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Review

Modelling non-invasive brain stimulation in cognitive neuroscience☆

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ABSTRACT

Non-invasive brain stimulation (NIBS) is a method for the study of cognitive function that is quickly gaining popularity. It bypasses the correlative approaches of other imaging techniques, making it possible to establish a causal relationship between cognitive processes and the functioning of specific brain areas. Like lesion studies, NIBS can provide information about where a particular process occurs. However, NIBS offers the opportunity to study brain mechanisms beyond process localisation, providing information about when activity in a given brain region is involved in a cognitive process, and even how it is involved. When using NIBS to explore cognitive processes, it is important to understand not only how NIBS functions but also the functioning of the neural structures themselves. We know that NIBS techniques have the potential to transiently influence behaviour by altering neuronal activity, which may have facilitatory or inhibitory behavioural effects, and these alterations can be used to understand how the brain works. Given that NIBS necessarily involves the relatively indiscriminate activation of large numbers of neurons, its impact on a neural system can be easily understood as modulation of neural activity that changes the relation between noise and signal. In this review, we describe the mutual interactions between NIBS and brain activity and provide an updated and precise perspective on the theoretical frameworks of NIBS and their impact on cognitive neuroscience. By transitioning our discussion from one aspect (NIBS) to the other (cognition), we aim to provide insights to guide future research.

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1. Introduction

Non-invasive brain stimulation (NIBS) methods, which include transcranial magnetic stimulation (TMS) and transcranial electric stimulation (tES), are used in cognitive neuroscience to induce transient changes in brain activity and thereby alter the behaviour of the subject. The application of NIBS aims at establishing the role of a given cortical area in an ongoing specific motor, perceptual or cognitive process (Hallett, 2000; Walsh and Cowey, 2000).

Physically, NIBS techniques affect neuronal states through different mechanisms. In TMS, a solenoid (coil) is used to deliver a strong and transient magnetic field, or "pulse", to induce a transitory electric current at the cortical surface beneath the coil. The pulse causes the rapid and above-threshold depolarisation of cell membranes affected by the current (Barker et al., 1985, 1987), followed by the transynaptic depolarisation or hyperpolarisation of inter-connected neurons. Therefore, TMS induces a current that elicits action potentials in neurons.

By contrast, in tES techniques, the stimulation involves the application of weak electrical currents directly to the scalp through a pair of electrodes (Nitsche and Paulus, 2000; Priori et al., 1998). As a result, tES induces a subthreshold polarisation of cortical neurons that is too weak to generate an action potential. However, by changing the intrinsic neuronal excitability, tES can induce changes in the resting membrane potential and the postsynaptic activity of cortical neurons. This, in turn, can alter the spontaneous firing rate of neurons and modulate their response to afferent signals (Bindman et al., 1962, 1964, 1979; Creutzfeldt et al., 1962), leading to changes in synaptic efficacy.

The application of NIBS involves different types of protocols: TMS can be delivered as a single pulse (spTMS) at a precise time, as pairs of pulses separated by a variable interval, or as a series of stimuli in conventional or patterned protocols of repetitive TMS (rTMS) (for a complete classification see Rossi et al., 2009). In tES, different protocols are established by the electrical current used and by its polarity, which can be direct (anodal or cathodal transcranial direct current stimulation: tDCS), alternating at a fix frequency (transcranial alternating current stimulation: tACS) or at random frequencies (transcranial random noise stimulation: tRNS) (Nitsche et al., 2008; Paulus, 2011).

In general, the final effects of NIBS on the central nervous system depend on a lengthy list of parameters (e.g., frequency, temporal characteristics, intensity, geometric configuration of the coil/electrode, current direction), when it is delivered before (off-line) or during (on-line) the task as part of the experimental procedure (e.g., Jacobson et al., 2011; Nitsche and Paulus, 2011; Sandrini et al., 2011). In addition, these factors interact with several variables related to the anatomy (e.g., properties of the brain tissue and its location, Radman et al., 2007), as well as physiological (e.g., gender and age, Landi and Rossini, 2010; Lang et al., 2011; Ridding and Ziemann, 2010) and cognitive (e.g., Miniussi et al., 2010; Silvanto et al., 2008; Walsh et al., 1998) states of the stimulated area/subject.

This review will focus only on the so-called "on-line" procedures. It will not include consideration of "off-line" protocols with TMS and tES, in which task performance is compared before versus after stimulation, but is not assessed during stimulation. Off-line stimulation involves neuronal activity changes that last beyond stimulation (i.e., short- and long-term potentiation or depression, homeostasis of the system, metaplasticity) and to a certain extent are different from the basic mechanisms of action by which NIBS directly modulates ongoing brain function in on-line protocols. Off-line protocols with TMS and tES induce a change in the state of stimulated area and therefore they can be compare to the concept of state dependency. In this case the change in the state is not induced by a task or subministration of a substance but by NIBS after effects.

We aim to present a unified framework for NIBS approaches. We will lay the groundwork by focusing on the theoretical and physiological mechanisms of action that historically have been applied to TMS and tES, building up a coherent view for explaining NIBS effects in cognitive neuroscience. The unifying theme of our perspective is the induction of neural noise, whose interactions with the task-induced state of the stimulated area will determine the final behavioural outcome. We believe that our perspective offers increased explanatory power for NIBS-induced effects, and will therefore provide added impetus for future applications.

2. Transcranial magnetic stimulation

2.1. The virtual lesion metaphor

The first idea concerning the effects of TMS was that of the "virtual lesion" approach (Pascual-Leone et al., 2000; Walsh et al., 1998; Walsh and Rushworth, 1999). By analogy with neuropsychological studies, but without many of the confounding factors that trouble patient studies (such as compensation mechanisms, diaschisis, dimension of the lesion and single-subject samples). The application of TMS could hinder the functioning of a given area for several milliseconds, and thereby establish a causal nexus between the stimulated brain region and a particular function. The idea follows the standard logic of inference. If cortical area A is involved in cognitive process X and is not involved in process Y, the alteration of the activity of area A will result in altered performance in X (and not Y); thus, area A plays a causal role in the performance of X (and not Y). In this sense, TMS describes a process in which theory is extracted from direct interventions and overcomes the fundamental limits of the correlative approaches of imaging techniques [e.g., functional magnetic resonance, positron emission tomography, electroencephalography (EEG)], providing an opportunity to test directly and non-invasively causal relationships between the brain and cognition. The first experiment that applied this logic in cognitive neuroscience was performed by Amassian et al. (1989). They stimulated the occipital cortex by spTMS, which was time-locked to the presentation of a visual stimulus, while the participants tried to detect the visual stimulus. The participants' error rate increased when TMS was applied between ~80 and 120 ms following the presentation of the visual stimulus. The authors concluded that the occipital cortex (i.e., where) makes a critical contribution to stimulus recognition only at that precise time window (i.e., when) (Amassian et al., 1989).

