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Editorial

Effects of non-invasive brain stimulation on attention: Current debates, cognitive studies and novel clinical applications

1. Introduction

Historical accounts of non-invasive brain stimulation date back as far as 43 AD with Scribonious Largus describing the use of electrical current to treat headaches (Pascual-Leone and Wagner, 2007). It was as late as 1976 though, that Anthony Barker and his group at the University of Sheffield first developed a device capable of generating peak fields of 2 T and in 1985 introduced transcranial *magnetic* stimulation (TMS), a non-invasive technique that uses principles of electromagnetic induction to focus current in the brain and modulate the function of the cortex (Pascual-Leone and Wagner, 2007).

TMS induces a current that elicits action potential in neurons. By contrast transcranial *electric* stimulation (tES) (which involves the application of small electrical currents directly to the scalp through a pair of electrodes, or an array in the case of HD-tDCS) is too weak to actively generate an action potential. Nonetheless tES can induce changes in the resting membrane potential and the postsynaptic activity of cortical neurons, and this in turn can alter the spontaneous firing rate of neurons and modulate their response to afferent signals, leading to changes in synaptic efficacy (Miniussi et al., 2013). The electrical current used, as well as its polarity can be direct (anodal or cathodal transcranial direct current stimulation (tDCS)), or alternating at a fixed frequency (transcranial alternating current stimulation (tACS)) or at random frequencies (transcranial random noise stimulation (tRNS)).

In this special issue we present the latest reviews, “stimulating” experimental findings and novel clinical applications on the effects of non-invasive brain stimulation on attention. So far the vast majority of studies in this field have focussed on motor function and we aim to highlight the significant progress made in the field of attention, both in terms of cognitive and clinical findings. That non-invasive brain stimulation as a tool has attracted the “attention” of many researchers and clinicians in the past 5 years, can be seen by the fact that a review of this topic by (Utz et al., 2010) in this journal (!) was among the Top 5 cited articles in Neuropsychologia over the last 5 years (http://www.journals.elsevier.com/neuropsychologia/).

This issue is also particularly timely, as non-invasive brain stimulation (tES in particular) has recently come under strong attack in reviews by Horvath et al. (2015a, 2015b). According to New Scientist (Jan 2015) brain stimulation received its second drenching, after Horvath and colleagues found in November 2014 that tDCS has no consistent *physical* effect (beyond MEP amplitude modulation, Horvath et al., 2015a). When, in a further review (Horvath et al., 2015b), they pooled data from more than 400 studies reporting changes in *cognitive* skills following a session of tDCS, they (again) failed to find evidence for effects in healthy populations. The review did not cover studies on attention (although this may be addressed in a forthcoming article) and the authors concede that there was not enough data to investigate how state dependency may influence effects (see also Shin et al. (2015), Painter et al. (2015), Learmonth et al. (2015) this issue and also Nitsche et al. (2015) on this and other important neglected influences such as montage, waveform applied, inter-individual differences etc.) and that over 70% of their analyses included only 2–3 papers. In fact this later point is the focus of a current re-evaluation by Price and Hamilton (2015b) who point out that, rather than running an analysis across all papers, Horvath et al. (2015b) subdivided each domain and performed numerous analyses that were all underpowered. Price and Hamilton (2015) further argue poignantly that 23 of the 59 analyses run, used data from early “on-line” measurements (data that were collected while stimulation was first commenced), when, as nearly all researchers in the field would agree, it is highly unlikely to observe behavioural effects immediately after the start of stimulation.

With this special issue we hope to provide a positive focus by presenting 4 invited novel reviews and 14 invited original reports that we – for the purpose of this editorial – divide into four sections with the first two sections focusing on basic cognitive findings – (1) uncovering spatial attention with TMS, (2) uncovering spatial attention with tES (tDCS) and arousal with tES (tRNS) – and the later 2 on clinical studies (3) clinical applications of brain stimulation and (4) Galvanic-Vestibular-Stimulation for neuromodulation.

2. Uncovering spatial attention and its timecourse with TMS

A clear sign of just how well TMS is established as a tool to investigate the neural correlates of attention is the review by Olk et al. (2015) which, even after focusing solely on studies investigating the effects of TMS on the control of attention and manual response selection in conflict situations, identified 204 relevant articles. The authors then review 18 articles which investigated conflict elicited in three well established paradigms: the Simon, Flanker and Stroop tasks.

From reviewing results of the Simon task, which is largely investigated with single and double pulse TMS after stimulus onset, they underline the important role of the frontal eye field (FEF) in the encoding of spatial attributes of stimuli critical for response conflict, the angular gyrus (AG) in orienting attention, with the left

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supramargininal gyrus (SMG) for the transformation of spatial information into code for action.

They further argue that the role of attention is deemed larger in the Flanker paradigm as flankers have to be ignored and attention paid to the target instead. When this is investigated with repetitive TMS, the right posterior parietal cortex (PPC) is clearly implicated in the allocation of spatial attention during stimulus encoding, as the left flanker effect is abolished by TMS over this area.

