field and horizontal or vertical white bars (ineffective sensory stimuli) at another. When the animal attended to the location of the effective stimulus at the time of presentation of either the sample (S) or the test (T), the cell gave a good response, but when the animal attended to the location of the ineffective stimulus, the cell gave almost no response (right), even though the effective stimulus was presented in its receptive field. Thus, the responses of the cell were determined by the attended stimulus. (b) Same stimuli as in (a), but the ineffective stimulus was placed outside the receptive field. The neuron responded similarly to the effective sensory stimulus, regardless of which location was attended [10].

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cortex, an area known to be important for attentive visual search and not for colour perception, the data are often obtained from naïve observers. However, if the state modulated is expertise and humans or monkeys are trained to make colour–saccade associations, the parietal cortex can be shown to be unnecessary for visual search [6] and responsive to colour [7]. That is, the functions of brain areas and the responses properties of their neurons change.
with state in a manner that can directly contradict the cardinal view of the functions of an area when naïve subjects are used.

State-dependency and brain recordings
The gold standard for evidence in cognitive neuroscience would seem to be single unit recordings because they are both spatially and temporally specific, and it is usually on the basis of single unit recordings that an area of cortex is labelled a ‘form area’, ‘colour area’, ‘motion area’ and so on. These labels can be misleading, however. There are, of course, differences in cortical response properties depending on whether an animal is anaesthetized, awake and fixating or awake and responding to stimuli (e.g. Refs [8,9]), but there are also differences because of physiological factors such as global synchrony or behavioural factors such as attention [10]. Box 1 details one example from anaesthetized animals and one from awake behaving animals which show that even basic receptive field properties, often used as the basis of neuronal taxonomy [11,12] are changeable [13]. It is clear from these examples that descriptions of neuronal response properties are specific to the particular state of the animal and the specific stimulus conditions used in a given experiment. However, when one makes statements concerning the effects of TMS or DC stimulation one predicates those statements on implicit assumptions about the state of these kinds of neuronal response properties, and in doing so information is lost.

State-dependency and brain stimulation: segregating overlapping populations
Brain stimulation techniques such as TMS and transcranial direct current stimulation (tDCS) are increasingly used to modulate neural activity to investigate brain-behaviour relationships. In TMS, electric current is used to induce a magnetic field with the objective of altering local electric fields in the brain; the magnetic field passes through the scalp and the skull of the subject inducing current that stimulates neural tissue. The stimulation induces an electric field both inside and outside the axon [14], creating a transmembrane potential, or a depolarization voltage [15].

A single pulse of TMS can modulate neural activity for up to a few hundred milliseconds [16]. In cognitive neuroscience, TMS is usually applied with the objective of interfering with the neural activity associated with the cognitive or perceptual function under investigation, thus producing a behavioural impairment (see Refs [17,18] for reviews). Although the initial state of the stimulated region is usually not a controlled variable in TMS studies of perception and cognition, there is sufficient evidence that the effects of online TMS are indeed state-dependent. Single-pulse TMS, for example, usually disrupts cognitive and perceptual functions when applied during the perceptual or cognitive process [17,18], but there are occasions when it has been reported to facilitate performance either as a function of the timing of TMS application [19,20] or of

Figure 1. (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 colour and orientation. The adaptation period of 30 s was followed by 20 experimental trials in which subjects were asked to report the colour of the test stimulus. Three TMS pulses were administered on each trial at stimulus onset asynchronies of 0, 50 and 100 ms after stimulus onset. (b) A schematic representation of 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. Redrawn from Ref. [25].
the onset of a perceptual or cognitive process [15], different neural populations are less influenced by central factors than when TMS is applied during a cognitive process. This difference in the initial activation state is likely to explain why the effects of TMS are different in the two circumstances (see also Refs [22–24]).