The virtual lesion approach refers to the possibility of causally ascertaining where cognition occurs in the brain. In this sense, TMS has borrowed experimental hypotheses from neuropsychology and, after extensive testing, has confirmed most of them (see Miniussi et al., 2012b; Walsh and Pascual-Leone, 2003; Wassermann et al., 2008). Due to its high temporal specificity, TMS has also been employed to study the time point at which a cognitive event occurs in the brain. For this purpose, spTMS is superior to rTMS because it confines the impact of stimulation to a small fraction of a second. Mental chronometry has been extensively applied to perceptual (e.g., Amassian et al., 1989; Corthout et al., 1999; Laycock et al., 2007; Marzi et al., 1998; Seyal et al., 1992) or higher-order cognitive processes (e.g., Ashbridge et al., 1997; Chambers et al., 2004; Harris and Miniussi, 2003; Kahn et al., 2005; Mottaghy et al., 2003) and has been useful in defining the temporal activation of single brain areas as well as ascertaining the relative temporal roles of different areas in the same cognitive process, along the continuum of information processing.

Although the 'virtual lesion assumption' is a very useful heuristic when interpreting the behavioural effects of NIBS, we need to develop a more sophisticated explanatory framework if we wish to

use NIBS to develop and test more complex theoretical models. The virtual lesion approach attributes an impairment of performance to a lesion, yet there is no actual evidence to support this assumption and it was not originally intended in that manner. Indeed, in its original definition, the concept was expressed as 'In the context of a task, the induced current operates as "neural noise"; that is, the pulse adds random activity in the midst of organised activity in the cortical region. This neural noise serves to delay or disrupt performance, and it is in this sense that TMS operates as a lesion' (Walsh and Rushworth, 1999, p. 127). As is frequently the case, taking an analogy too literally and transforming it into a mechanism of action is unproductive in science. We should consider the term lesion to be equivalent to a lack of neural activity as a whole and, consequently, a missed opportunity to process information. By contrast, the acute impact of stimulation can be positive in the sense of induced neural activity in pools of cortical neurons underneath the coil, even if that neural activity might interfere with the opportunity to process specific information because it competes with the neural activity that represents the stimulus. Thus the useful heuristic used to describe the final results cannot be used to interpret the functional mechanisms of the effects induced; as such the effects that are highlighted in TMS studies cannot be directly compared with those of lesion studies. Furthermore, the use of TMS as a disturbance apparatus has never produced a categorical failure in the subject's performance similar to the effects observed in neuropsychological patients. The type of effect obtained is often related to an increase in the length of time required for information processing (e.g., increased reaction time), and if a reduction in the subject's performance is observed, it is most likely explained by the complexity of the processing that is needed to solve the task (Manenti et al., 2008). In this context, we should consider TMS to be a tool that injects activity that competes or interacts with resources to solve the task, thus slowing or hindering task execution. Moreover, TMS has also been shown to enhance performance on many perceptual and cognitive tasks (for a review see Vallar and Bolognini, 2011), often to the surprise of the researchers involved, and leading to contradictory explanations in the virtual lesion framework. Indeed, one of the limits of the virtual lesion hypothesis is that it only postulates an impairment of performance, while any positive results have been addressed as a paradoxical effect. Another shortcoming with the "virtual lesion" framework is that its meaning is unclear – what form does a "virtual" lesion take and how is it generated? TMS may interrupt the relevant signal by terminating neuronal activity or it might induce interfering activity (neural noise) in the stimulated area; both would modify performance but through completely different mechanisms of action (Ruzzoli et al., 2010).

At this point, based on the literature, we can trade some of the simplicity of the virtual lesion approach for increased explanatory power by examining possible alternative hypotheses. Clearly, this step forward will not invalidate the standard logic of inference (area A plays a causal role in the performance of process X but not Y). The logic will be the same, but it will allow us to draw the conclusions from a more informed perspective, above all taking into account that we are stimulating a complex adaptive system.

2.2. Signal reduction versus noise generation

TMS introduces activity by depolarising neurons (Ruohonen, 2003). For example, a study that aimed to directly measure the effects induced by TMS at the cellular level (Moliadze et al., 2003) demonstrated that spTMS induces a neuronal facilitation effect, enhancing evoked activity during the first ~500 ms, and thereafter decreasing this activity for up to a few seconds. The duration of these effects was modulated by the intensity of stimulation, and increasing stimulus intensity led to an early partial suppression of activity approximately 100–150 ms, followed by stronger facilitation. How can depolarisation of neurons cause interference?

Neural coding is concerned with the way in which sensory information is represented in the brain by neurons. One of the ways to code the signal intensity/strength is related to neuron firing frequency or rate coding, where significant events are encoded by the average activity of a pool of neurons (e.g., Adrian, 1928; Bialek and Rieke, 1992) (consider that this is a simplification, and other types of temporal coding exists as well). Neurons respond to the increased strength of a stimulus by increasing their firing frequency and by increasing the number of firing neurons (population coding). In behavioural terms, we can say that the activation of a small number of neurons and/or a low firing rate (i.e., a weak signal) will produce a slow reaction time (RT) and a low level of accuracy in detecting the stimulus target. If the number of neurons and the frequency rate increase, the RT will likely be faster, and the accuracy may be higher.

Nevertheless, the final response given by the system will be based not solely on the strength of the signal that codes for the target but on the ratio between that signal and other irrelevant activity that we can define as noise (see Fig. 1a and b no NIBS conditions). Thus, the accuracy in detecting the target will be based on the relation between signal and noise (i.e., the signal-to-noise ratio). If TMS increases the neural noise, it will change the ratio between the activity of neurons that code for the target and the activity of other neurons (non-specific activity for the task), decreasing the final performance. This effect could be interpreted as the generation (increase) of background neural activity (noise) by TMS, activity that is unrelated with respect to the relevant information/signal carried by the stimulated area (Fig. 1b NIBS high coherence). Nevertheless the TMS-induced activity is not totally random; that is, the activity induced by TMS may not be independent of the stimulus-induced neural activity or what we refer to as the 'state of the area' (see the state-dependency described below) (Pasley et al., 2009), in which case the effect of TMS is not statistically pure noise (Harris et al., 2008; Ruzzoli et al., 2011) (see Fig. 1b NIBS conditions). The probability that a neuron will be activated by a magnetic pulse depends on its neurophysiological state and on its spatial and anatomical characteristics, in relation to the induced electric field (Amassian et al., 1992; Roth, 1994) as illustrated in Fig. 2. Moreover, because the signal can only be defined in conjunction with a well-defined state of the system, defining the assumed nature of the system and the task demand helps to define signals.

