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Author for correspondence:
Hannah Hobson
e-mail: hannah.hobson@kcl.ac.uk

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Important methodological issues regarding the use of transcranial magnetic stimulation to investigate interoceptive processing: a Comment on Pollatos *et al.* (2016)

Michel-Pierre Coll, Tegan Penton and Hannah Hobson

MRC Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, Psychology and Neuroscience, King's College London, University of London, London SE5 8AF, UK

HH, 0000-0002-7952-475X

1. Introduction

In the field of interoception research, one outstanding question is the precise nature of the neural networks underlying interoceptive processing [1]. The anterior insula (AI) is a key component of contemporary interoception models [2]. However, most evidence implicating the AI in interoceptive processing is correlational and it remains unclear what its precise role in interoception is.

This issue was tackled by Pollatos and co-workers [3]. Using an inhibitory form of transcranial magnetic stimulation (TMS), continuous theta burst stimulation (cTBS), they aimed to provide causal evidence for the involvement of the AI in interoception. The main results suggest that stimulation aiming to inhibit the AI or the somatosensory cortex disrupted performance, and confidence in this performance, for interoceptive tasks relative to stimulation applied to an occipital control site. The same stimulation also altered the heartbeat evoked potential (HEP), an EEG measure thought to index cortical processing of one's heartbeats [4]. The authors interpreted these findings as the impairment of certain aspects of interoceptive processing following cTBS to the right AI, concluding that "cTBS is an effective tool to investigate the neural network supporting interoceptive processes" [3, p. 1].

This study should be commended for its originality, the use of a within-subject design, and multiple concurrent multimodal measures of interoceptive processing. However, two critical issues cast doubt on the conclusions that can be drawn from these data.

2. Which brain regions were stimulated?

The AI is a deep cortical region, positioned behind frontal cortical regions (including the inferior frontal gyrus and operculum). Because of the AI's neuroanatomical position and depth, it is doubtful that TMS could directly reach this region with the parameters used by Pollatos and co-workers. While anatomically near regions to the AI such as the auditory cortex have been targeted in other areas of research (e.g. using TMS to modulate tinnitus symptoms [5]), it is unclear whether the observed effects are due to stimulation of deeper regions or more lateral association areas that are more likely to be modulated by TMS (e.g. [6,7]). TMS administered using a figure-of-eight coil is thought to only stimulate brain regions 1.5–3 cm below the scalp [8], while insula depth is estimated at 4–5 cm [9]. Direct stimulation to the cortical depth of the AI may be achieved using double-cone or helmet-shaped coils, although focality of the electrical field is compromised in comparison with superficial cortical stimulation [9].

To establish if TMS could reach the AI with the stimulation parameters employed by Pollatos and co-workers, we used the SimNIBS software [10] to run calculations of the electric field induced using these parameters. All parameters and results of this simulation are accessible online (https://osf.io/5qbcs/). As shown in figure 1, the results of this simulation suggest that with

