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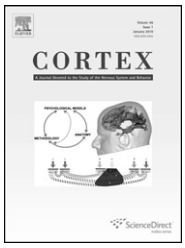

Discussion forum

The mechanism of transcranial magnetic stimulation in cognition

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Despite the widespread usage of transcranial magnetic stimulation (TMS) in clinical and basic research, the exact mechanisms of action and interactions with ongoing neural activity remain unclear. However, thanks to recent biophysical studies on electromagnetic induction of neural tissue (Wagner et al., 2009) we now know more about some basic properties of TMS effects. This basic knowledge is important in planning and interpreting TMS studies and in cognitive neuroscience experiments a theoretical framework is also necessary.

TMS data have traditionally been interpreted in the ''virtual brain lesion'' framework (Walsh and Cowey, 1998). The terminology was proposed by analogy with neuropsychological and animal lesion studies and TMS is described as inducing a temporary, reversible lesion in the stimulated area, avoiding problems related to cortical plasticity and functional reorganisation (Walsh and Pascual-Leone, 2003). Based on this interpretation, TMS has been utilised to define the putative role of areas during the execution of cognitive tasks, and this approach has been very productive.

Semantically, the term ''virtual lesion'' identifies the effect induced by TMS as blocking the function of a population of neurons that are temporarily ''lesioned'' by the TMS pulse. Nevertheless, the TMS pulse induces a depolarisation of a group of neurons that in turn might activate other neurons, and the final behavioural outcome depends on the role of the stimulated area in relation to the network engaged in such a task (Sack and Linden, 2003). The ''virtual lesion'' hypothesis has, however, confused people on the issue of how TMS can possibly lead to enhanced performance (e.g., Harris et al., 2008b; Walsh et al., 1998). In addition, the brain may also compensate for interference either within an area or across a circuit because it does not react passively to cortical stimulation and because the state of activation and the task demand influence the response (e.g., Bestmann et al., 2008; Ruff et al., 2009; Siebner et al., 2009; Silvanto et al., 2008). Finally, the virtual lesion term is just that, words, and it is not informative about the possible mechanisms of action of TMS. It is unclear whether one best describes TMS as suppressing neural signals, or if it adds random neural activity in the stimulated area (Walsh and Cowey, 2000; Harris et al., 2008a). The result in both cases will be altered information processing, but we have one ''hypothesis'' (if for the sake of argument we can aggrandise the analogy in that way) and (at least) two possible mechanisms of action (i.e., either suppression of the relevant signal or addition of random neural noise).

For these reasons, we now have a choice: a separate explanation for each disruption or enhancement, or a mechanistic explanation of one effect producing positive or negative effects depending on the task, timing of TMS and areas involved. Nevertheless, it seems that because a great deal of TMS research does adopt a ''point and shoot'' methodology and conceptualises results as negative (''lesion'') or positive (''paradoxical'') it is clear that some change in terminology or reconceptualization of the effects of TMS should be discussed. Interpretations of data can go beyond a simple relationship between an anatomical area and impairment of behaviour as suggested by the virtual lesion terminology.

The key point is that we need to dissociate the language of physiological effects from those of behavioural effects (Miniussi

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et al., 2008; some papers unfortunately term disruptions as "due to inhibition" and facilitations as "due to excitation"). Our suggestion here is that behavioural effects are described in terms of models of the psychological measures. The best available model of decisions for most psychological experiments is signal detection theory (SDT: Green and Swets, 1966) and this allows one to dissociate statements of effects from premature statements about mechanism.

The behavioural outcome of a system (e.g., reaction times or accuracy) represents the final output of a population of neurons whose activity is based on the functional attitude of the activated system (i.e., its morphology and state) and the task demands (i.e., input). Those neurons that respond in the same way to the task-goal will display signal correlation, represented as similar tuning curves that will contribute to the final output (Stein et al., 2005). There is also another source of activity that does not contribute to the goal and will determine the trial-to-trial response variability (Stein et al., 2005). We can define this activity as *neuronal noise*, a term that describes the "random" activity of neurons that is not associated with the encoding of behaviourally relevant variables. Noise is generally considered the main factor that limits the capacity of information processing by the brain and its effects could be of theoretical interest in a biological context (e.g., Ermentrout et al., 2008; Stein et al., 2005). In general, noise decreases performance, but nonlinear systems, like the brain, can use noise to enhance performance through stochastic resonance (Moss et al., 2004). The presence of neuronal noise might confer to neurons more sensitivity to a given range of weak inputs, i.e., those neurons "randomly activated" and that go in the same direction of the signal, thereby rendering the noise in the signal (Stein et al., 2005). Noise can either interfere with or facilitate performance. It is easy to imagine how random noise can interfere with performance, for example by either introducing temporally random firing or obstructing synchronised interactions between populations. The opposite may be observed if the induced activity is somehow synchronised with the temporal coding between neural populations (i.e., neural synchronisation or phase locking) at an adequate intensity (i.e., optimum level) (Ermentrout et al., 2008; Stein et al., 2005).

We can now return to how to interpret TMS effects produced by interactions with ongoing neural activity. We could refer to this activity as neural noise because it is activity artificially induced in the system. Thus, TMS could modify system activity by altering whatever information is carried by a precise induced neural firing pattern. This effect could be interpreted as the TMS generating neural activity (noise) with respect to the relevant information carried by the stimulated area (signal). Nevertheless, TMS will influence not only neurons that contribute to noise but also those that code for correct responses (i.e., the finalised activity, or signal). TMS may induce neuronal activity that adds to the *ongoing neural activity* as a complement to the extant activity pattern (i.e., activated by state and task demand), which can be considered both as noise and as part of the signal, depending on the neuron population that will be activated.

In this framework, it is also possible to explain facilitatory results in terms of the strict relationship between noise and signal in the nervous system: enhanced performance, for example, may be observed with an optimum level of noise. It is also possible to explain different effects induced in the same area, depending on the task demands and stimulation parameters. Thus, the relationship between signal and noise seems to offer a better view of the induced effects when considering that both have the same nature (neural activity) and that they provide complementary rather than mutually exclusive information.

It is clearly important that we pursue more precise descriptions of TMS-induced effects to allow more sophisticated inferences (beyond area X is necessary for function Y). Such a theoretical framework is necessary to interpret the effects of double dissociations, cortico–cortical interaction, state and plasticity and will therefore improve the range of parameters at our disposal in programmes of rehabilitation. Such an opportunity to have a formal framework in which precise behavioural TMS effects can be discussed it will also lead to more complex modelling of TMS effects on brain tissue.

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