Communication in the nervous system also relies on the temporal component of the firing rate of a neural population. The precise timing of action potentials, and in particular the temporal relationship of action potential generation between neurons, is a significant element in neural communication (temporal coding, Bialek and Rieke, 1992). In a given area at a given time, many signals converge, but only those that will be associated in time (have a similar distribution, see Wu et al., 2002) will give rise to effective communication mechanisms (Bi and Poo, 2001). TMS-induced noise can interfere with performance because it can increase the number of neurons that fire without temporal synchronisation, thus obstructing the synchronised conversation between neurons that code for the goal. Therefore, neuron responses will not vary linearly with the characteristics of the stimulus, and the variance of the internal stimulus distribution will increase, so that the temporal coding of discharge by a given population will not be ensured. Consequently, communication at a higher hierarchical level that relies on the timing of the spiking of converging information from different areas will not be possible (Guyonneau et al., 2004; Masquelier and Thorpe, 2007). This is just a different way to see the action of NIBS on neurons, while the effects on the systems will be the same regardless of the fact that the information is carried by rate or temporal coding.

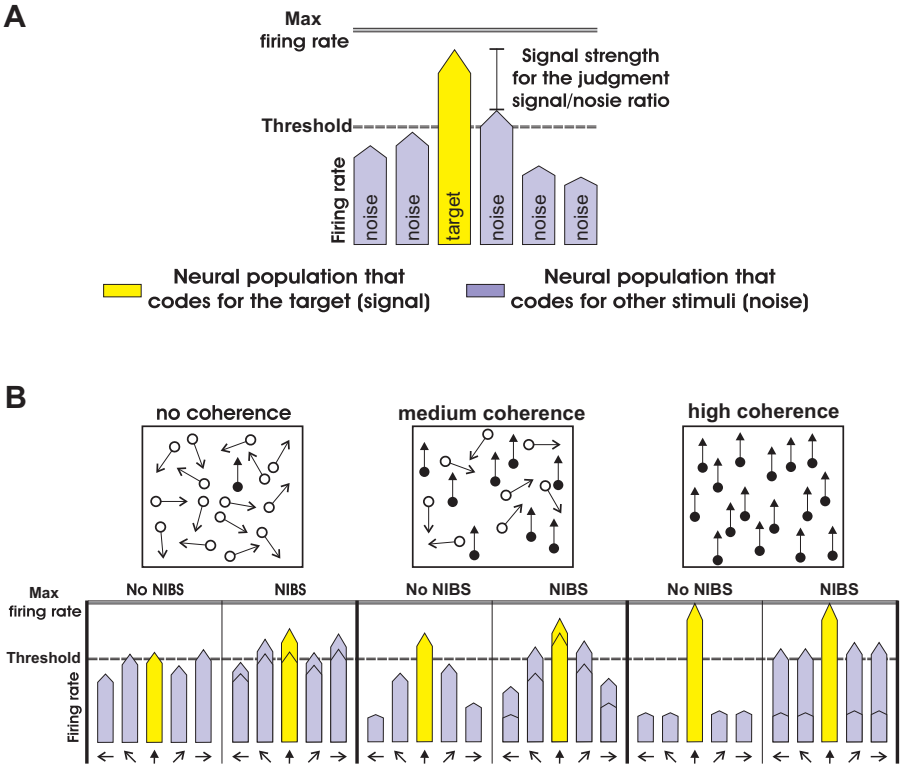


Fig. 1. (A) This figure illustrates the relation between target signal and other non-target signals. Those neurons that respond according to the task-goal are displayed as target signal (yellow), all other sources of activity that are not associated with the final task-goal are defined as neuronal noise (purple). The threshold represents the minimum intensity of a signal to reach the level to be included in the final subjective judgement. The vertical bar indicates the signal strength for the judgement, its dimension represents the features of the final behavioural outcome of a system e.g., the speed of reaction times or degree of accuracy. The larger the difference, the faster/better the behavioural performance. (B) The no NIBS plots illustrate the interaction between target signal and non-target activity (noise) when an observer tries to identify the direction of motion of a moving stimulus (upper part of the figure), depending on the difficulty of the task (low vs. high motion coherence). The NIBS plots represent possible effects of NIBS on the neural population whose activity is based on the task demands. The final behavioural outcome will depend on the final neuronal patterns. This pattern will be given by the interaction between the present state and NIBS induced activity. NIBS = non-invasive brain stimulation. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

As stated previously, the virtual lesion hypothesis can only predict impairments of performance; any positive results are considered paradoxical. But, based on the neural noise generation hypothesis, it is easy to explain either outcome. Noise is the major source of variability because it is random activity that is uncorrelated within itself and with the goal of the task and will result in the impairment of performance. Nevertheless we should consider that noise pervades every level of information processing in the nervous system, from receptor signal transduction to the final behavioural response (Faisal et al., 2008). Moreover, in non-linear systems, such as the brain, information at the threshold level can be better processed within an optimum level of noise (compared to without noise), as suggested by the concept of stochastic resonance. This can be considered a potential benefit of noise (Kitajo et al., 2003, 2007; Miniussi et al., 2010; Moss et al., 2004; Ruzzoli et al., 2010; Schwarzkopf et al., 2011) because the induced noisy activity may be synchronised with the ongoing relevant signal (Ermentrout et al., 2008; Stein et al., 2005). In this context the presence of neuronal noise might confer to neurons more sensitivity to a given range of weak inputs (Kitajo et al., 2003, 2007), thereby rendering the signal "stronger" or even "synchronised" (see Fig. 3). TMS may induce neuronal activity that adds to the ongoing neural activity, which can be considered to be part of the signal and not random noise depending on the neurons that will be activated by the task and the stimulus.

The noise generation hypothesis in NIBS can be understood within a slightly different framework based in psychophysics (Solomon, 2009). This perspective was tested experimentally by Abrahamyan et al. (2011), who applied spTMS at different intensities over V1 and concurrently measured the threshold for detection of a visual stimulus. They found that, at weak intensities below the phosphene threshold, TMS significantly improved performance. The study also confirmed the well-established effect that high TMS intensities (above the phosphene threshold) decreases subjects' visual sensitivity (Amassian et al., 1989). Abrahamyan and colleagues argued that TMS acts as a "pedestal" (Nachmias and Sansbury, 1974) to increase the response of the visual system, and this increase could result in an improvement or a decrement in sensitivity depending on the scale of the sensory and TMS-induced inputs. We return to this description in more detail later, when describing the biphasic input-response function that characterises the behaviour of neural systems.