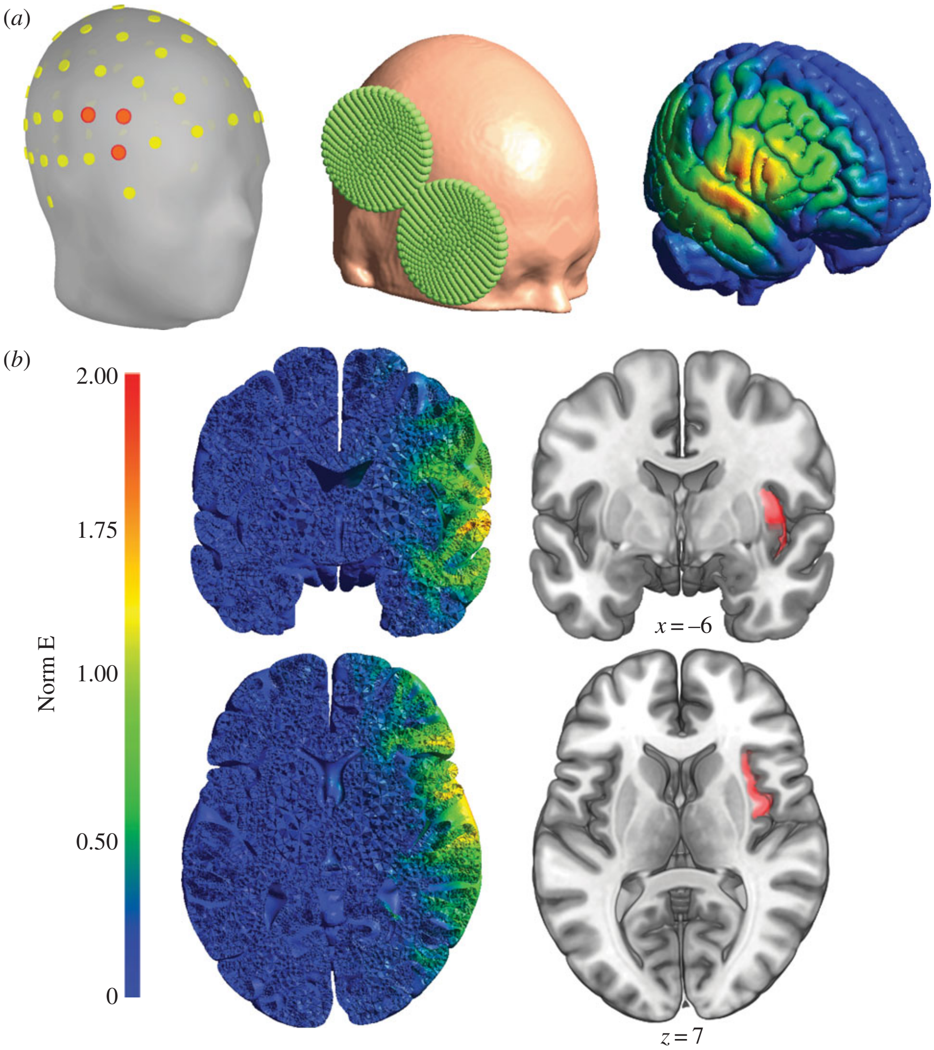

Figure 1. Panel (*a*) illustrates the EEG electrodes (left) used to select the coil position and orientation (centre) and the resulting surface normalized electric field strength (Norm E, right). Panel (*b*) shows coronal and horizontal slices of the simulation results (left) suggesting that only a negligible portion of the electric field elicited by these stimulation parameters does reach the anterior insula (highlighted in red on the right).

these stimulation parameters, only a negligible portion of the electric field reaches the AI.

In their discussion, the authors concede that "there is no guarantee of reaching the AI with a TMS coil positioned over the skull" (p. 8), but then argue that their pattern of results seems specific enough to say that the anterior part of the insula was indeed targeted. In the light of our simulation results, we contend that it is unlikely that AI activity was directly influenced by the stimulation. We therefore suggest two possible reinterpretations of Pollatos and co-workers' results. Firstly, it is possible that the AI may have been *indirectly* disrupted via inhibition of cortical regions it is connected to. Indeed, there is evidence that TMS can affect activity of deeper regions through stimulation of connected cortical areas. For example, cTBS to other frontal regions (dorsolateral prefrontal cortex) has been shown to indirectly suppress insula activation through modulation of fronto-insular connectivity ([11], see also [12]). As direct stimulation of the AI in Pollatos *et al.*'s experiment was unlikely, one reinterpretation of this data is that worsening of interoceptive performance was the result of indirect modulation of AI activity, via inhibition of more superficial cortical regions.

Alternatively, affected regions in the ventrolateral prefrontal cortex may make a unique contribution to interoceptive processes (indeed, the frontal opercular regions are also activated during interoception tasks; see [13,14]), or during non-interoceptive aspects of interoception tasks. These cortical regions are considered to play an important role in language and decision-making [15,16], disruption to which could feasibly have impacted on the tasks used by Pollatos and co-workers.

3. Are these effects specific to interoception?

Without control tasks however, the nature of this disruption is unclear, leading us onto our second point: it is unclear whether affected performance on the interoception tasks was specific to interoception, or reflective of a more general transient cognitive impairment. Future researchers wishing to use similar methods to examine the role of brain regions in interoceptive processing will of course need to consider which control tasks best suit their experimental question, but it is crucial to use a control task that is similar in nature and difficulty to the interoceptive tasks in order to ensure that decrease in performance is not related to alteration of general processes such as attention, memory or sensation. Such tasks include, but are not limited to, time estimation [17], tone perception [18] and tactile perception [19].

The absence of a control condition is also problematic for the EEG measures used. Indeed, the authors measured the HEP over right fronto-central sites close to the AI and somatosensory stimulation sites, but further from the occipital control site. It is therefore possible that cTBS over the right fronto-central areas altered the electrical brain response of these areas in a non-specific manner. To claim that the disruption of electrocortical potentials caused by the stimulation is specific to the HEP, it is necessary to show that stimulation effects are not generalized to other non-interoceptive evoked potentials (e.g. visual or somatosensory evoked potentials).

In conclusion, non-invasive neurostimulation is arguably one of the most informative tools available in cognitive neuroscience and has certainly been underused in the study of interoception. The recent report of Pollatos and co-workers is in this regard an innovative exploratory study. However, we wish to emphasize that stimulating the AI using this technique is a challenging endeavour, and should be carried out with appropriate cautions and control conditions.

Competing interests. The authors declare no conflict of interest.

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