We have recently investigated this issue directly by using colour adaptation to manipulate the activity levels of functionally distinct neural populations before application of TMS [25]. We found that phosphenes induced from the early visual cortex after colour adaptation take on the colour qualities of the adapting stimulus (Figure 1). A similar facilitation of the adapted attribute (and inhibition of unadapted attributes) was found in a psychophysical task in which TMS was applied online. As neurons encoding the colour of the adapting stimulus were less active because of lowering of the resting potential of the neuron [26,27], the finding that phosphenes took on the colour of the adapting stimulus might imply that TMS stimulates the less active neural populations relatively more than already active neural populations. A similar pattern of results was found in a study in which this TMS-adaptation paradigm was used to study visual motion perception. After adaptation to simple translational motion, TMS facilitated the perception of the adapted direction and impaired the detection of the opposite direction [28]. This phenomenon can also explain how online TMS impairs cognitive functions by preferentially facilitating attributes encoded by neurons not involved in the cognitive function under investigation [24,29]. Furthermore, the TMS-adaptation paradigm considerably enhances the functional resolution of TMS. By manipulating neural activation states before application of TMS, one can control which neural populations are facilitated by TMS. This effectively enables TMS to be used to selectively target specific neural populations, enabling TMS studies to reveal not only the necessity of cortical regions in cognitive functions but also the receptive field properties and the neural tuning of the stimulated region (Box 2).

In offline, repetitive TMS (rTMS) paradigms, stimulation is applied before presentation of a task either for a few tens of seconds, as in the theta burst paradigm, or for

**Box 2. Enhancing the functional resolution of TMS: the TMS-adaptation paradigm**

In a typical study, TMS is applied with the objective of determining the necessity of a cortical region in a given cognitive or perceptual function. The logic behind this approach is that TMS interferes with the neural processing associated with a given function, thus producing a behavioural disruption. The state-dependent effects described in the main text can explain the nature of that interference as they show how TMS interacts with the ongoing activity in the targeted region. Perhaps even more importantly, state-dependency enables one to control which neural populations are preferentially facilitated by TMS. For example, one can preferentially facilitate neurons tuned to leftward motion by adapting these neurons before application of TMS [28]. State-dependency can, thus, be used to target specific neural populations ‘within’ the stimulated region. The combination of adaptation and TMS can also be used to determine the neural properties of the stimulated region. The principle is simple: if TMS applied over a given area facilitates the detection of the adapted attribute, this indicates that neurons in that area were adapted by and, thus, tuned to the adapting stimulus. By contrast, if no facilitation is found, this indicates that adaptation did not modulate neural activity in that region; this in turn implies that neurons in the stimulated region are not tuned to the adapted attribute. The validity of this TMS-adaptation (TMSA) paradigm has been confirmed by stimulation of visual areas such as V1/V2 and V5/MT in which the receptive field properties are relatively well known [52,53].

**Figure 2.** Preconditioning modulates the effects of repetitive TMS. (a) In the study by Siebner et al. [33] a 10 min session of anodal, cathodal or sham tDCS was given to the left primary motor hand area (M1). For anodal tDCS, the anode was placed over the left M1, and the cathode was placed over the right eyebrow. Polarity was reversed for cathodal tDCS. At 10 min after the end of the tDCS session, 900 biphasic pulses of 1 Hz rTMS were given to the left M1 at 85% of resting motor threshold. Corticospinal excitability was probed with single-pulse and paired-pulse TMS over the left M1 before tDCS, after tDCS, and twice after rTMS. The figure plots the amplitude of a standard test MEP evoked by a single TMS probe stimulus at different times before and after the two types of conditioning. The aftereffects of 1 Hz rTMS were crucially dependent on the preconditioning by tDCS over the left M1. 1 Hz rTMS reversed polarity-specific effects induced by anodal or cathodal tDCS. Sham tDCS had no impact on corticospinal excitability. (b) The study by Lang et al. [33]. Anodal, cathodal or sham tDCS was applied to the left primary motor hand area (M1) for 10 min after which 100 biphasic pulses of 5-Hz rTMS were given to the left M1 at individual active motor threshold (AMT). The amplitude of MEPs was used to probe changes in corticospinal excitability induced by transcranial stimulation. Relative changes of MEP amplitudes within the first and second block of post-rTMS measurements (POST-1 and POST-2) compared with mean amplitudes immediately before rTMS (INTER). The type of preconditioning (tDCS) had a strong effect on the magnitude and direction of aftereffects produced by subsequent 5-Hz rTMS. The 5-Hz rTMS given after ‘inhibitory’ preconditioning (cathodal tDCS) resulted in a significant increase of corticospinal excitability. Conversely, 5-Hz rTMS after ‘facilitatory’ preconditioning (anodal tDCS) caused a decrease in corticospinal excitability. No effects on corticospinal excitability occurred after sham preconditioning. Error bars represent standard error of mean (SEM).
tens of minutes if using a low frequency repetitive paradigm, with the objective of inducing longer lasting change in cortical excitability. Although the neural mechanisms of the long-lasting effects of offline rTMS are different from those induced by single-pulse TMS (see Ref. [30] for a review) they have also been shown to be state-dependent. In a study by Brighina et al. [31] 1 Hz rTMS over the occipital cortex led to an increase in visual cortex excitability in subjects affected by migraine with aura. By contrast, in normal subjects a decrease in visual cortex excitability was observed. This study shows that changes in cortical excitability induced by neurological conditions such as migraine can have an important impact on the effects of TMS.