Experimental evidence supporting the noise generation hypothesis has been provided independently by different TMS studies (Rahnev et al., 2012; Ruzzoli et al., 2010; Schwarzkopf et al., 2011; Waterston and Pack, 2010), and the final result is the physiological sum of the underlined complex activity of subpopulations of neurons that coexist in the stimulated area (Rahnev et al., 2012). Thus, abandoning the virtual lesion approach in favour of the definition of the precise mechanisms of action makes it possible to test new hypotheses and to expand the prospective applications of TMS.

2.3. State dependency

As described above, we cannot deduce pure TMS-induced effects because the effects of TMS are proportional to the level of neuronal activation during the application of the pulses (Epstein and Rothwell, 2003). In the motor system, for example, the amplitude

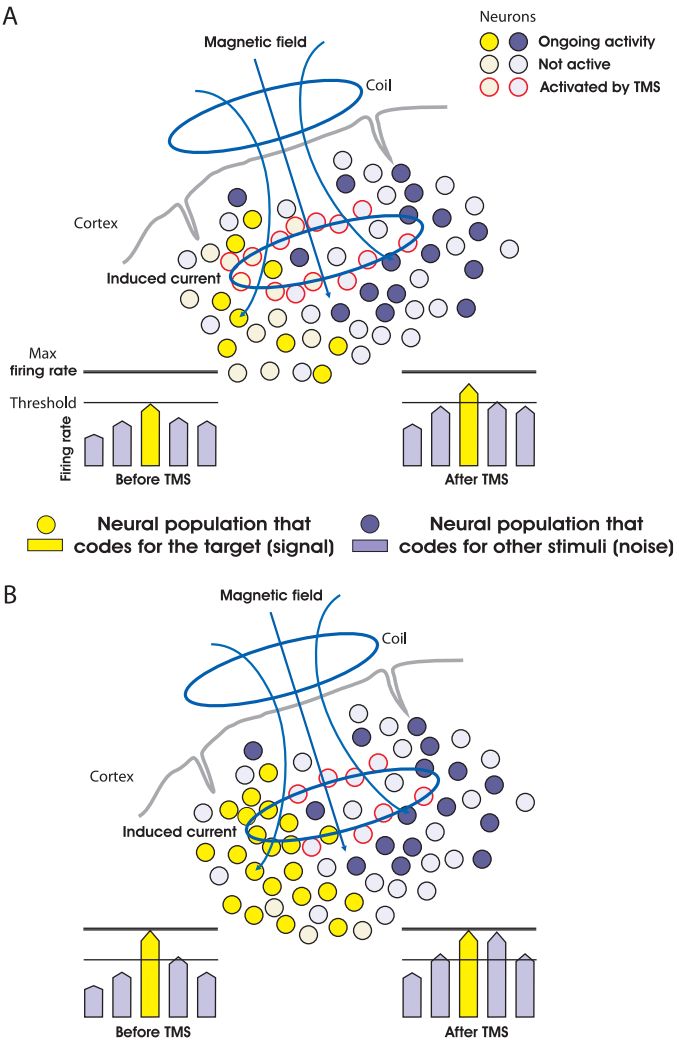


Fig. 2. The figure depicts the situation where the random neural noise induced by transcranial magnetic stimulation (TMS) will interact with the system state. Circles represent the hypothetical state of neurons. The final pattern will depend on the relation between activated and non-activated neurons and the location of the induced electric field. The final behavioural outcome will likely be an improvement in performance in (A) or a worsening of performance in (B).

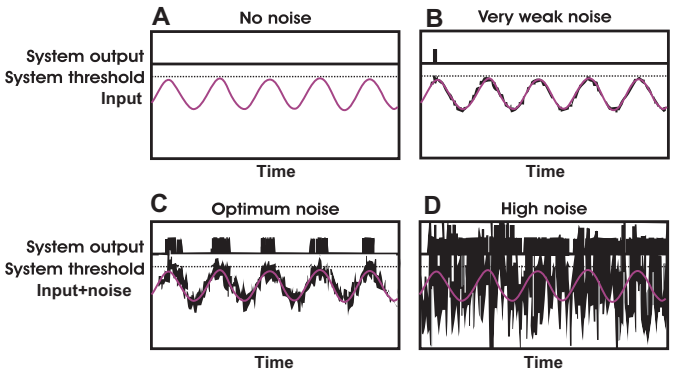


Fig. 3. Stochastic resonance. The amount of noise introduced in the subthreshold sinusoidal signal can change the final output. The final signal results in: (A) No output when no noise is introduce. (B) Very little output when presented in the presence of weak noise. (C) The best signal representation when combined with optimum level of noise. (D) Random and indistinguishable from noise alone, when high noise is introduced (from Ward et al., 2006).

of the motor-evoked potential can be increased by the voluntary contraction of the target muscle (Rothwell et al., 1987) and cortical connections can also be 'modulated' by the system state (Ferbert et al., 1992). This dependence on state was first articulated, in the TMS field, by Silvanto (see also Moliadze et al., 2003; Sack and Linden, 2003; Silvanto et al., 2008). According to state-dependency, TMS will affect the "less-active neurons within the stimulated area". In a well-designed experiment, Silvanto et al. (2007) adapted subjects to a red/green screen. After colour adaptation, delivery of spTMS over the occipital cortex elicited phosphenes that took on the same colour as the adapting stimulus. Similarly, adaptation to a motion stimulus allowed TMS to facilitate the detection of motion in the adapted direction, while impairing the detection of motion in the opposite direction (Silvanto et al., 2007). State-dependency has been tested and validated under different experimental protocols (i.e., priming or adaptation) and for different brain areas (Cattaneo et al., 2008, 2010). Pasley et al. (2009) attempted to provide physiological support for this hypothesis. They applied rTMS to the visual cortex of anaesthetised cats and observed spontaneous and visually evoked neural activity in terms of variability. They found that the higher the pre-TMS level of activity, the greater the impact of TMS during spontaneous activity. By contrast, for evoked activity (evoked by a visual stimulus), the greater the baseline activity, the lower the power of the effect induced by TMS (Pasley et al., 2009). Clearly, state dependency again does not provide an explicit mechanism of how TMS affects cognition; however, state dependency is an approach that does allow neuroscientists to reconsider the importance of the stimulated area based on its functional activation during a particular task. Using this practical approach we have the opportunity to disentangle the role of different neural populations within the stimulated area. In this context, we could consider state dependency a form of metaplasticity that describes the activity-dependent modification of the system (Abraham, 2008; Bienenstock et al., 1982).