In fact related to this, an important aspect of attentional control is the differential contribution of the two cerebral hemispheres and several competing theories on the mechanisms underlying attentional control have emerged over the years. Yet despite their substantial differences, all emphasise the importance of hemispheric asymmetries. TMS has proven particularly successful in teasing their relative roles apart, as it allows a selective perturbation of the dorsal and ventral fronto-parietal network. In their article (Duecker and Sack, 2015) first review the TMS literature with respect to hemispheric asymmetries within the dorsal attention network. They then discuss the relative contributions of the Heilman and Kinsbourne attention models. The PPC in particular appears to show a clear contralateral attention bias for each hemispace as well as competition between them. In contrast, the right frontal eye field seems to be involved in shifting attention towards both hemifields, whereas the left frontal eye field seems to be involved in shifting attention toward the contralateral hemifield only. In the light of this evidence, the authors propose a revision of the original Corbetta attention model (Corbetta and Shulman, 2002, 2011) and introduce their hybrid model of hemispheric asymmetries in attentional control. They also link this novel model to the pre-dominance of spatial neglect after right hemisphere damage, arguing that these hemispheric asymmetries within the dorsal fronto-parietal network play a distinctive role in spatial neglect. Finally, they outline future perspectives derived from their model, arguing that the PPC and the frontal cortex could be further subdivided into multiple spatial maps of the contralateral visual field which appear to be functionally different. Each of them could be targeted by high resolultion TMS to investigate their distinctive contributions to different aspects of spatial attention on a much smaller spatial scale than investigated so far.

As part of the attention network, the PPC and the dorsolateral prefrontal cortex (DLPFC) are also involved in spatial priming. We know that top-down control can modulate processing at target and distractor positions over a sequence of trials, leading to positive priming at prior target positions and negative priming at prior distractor positions. The exact time course, as well as the interplay of the right DLPFC and right PPC during spatial priming, is investigated precisely by (Kehrer et al., 2015) in their TMS study. They applied single TMS pulses over the right PPC, the right DLPFC or over the vertex (sham stimulation) at different time intervals after onset of a probe display, during a spatial negative priming paradigm. Both suppression of the negative priming effect at a previous distractor position, and enhancement of positive priming at a previous target position was found if a TMS pulse was applied 100 ms after the probe display onset, either over the right DLPFC or the right PPC. Kehrer et al. thus suggest that top-down mechanisms within the right fronto-parietal attention network are compromised during TMS interference in this time window.

Olk et al. (2015) conclude that future TMS studies might benefit from capitalising on measurements other than reaction time and accuracy and suggest that the monitoring of eye-movements could be a fruitful approach, a challenge that is directly taken on by Cazzoli et al. (2015). They assessed, for the 1st time, how TMS over the right FEF modulates eye movements in a free visual exploration task, by applying continuous theta burst (cTBS) TMS consisting of 801 pulses over 44 s (at 90% of motor threshold) over the right FEF, compared to a vertex and no stimulation condition. cTBS over the right FEF decreased cumulative fixation durations in far left and right space, and increased duration in the central region, thus producing a narrowing of visual attention deployment. The authors draw two important conclusions from this data: 1st they point out that this behaviour is very different from that produced when cTBS is applied over the right PPC, which produces neglect-like patterns, in that left cumulative fixation durations are reduced, similarly to the reduced left flanker effect that Olk et al. (2015) describe after right PPC TMS. Secondly previous research has suggested that the application of TMS over the right FEF produces bilateral effects in covert attentional shifting. Cazzoli et al.'s results support the view that the right FEF is also involved in the bilateral control of peripheral overt visual attention. Put differently: it controls the widening or narrowing of visuospatial attention in a concentric fashion, which is an appealing finding not only for basic science but also helpful in explaining the phenomenology of clinical syndromes such as Balint´s syndrome or neglect, both of which often show this bilateral constriction of the attentional field.

In fact Lane et al. (2014) go a step further, presenting the 1st study to show the critical involvement of the right FEF in 4 components of spatial processing, i.e its impact on the processing of distance as well as spatial ego and allocentric reference frames. Using TMS to dissociate spatial aspects of conjunction search in relation to both ego vs allocentric spatial coding and near vs far space processing in a single task, they delivered either TMS or sham blocks over the right PPC, ventral occipital cortex (VO) or FEF, (5 pulses delivered at 10 Hz at array onset at 65% of machine output (1.3 T)). Performing a conjunction visual search task, participants had to decide if a target was either to their left or right (egocentric frame) or to the left or right of a reference object (allocentric frame), both in near and far space. Compared to Sham, TMS to the right FEF increased reaction times for all 4 conditions; no effects were shown for right VO, whereas TMS to the rPPC increased RTs for near egocentric space only. The authors argue that the rFEF results reflect the involvement of this region in controlling spatial attention (in line with earlier arguments made by Olk et al. (2015) and Cazzoli et al. (2015)), a process essential for all the conditions of conjunction visual search of this study.

Painter et al. (2015) provide a first insight into the importance of considering individual differences when carrying out non-invasive brain stimulation with attention paradigms. They failed to find any group level effects when they applied cTBS TMS consisting of 600 pulses over 40 s (at 70% of motor threshold) over either the right TPJ, intraparietal sulcus (IPS) or visual area MT (as control site) after participants performed a contingent capture task, in which they made speeded responses to colour defined targets that were preceded by spatial cues in either the target or distractor colour.

Cues with a target colour captured attention to a greater extent than those with the distractor colour, in line with contingent capture. Yet only analyses of individual differences, via the creation of individual target and distractor scores, revealed that target capture scores were positively correlated pre-post cTBS for all stimulation sites, while distractor scores for right TPJ and IPS pre/post cTBS were uncorrelated, suggesting that right TPJ and IPS stimulation affected distractor capture in a manner dependant on individual differences. Moreover, the effects of right TPJ stimulation were predicted by pre-stimulation distractor suppression, and the authors thus suggest that dorsal–ventral network communication (Corbetta and Shulman, 2002) during contingent capture may occur via distractor suppression rather than target enhancement.

This study underpins the important point that the effects of brain stimulation not only depend on particular stimulation