There is also physiological evidence for the state-dependency of offline TMS in the motor system. Siebner et al. [32] and Lang et al. [33] showed that preconditioning motor cortical excitability using tDCS modulates the direction of effects induced by subsequent rTMS. When the level of excitation of the corticospinal projection is high, a subsequent period of 1 Hz rTMS leads to a lasting reduction in corticospinal excitability [34]. Conversely, when corticospinal excitability is reduced before application of rTMS, the same 1 Hz rTMS causes a sustained increase in corticospinal excitability (Figure 2). Lang et al. [35] showed that similar state-dependent effects can also be obtained with high frequency rTMS. These findings show the importance of state-dependency in our understanding of basic physiological mechanisms and they are also important in considerations of therapeutic interventions (see Ref. [34] for a recent review). This kind of sophisticated paradigm is more common in studies of the motor system but there is great potential in importing these types of methods into cognitive studies (Box 3).

In the studies discussed earlier, state-dependent TMS effects were obtained from a few minutes up to an hour after the initial manipulation of the neural activation state. There is evidence, however, that manipulation of neural activity can have an impact on rTMS applied even on the following day. Valero-Cabre et al. [35] applied 30 daily sessions of 1 Hz rTMS to modulate activity in the posterior parietal cortex and associated neural systems in two intact cats, and assessed the visuospatial orientation behaviour of the animals before and after each stimulation session. The key finding of the study was that the behavioural disruption induced by TMS built up over the 30 days of stimulation: the severity as well as the spatial extent of the rTMS-induced stimulus detection impairment in the contralateral hemifield progressively increased. Nonetheless, 60 min after each TMS session, the behaviour of the animals returned to baseline levels. Furthermore, no lasting behavioural effect were found at any time across the study when subjects were tested 1 or 24 h post-rTMS, implying that TMS did not induce any permanent behavioural effects. This study demonstrates that the past history of periodically cumulative rTMS sessions builds up a lasting ‘memory’, resulting in increased facilitation to subsequent TMS-induced disruptions. Such a phenomenon enables a behavioural effect of progressively higher magnitude, but equal duration, in response to individual TMS interventions.

These studies demonstrate that the initial cortical activation state has an important role in determining the behavioural and perceptual outcome of brain stimulation; understanding state-dependency is, therefore, crucial for accurate interpretation of TMS studies.

State-dependency and combined brain stimulation and recording

As discussed earlier, the neural impact of an external stimulus is not determined only by the properties of that stimulus but also on the initial activation state of the activated brain region. Studies combining brain stimulation with neuroimaging techniques such as electroencephalography (EEG) and functional magnetic resonance imaging (fMRI) have also begun to provide evidence that concurs with this view. That TMS has different effects on the motor system as a function of sleep, alcohol, learning and expectancy is well known (e.g. Refs [36–38]) but here we concentrate on studies pertinent to perception and cognition. A recent study investigated how fluctuations of oscillatory brain activity in the α-frequency band (8–14 Hz) modulate the impact of brain stimulation [39]. Decreased oscillatory activity in the α-frequency band is thought to reflect a state of enhanced cortical excitability, and increased activity to reflect a state of cortical idling or inhibition in which excitability is reduced [40,41]. Romei et al. [42] determined the relationship between the α-band resting oscillatory activity and the efficacy of TMS in inducing visual percepts (phosphenes) and found a correlation between the occipital α-band power of subjects and the stimulation intensity required for inducing phosphenes. The authors [42] concluded that the highly synchronous volleys of activity elicited by TMS might be more likely to be perceptually effective during desynchronized cortical activity than during synchronous volleys of α-oscillations because the synchronous neural activity induced by TMS contrasts more strongly with low than high α-activity. In a further study, Romei et al. [40] found that subsecond fluctuations in the α-frequency band of each subject modulated the impact of TMS, demonstrating that state-dependent effects can be obtained over extremely short time scales. Like single unit receptive fields (Box 1), the responses of the larger areas of visual cortex stimulated by TMS are dependent on global levels of α synchrony. This finding reveals the neural state-dependency of brain stimulation and also corroborates the perceptual and behavioural findings that TMS preferentially stimulates the less active neurons in a population [25,26].