2.4. Entrainment

A more recent application of TMS is based on what is known as the entrainment hypothesis (Thut and Miniussi, 2009; Thut et al., 2011a, 2012), that is, the possibility of inducing a particular oscillation frequency in the brain by means of an external oscillatory force (e.g., rTMS, but also tACS). The physiological basis of oscillatory cortical activity lies in the timing of the interacting neurons; when groups of neurons synchronise their firing activities, brain rhythms emerge, network oscillations are generated, and the basis for interactions between brain areas may develop (Buzsàki, 2006). Different cognitive states are associated with different oscillatory patterns in the brain (Buzsàki, 2006; Canolty and Knight, 2010; Varela et al., 2001).

Recently, Thut et al. (2011b) directly tested the entrainment hypothesis by means of a concurrent EEG–TMS experiment. They first determined the individual source of the parietal–occipital alpha modulation and the individual alpha frequency (magnetoencephalography study). They then applied rTMS at the individual alpha power while recording the EEG activity at rest. The results confirmed the three predictions of the entrainment hypothesis: the induction of a specific frequency after TMS, the enhancement of oscillation during TMS stimulation due to synchronisation, and a phase alignment of the induced frequency and the ongoing activity (Thut et al., 2011b). If associative stimulation is a general principle for human neural plasticity in which the timing and strength of activation are critical factors, it is possible that synchronisation within or between areas using an external force to phase/align oscillations can also favour efficient communication and associative plasticity (or alter communication). In this respect associative, cortico-cortical stimulation has been shown to enhance coherence

of oscillatory activity between the stimulated areas (Plewnia et al., 2008). Here, another form of stochastic resonance, the coherence resonance (Longtin, 1997), can be introduced. In coherence resonance, the addition of a certain amount of noise in an excitable system results in the most coherent and proficient oscillatory responses. The brain's response to external timing-embedded stimulation can result in a decrease in phase variance and an enhanced alignment (clustering) of the phase components of the ongoing EEG activity (entraining, phase resetting) that can change the signal-to-noise ratio and increase (or decrease) signal efficacy. In this context, phase resetting or shifting can synchronise inputs and favour communication and, eventually, Hebbian plasticity (Hebb, 1949). Thus, rhythmic stimulation may induce a statistically higher degree of coherence in spiking neurons, which facilitates the induction of a specific cognitive process (or hinders that process). Here, the perspective is slightly different (coherence resonance), but the underlining mechanisms are similar to the ones described so far (stochastic resonance) and the additional key factor is the repetition at a specific rhythm of the stimulation.

There are indications in TMS–EEG research that entrainment is plausible because of the characteristics of the EEG responses to a single TMS pulse. The spectral compositions of the EEG responses resemble the spontaneous oscillations of the stimulated cortex. For example, TMS of the "resting" visual (Rosanova et al., 2009) or motor cortices (Veniero et al., 2011) triggers alpha-waves, the natural frequency at the resting state of both types of cortices.

With the entrainment hypothesis, the noise generation framework moves to a more complex and extended level in which noise is synchronised with on-going activity. Nevertheless the model to explain the final outcome will not change, stimulation will interact with the system and the final result will depend on introducing or modifying the noise level.

The entrainment hypothesis makes clear predictions with respect to on-line repetitive TMS paradigms' frequency engagement as well as the possibility of inducing phase alignment, i.e., a reset of ongoing brain oscillations via external spTMS (Thut et al., 2011a, 2012; Veniero et al., 2011). The entrainment hypothesis is superior to the localisation approach in gaining knowledge about how the brain works, rather than where or when a single process occurs. In this sense, TMS is likely the best available method to test a renewed topic in neuroscience: the role of brain oscillations. In fact, it is tempting to speculate that one TMS pulse will phase-align the natural, ongoing oscillation of the target cortex. When additional TMS pulses are delivered in synchrony with the phase-aligned oscillation (i.e., at the same frequency), further synchronised phase-alignment will occur, which will bring the oscillation of the target area in resonance with the TMS train. Hence, we expect entrainment in cases of frequency-tuning of TMS to the underlying brain oscillations (Veniero et al., 2011).

3. Transcranial electric stimulation

As previously reported, tES (tDCS, tACS, and tRNS) is a non-invasive method of cortical stimulation in which weak direct currents are used to polarise target brain regions. The most used and best known method is tDCS, as all considerations for the use of tDCS have been extended to the other tES methods. The hypotheses concerning the application of tDCS in cognition are very similar to those of TMS, with the exception that tDCS was never considered a virtual lesion method. It has been suggested that, depending on the polarity of the stimulation, tDCS can increase or decrease cortical excitability in the stimulated brain regions and facilitate or inhibit behaviour accordingly, thereby enabling the investigation of the causal relationships between brain activity and behaviour by means of neural modulation. As previously mentioned tES does not induce action potentials but instead modulates the neuronal response threshold so that it can be defined as subthreshold stimulation. Changes in the neuronal threshold result from changes in membrane permeability (Liebetanz et al., 2002), which influence the response of the task-related network. It is possible to hypothesise the same mechanism of action for tES methods as for TMS, i.e., the induction of noise in the system. However, the neural activity induced by tES will be highly influenced by the state of the system because it is a neuromodulatory method (Paulus, 2011) and its effect will depend on the activity of the stimulated area. Therefore, the final result will depend strongly on the task characteristics, the system state and the way in which tES will interact with such a state.

3.1. Transcranial direct current stimulation

tDCS induces membrane depolarisation (anodal stimulation) and hyperpolarisation (cathodal stimulation) (Liebetanz et al., 2002; Nitsche et al., 2003a,b, 2004, 2005). From a methodological perspective, most of the general concerns for TMS are valid for tDCS, with some exceptions: tDCS does not induce depolarisation and therefore will only induce the firing of neurons that are near threshold, which means that neurons not influenced by the task are less likely to discharge. From a cognitive neuroscience standpoint, the effect of applying anodal tDCS during task execution is considered to induce facilitation, while cathodal tDCS should induce inhibition of task performance. In this sense, it is believed that tDCS primes the behavioural system by increasing/decreasing cortical excitability and producing corresponding effects in the cognitive system. Therefore, tDCS-induced effects are more likely to be sensitive to the state of the network that is active at that moment. Thus, the polarisation of neurons in combination with ongoing synaptic input can be contextualised in a framework of synaptic co-activation. This is evocative of Hebbian-like plasticity mechanisms as the combination of tDCS with task execution is like the co-activation of a specific network. The spatial and temporal resolution of the tDCS effects are somewhat reduced compared with those of TMS, but this drawback may be overcome by considering the state of the system, as previously described.

While the main framework of a "facilitatory" anodal stimulation and a "worsening" cathodal stimulation is well-grounded, it is only valid for the use of tDCS on the motor system (Nitsche et al., 2008). Anodal tDCS facilitative behavioural effects have been identified for several functions, but the relation between facilitation and inhibition is often quite complex (Jacobson et al., 2011). In many cognitive neuroscience experiments, the stimulation of non-motor areas has led to the observation that behavioural effects are often not unequivocal, with anodal stimulation usually inducing facilitation and cathodal stimulation inducing a range of effects (Jacobson et al., 2011). Here, the point is that the neurophysiological dimension cannot be used as a simple mechanistic approach for mapping onto behavioural effects (Miniussi et al., 2010). It can be suggested that anodal tDCS may induce facilitation when the task is well-trained or familiar, but such facilitation is not present during the performance of a novel task (Dockery et al., 2009). For example in a well-established skilled task, such as naming, the noise is reduced, so that the signal emerges clearly from the noise, and anodal stimulation can facilitate faster processing. In the same task, cathodal tDCS would reduce the possibility of firing in response to a stimulus, but because the signal is strong enough to elicit a response, the probability that cathodal stimulation can interfere with task execution is quite low. In a novel task, the context is different: there is more background noise because the neural networks are not consolidated, and many signals close to the target signal will be present. In this case, an increase in noise by anodal tDCS will not help task execution as it will increase the signal but also the noise, which

is close to the threshold. Nevertheless, in such situations, cathodal tDCS can induce facilitation by reducing the general noise and helping the signal emerge (Antal et al., 2004; Dockery et al., 2009). Antal et al. (2004) found that cathodal tDCS applied to the left visual middle temporal area (MT-V5) improved performance in a visuomotor coordination task when a large amount of visual noise was present in the visual stimulus. Therefore, cathodal tDCS appears to act as a neuronal filter that reduces noise. The idea is the same as that of the neurophysiological mechanism called 'lateral inhibition' – a mechanism that can reduce the neural activity due to a non-relevant signal (noise) together with that due to the relevant signal, sharpening the profile of the excitatory response and improving the final performance. Therefore, we cannot consider tDCS to be a simple neuromodulatory method in which anodal-tDCS increases excitation to induce behavioural facilitation and cathodal tDCS yields the opposite effect via inhibition. The neural noise induced by the stimulation will affect the performance depending on the state of the system, which is mainly determined by the task input. In this sense, tDCS neuromodulation will interact with the level of excitation of the system, driven by the task to shape the final result (Bienenstock et al., 1982). Once again, the level of noise introduced in the system will be the key factor in shaping the final result.

In contrast to TMS, tDCS is a continuous stimulation procedure. Continuous stimulation can engage neurophysiological homeostasis mechanisms, which serve to maintain neural activity within a normal functional range (Siebner et al., 2004). In this context, it could be suggested that neurons can adjust the threshold of the system based on the constant input. This type of mechanism could therefore alter the final effect of the stimulation in terms of excitatory or inhibitory responses of the stimulated area, particularly in the context of a complex framework.

3.2. Transcranial alternating current stimulation

tACS allows the brain to be stimulated at specific frequencies: like rTMS, it has been suggested that tACS can modulate ongoing neuronal activity (Zaehle et al., 2010) and related behaviour (Kanai et al., 2008) by inducing specific brain oscillations. We can theoretically predict that this mechanism will produce a frequency 'entrainment' in the stimulated cortical region or in the connected areas during a prolonged stimulation. Using tACS (as for rTMS), an oscillatory current can be delivered to the cortex to induce it to oscillate at that particular frequency, which is area-dependent (Kanai et al., 2008). An advantage of tACS is that there are fewer safety concerns for this method than for rTMS (Rossi et al., 2009), and therefore there are no restrictions on the frequency that can be used. The idea is that, like for TMS, the so-called 'rhythmic approach' (Miniussi et al., 2012a; Thut and Miniussi, 2009) refers to the possibility of investigating how tACS interacts with oscillatory brain activity in order to establish a causal relationship between brain oscillations and cognition.

Several authors applied tACS over the primary motor area with the aim of specifically influencing brain oscillations. Stimulation was applied at different frequencies during motor tasks, and a significant improvement in performance was observed at the alpha frequency stimulation (Antal et al., 2008; Feurra et al., 2012; Joundi et al., 2012; Pogosyan et al., 2009). It has been also shown that changing the local activity with tACS may affect the functional networks that are responsible for motor performance and improved task execution (Joundi et al., 2012). In vision, Zaehle et al. (2010) demonstrated that tACS was able to modulate EEG oscillations, in particular at alpha frequency when subjects were at rest (no task was involved). In contrast, Kanai et al. (2008) reported that occipital stimulation most effectively induced phosphenes when applied at the alpha frequency in darkness; whereas, the beta frequency was more effective in the light (but see Schutter and Hortensius, 2010; Schwiedrzik, 2009).

The effect of tACS may rely on the intrinsic resonance of the system. Resonance is the tendency of a system to oscillate with greater amplitude at specific frequencies than at others; these frequencies are related to the specific structure of a given system. At these specific frequencies, even small alternating currents can produce larger amplitude ringing than the input because the system stores vibrational energy. An easily recognised example is given by the wind-induced collapse of the Tacoma Narrows Bridge (http://www.youtube.com/watch?v=j-zczJXSxnw). The wind provided a weak external periodic frequency that matched the bridge's natural structural frequency, inducing large oscillations that destroyed the bridge. The same may occur in the cortex, which produces frequencies in a range of 0.01 up to 600 Hz. Applying a weak alternating current at a suitable frequency is a cooperative effect that can produce larger amplitude ringing, increasing synchronisation. Resonances have now been described in various central neurons (Hutcheon and Yarom, 2000). Furthermore, in a recent in vitro study (Deans et al., 2007), it was shown that very weak extracellular alternating electric fields have the ability to entrain an oscillating network (Deans et al., 2007; Radman et al., 2007; Reato et al., 2010). Thus, if a given network is carried near the threshold level (prone to activation), a small polarisation may drive the neuronal discharge that will induce phosphene perception.

It has been suggested that the cortex may actually respond to external stimulation (i.e., TMS), producing natural local frequencies (Rosanova et al., 2009; Veniero et al., 2011) depending on the ongoing activity. Given the neuromodulatory characteristics of tACS and previous TMS results, we may be able to modulate cortical oscillations with tACS but are likely unable to superimpose an "out of condition/unnatural" frequency on the system. As with TMS, coherence resonance can be the key mechanism for the addition of certain amounts of noise that make system oscillatory responses more coherent and proficient. In other words, tACS produces a small amount of activity (noise) that is close to the system oscillatory phase (synchronised), and this small amount of activity will sum with the system's response in coherence resonance (Fig. 3), increasing the signal-to-noise ratio and improving performance (or decreasing it). Once again, the concept of stochastic resonance can be used in this framework: a weak periodic stimulation entrains the system fluctuation, enhancing the biological signal. Although very suggestive, these considerations are only speculations, and even if tACS may be considered an important device for manipulating cortical oscillatory activity, adequate support is lacking (Brignani et al., 2013; Schwiedrzik, 2009).