Box 3. Outstanding questions

- Initial cortical activation state can be modified with a wide range of psychophysical manipulations such as adaptation and priming; do these produce similar state-dependent effects of TMS?
- Can state-dependency be used to enhance the functional resolution of tDCS?
- State-dependent effects have been observed at different time scales, lasting from a few minutes to 24 h. Are these effects based on different neural processes?
- Is the TMSA paradigm useful for the study of higher-level cognitive processes such as language and number processing?
State-dependency and brain interactions

Many cognitive and perceptual functions rely on networks consisting of multiple cortical areas, the functional connections between various regions in a network are dynamic in nature, and it is the dynamics that underlie state-dependency. As the following experiments demonstrate, depending on the motivational state of the animal and the nature of the incoming signal, two areas can be either facilitate or inhibit each other’s response to that signal.

Recent developments in analysis techniques have enabled fMRI studies to shed light on how functional connectivity is modulated by factors such as attention. Dynamic causal modelling (DCM) involves the explicit modelling of activity within, and among, regions of a hypothesized neural network [41,42]. In DCM, a neuronal model of interacting cortical regions is constructed with neurophysiologically inspired parameters which are estimated such that the predicted blood oxygenation level dependent (BOLD) series, which results from converting the neural dynamics into hemodynamics, correspond as closely as possible to the observed BOLD series [43,44]. Marreiros et al. [44] have recently used this approach to study the modulatory impact of visual attention on the connectivity between the two visual areas, the primary visual cortex (V1) and the motion-selective area V5/MT as a function of the initial activation state in the cortical network. Their analysis revealed that attention to motion enhances the connectivity between V1 and V5/MT. This modulation is likely to be perceptually significant as interactions between these two regions have been shown to be crucial for the conscious perception of motion (e.g. Ref. [44]).

The state-dependency of the effects of brain stimulation on cortico-cortical interactions has been studied recently in the context of voluntary motor action. Bestmann et al. [45] used TMS concurrently with event-related fMRI to study whether causal influences from left dorsal premotor cortex (PMd) upon contralateral (right) motor areas depend on the current state of the motor system. This was achieved by applying short bursts of high- or low-intensity TMS to left PMd during single isometric left-hand grips or during rest. TMS to left PMd affected activity in contralateral right PMd and primary motor cortex (M1) in a state-dependent manner. During active left-hand grip, high (versus low)-intensity TMS led to activity increases in contralateral right PMd and M1, whereas TMS produced an activity decrease during no-grip rest. These findings demonstrate that the left PMd can exert state-dependent interhemispheric influences on contralateral cortical motor areas relevant for a current motor task. They also highlight the fact that an external signal (in this case brain stimulation) can either facilitate or inhibit cortico-cortical functional connectivity depending on the initial states of these regions (Figure 3).

State-dependent cortico-cortical interactions have also been observed in the visual system. Ruff et al. [46] showed using combined TMS and fMRI, that stimulation of the right intraparietal sulcus (IPS) elicits a pattern of activity changes in visual cortex that strongly depends on current visual context. Specifically, TMS affected the BOLD signal in V5/MT only when moving stimuli were present to drive this visual region, whereas TMS-elicited BOLD signal changes were observed in areas V1-V4 only during the absence of visual input.

In summary, these studies demonstrate how changes in the activation state of a cortical region modulate the functional interactions of that region with other brain areas. Although attention is a well-studied example of how the initial activation state influences cortical processing and cortico-cortical interactions, other, less studied factors (such as previous sensory input) are likely to be equally important.

Conclusions

The impact of any external stimulus is dependent on not only on the properties of that stimulus but also on the
initial state of the stimulated system. This principle has been acknowledged in the neurosciences for a long time, as Sherrington’s quote in the Introduction demonstrates. In psychology, paradigms such as adaptation and priming are well-known examples of how the impact of a sensory stimulus is dependent on the state of the perceiver. It is, therefore, not surprising that the effects of brain stimulation are also strongly dependent on the state of the stimulated region.

State-dependency is an important factor in understanding the mechanisms through which brain stimulation modulates neural activity and behaviour. Furthermore, state-dependency can be used to enhance the functional resolution of brain stimulation. As we have discussed earlier, combining TMS with paradigms such as adaptation enables one to target specific neural populations and enables TMS to be used to investigate receptive field properties in the stimulated region (Box 2).

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