3.3. Transcranial random noise stimulation

tRNS involves the application of a random electrical oscillation spectrum over the cortex. At present, tRNS can be applied in three frequency ranges: the entire spectrum (from 0.1 to 640 Hz), in the low band (0.1–100 Hz) or in the high band (101–640 Hz) (Terney et al., 2008). This technique is newer than other tES applications; therefore, exploration of its possible mechanisms of action in cognition has been limited.

Terney et al. (2008) recently showed that ten minutes of tRNS on the motor cortex at high frequency bands is able to positively modulate cortical excitability (i.e., increase the amplitude of motor-evoked potentials). Behavioural improvement in a motor learning task also resulted from the application of the entire frequency spectrum (Terney et al., 2008). In a recent study, Fertonani et al. (2011) applied tRNS to the visual system and compared the high/low frequency bands to other tES techniques (anodal/cathodal tDCS). High-frequency tRNS on the visual cortex of healthy subjects during a visual perceptual learning task was found to significantly

improve performance more than anodal tDCS, which was previously thought to be the best method to positively modulate behaviour. The authors suggested that the mechanism of action of tRNS might be based on the repeated subthreshold stimulations that prevent homeostasis of the system (Fertonani et al., 2011). This effect might potentiate the activity of the neural populations involved in a task and, in turn, facilitate transmission between neurons.

Also the effects of tRNS may be explained in the context of the stochastic resonance phenomenon; tRNS is a random-frequency stimulation that might induce random activity in the system (i.e., noise). The presence of neuronal noise might serve as a pedestal to boost the sensitivity of the neurons to a given range of weak inputs (i.e., the neurons with the same directionality as the signal), thereby increasing the signal-to-noise ratio. Therefore, as described for TMS, tDCS and tACS, the effect of tRNS on neuronal activity may not just be the random addition of noise but may be related to the functional activation induced by the task.

In conclusion, even if the mechanism of action of tES is different than that of TMS (neuromodulation vs. depolarisation), we can assume that, like TMS, tES induces neural activity in the stimulated area, which can theoretically be defined as noise. Nevertheless, when compared to TMS, the noise induced by tES will never be random but will depend on stimulation parameters, specifically, the system state and input. This is because tES cannot induce a direct over-threshold depolarisation but can modulate the firing rate of the stimulated area. Such induced activity will consequently shape behavioural measurements.

4. A unified hypothesis of the functional effects of NIBS: noise generation in a non-linear system

In TMS, the magnetic pulse causes the rapid and above-threshold depolarisation of cell membranes affected by the current, leading to the transynaptic depolarisation or hyperpolarisation of connected cortical neurons. Therefore, TMS activates a neural population that, depending on several factors, can be congruent (facilitate) or incongruent (inhibit) with task execution. tES induces a polarisation of cortical neurons at a subthreshold level that is too weak to evoke an action potential. However, by inducing a polarity shift in the intrinsic neuronal excitability, tES can alter the spontaneous firing rate of neurons and modulate the response to afferent signals. In this sense, tES-induced effects are even more bound to the state of the stimulated area that is determined by the task conditions. In short, NIBS leads to a stimulation-induced modulation of activity that can be substantially defined as noise induction. Nevertheless, such induced noise will not be just random activity but will depend on the interaction of many parameters, from the characteristics of the stimulation to the task performed. In other words, the noise induced by NIBS will be influenced by the state of the neural population of the stimulated area (Fig. 2).

The relation between signal and noise can be understood within a simple and precise framework based on a sigmoid input-response function. In biological systems, the strength of the response to a given input is rarely a linear function of the strength of the input. In neuroscience, there is ample evidence that the response (typically the firing rate) of individual neurons to varying levels of input intensity is described by a sigmoid (S-shaped) function, of the sort shown in Fig. 4A (Carandini and Ferster, 1997; Sclar et al., 1989). Assuming the strength of a stimulus is fixed (at *s*), varying only the strength of the noise (*n*) will change the overall input strength (horizontal axis). Neurons show very little change in their response (vertical axis) to very weak input strength, but as the strength of stimulation passes a "threshold" the response strength rapidly increases, marked by the upward inflexion of the input-response curve. Thereafter, as input

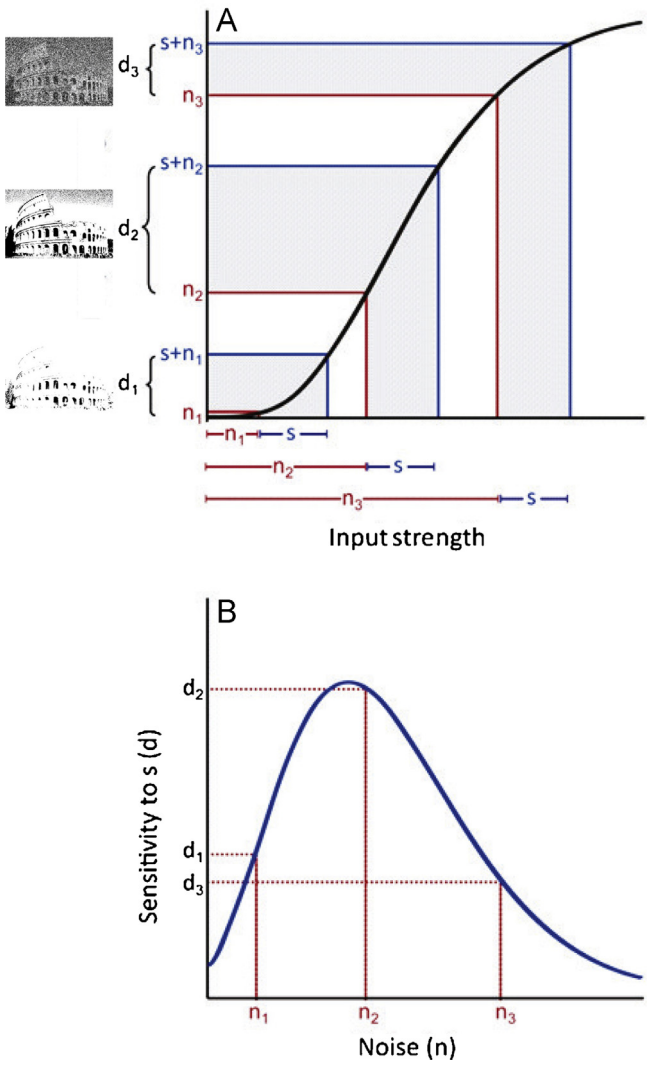


Fig. 4. (A) A sigmoid input-response function. A fixed signal, *s*, is added to differing levels of noise, *n*. The differential response, *d*, to *s* varies as a function of the size of *n*: when *n* is low (n_1) or high (n_3), *d* is smaller than when *n* is at an intermediate level (n_2). The function shown here is based on a cumulative gamma function. (B) The first derivative of the function in panel A, corresponding to the slope of that function. It shows how, *d*, the sensitivity of the response to *s*, changes across all values of *n*.

strength increases further, the neuronal response begins to "saturate", where the function begins to flatten. Thus, the responsiveness of a neuron to variation in input strength – its discrimination sensitivity – is reflected in the slope of the sigmoid input-response function: discrimination sensitivity is low with very weak input, increases for input at an intermediate range of intensity, and then decreases again as input approaches the saturation point.

A similar sigmoid-like function is known to underlie behavioural responses to stimulation in many sensory systems, although in this case the shape of the input-response function is derived by reverse inference from changes in discrimination sensitivity. For example, human participants are relatively poor at detecting a very weak sensory stimulus, and can only discriminate between the presence versus absence of the stimulus when its strength exceeds a threshold. However, they are often much better at discriminating between a stimulus that is at this threshold versus one that is just above the threshold. This increase in discrimination sensitivity, usually measured as a decrease in discrimination thresholds, is known as the "pedestal effect", and has been shown to operate at low sensory

inputs in visual, auditory and tactile domains (for recent review see Solomon, 2009). As stimulation intensity increases further, discrimination sensitivity declines according to "Weber's law", in which the size of the "just-noticeable difference" is a fixed ratio of the average intensity of the stimuli being discriminated. The overall pattern of initial improvement and then decline in discrimination sensitivity, described as a "dipper function" when plotting discrimination threshold against stimulus intensity, speaks to an underlying sigmoid function relating stimulus strength to perceptual response: the function is flat for very weak stimuli, becomes steeper for stimuli at low to intermediate intensities, before progressively flattening again at higher intensities (Fig. 4A).

Performance in any situation depends on accurate detection of signal above noise. For example, if an observer tries to identify the direction of motion of a moving stimulus, his or her ability will depend on the strength of the coherent motion signal above all background motion signals. In neurophysiological terms, correctly identifying direction of motion from the response of a population of motion-sensitive neurons (e.g., in area MT) will depend on the difference between the baseline response rate among all neurons in the entire population, which constitutes the level of noise, and the response of those specific neurons that code for the stimulus' motion (see Fig. 1A). Thus, to identify the signal, the observer must compare the response to noise with the response to signal plus noise. A key property of the input-response function described in the preceding paragraph is that the observed difference in response between two levels of input will depend on the absolute magnitudes of those inputs. Consider, for example, three different levels of noise input, n_1, n_2, and n_3, as depicted in Panel A of Fig. 4. To each level of noise, a stimulus of fixed strength, s, is added. Even though the size of s is the same in each case, the response to s differs depending on the level of noise as it is transduced through the sigmoid input-response function. In the example shown, the difference, d, in response to $s+n$ versus n is larger for $s+n_2$ than for either $s+n_1$ or $s+n_3$. The improvement in detection of s when noise is increased from a very low level, at n_1, to an intermediate level, at n_2, explains the stochastic resonance effect that is sometimes observed when uncorrelated input (noise) is introduced into a system. The frequent observation that large amounts of noise, such as at n_3, impair performance is explained by the decrease in the difference in response to $s+n$ versus n. The complete function relating the detectability of s to n is shown in Panel B of Fig. 4. Clearly as described before, the effects of brain stimulation will be proportional to the level of neuronal activation during the application of the pulses, the so-called state dependency as represented in Fig. 5. It should be noted that a shift in the sigmoid input-response function can be induced also by off-line NIBS protocols.

We propose that the response properties described here present a very useful way to understand the impact of NIBS on brain function and behavioural performance. Given that NIBS necessarily involves the relatively indiscriminate activation of large numbers of neurons, its impact on a neural system can be easily understood as introducing or amplifying noise (or a possible reduction of noise in the case of cathodal tDCS). The framework proposed here offers the opportunity to understand how NIBS, by altering levels of noise, could usually impair, but sometimes improve performance on a task, depending on the amount of noise introduced, the existing level of noise in the system or in the task, and the size of the signal. Another important advantage to this approach is that this single framework can be applied readily across the relevant domains. As described here, it can be applied equally to consideration of responses of individual neurons, population responses of neurons, or the behaviour of a subject performing a task. Thus it provides a theoretical basis for translating explanatory concepts and interpretation of findings across different levels of the system.

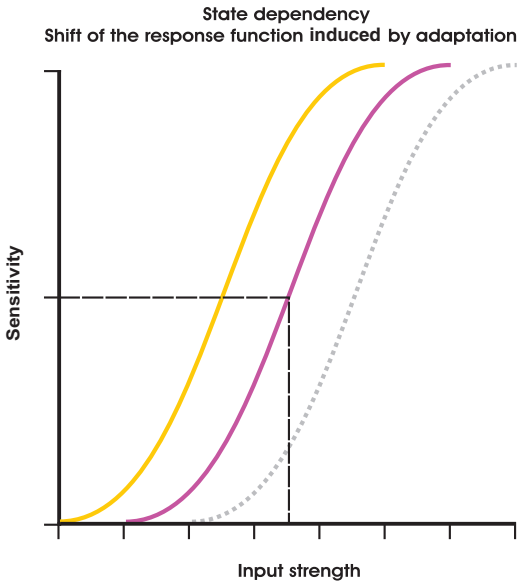


Fig. 5. How a sigmoid input-response function can be modified by adaptation. Adaptation can also be induced with an off-line NIBS protocol, changing the state of the subjects and therefore the final relation between input strength and sensitivity (i.e., state dependency).

5. Conclusions

In sum, although the types and number of neurons "triggered" by NIBS are theoretically random, the induced change in neuronal activity is likely to be correlated with ongoing task-relevant activity, yet even if we are referring to a non-deterministic process, the noise introduced will not be a totally random element. Because it will be partially determined by the experimental variables, we could estimate the level of noise that will be introduced by the stimulation and by the task and potentially determine the interaction between the two levels of noise (stimulation and task). Clearly, with transcranial stimulation, we will never be able to induce stimulation with a focused and highly targeted signal to a clearly defined area of the brain to establish a unique brain-behaviour relationship; therefore, the only definition that we can apply to the introduced stimulus activity in the brain stimulation is 'noise.' The neural effects of NIBS protocols have the potential to offer important insights into the mechanisms that underlie the capacities of the central nervous system and will aid the evaluation of neurocognitive theories of the behaviour-brain relationship. The opportunity to directly influence brain activity in a clear theoretical framework raises even more exciting possibilities for future basic and clinical neuroscience studies involving NIBS.

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