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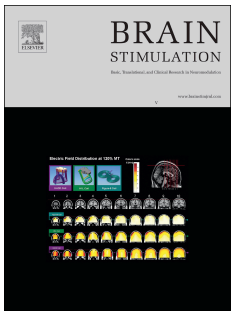

Theta network centrality correlates with tDCS response in disorders of consciousness

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Theta network centrality correlates with tDCS response in disorders of consciousness

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Dear Editor,

Transcranial direct current stimulation (tDCS) applied over the dorsolateral prefrontal cortex (DLPFC) has induced promising behavioral improvement, both in acute and chronic minimally conscious state (MCS) patients [2,3]. We previously defined a tDCS-responder as a patient who demonstrates a new sign of consciousness following stimulation, which was neither present beforehand, nor before or after the sham stimulation [2]. In a study investigating the metabolic and structural differences between DLPFC-tDCS-responders and non-responders, we have identified that tDCS-responders presented a preservation of brain metabolism and grey matter integrity under the stimulated area, but also in the thalamus and the precuneus, areas involved in consciousness recovery [4]. Even if these results provided relevant insights into potential biomarkers of responsiveness, the access to such neuroimaging techniques (positron emission tomography and magnetic resonance imaging) remains limited. Recently, it has been demonstrated that high-density electroencephalography (hdEEG) network metrics in the alpha band correlates with the level of consciousness [5]. In addition, a strong correlation between brain metabolism and hdEEG network metrics was reported, making this bedside assessment a robust way to evaluate patients' brain function.

Here, we report the results of a retrospective study aiming at evaluating the difference in brain activity and connectivity between responders and non-responders by means of hdEEG performed before the patients' inclusion in the tDCS protocol. We included patients who were enrolled in a one day or 5-day DLPFC-tDCS protocol, as previously described [4]. Our prior studies included 46 MCS patients in single stimulation or 5-day tDCS protocols [2,3]. Eight of these patients who were later identified as tDCS-responders underwent an hdEEG beforehand tDCS and were

included in the current study (4 TBI, 5.2±3.4 years post-onset, baseline CRS-R: 9.6±2.6, 41.0±12.7 years old, 4 male). The responders group was matched with a group of 13 non-responders with similar etiology, time since injury, baseline CRS-R scores, age and gender (9 TBI, 2.4±1.9 years post-onset, baseline CRS-R: 9.0±3.7, 37.7±12.4 years old, 8 male). Demographic data for both groups can be found in supplementary table 1. Note that some patients were already included in our previous study [4]. The hdEEG consisted of 15 minutes of resting state acquired with a 256-channel saline electrode net (Electrical Geodesics (EGI)). Data analysis was conducted as described in Chennu et al. (2017) [5] (see supplementary material). Briefly, we first looked at power spectrum differences in every bandwidth (delta, theta, alpha and beta). Then, we used graph theory to visualize and quantify spectral connectivity. The datasets analyzed during the current study are available from the corresponding author on reasonable request. We did not find any statistically significant differences in power fo any bandwidths, even if we visually observe a higher theta activity (Figures 1A and 1B) in responders. Increased theta band connectivity was observed in responders (Figures 1C and 1D), though median connectivity across all channel pairs was not significantly different. Responders showed higher network centrality in the theta band (indicating the presence of 'rich-club' hubs), as measured by standard deviation of node-wise betweenness centrality (Figure 1E). Further, there was a positive correlation between this metric and behavioral improvement (i.e., delta CRS-R score after tDCS versus before) in individual patients (Figure 1F). The group difference in theta betweenness centrality was stable across a range of network connection densities (Figure 1G).

In this retrospective study, we specifically found a difference in the centrality of theta band networks between responders and non-responders, with responders presenting more robust theta networks with stronger betweenness centrality. Additionally, a positive correlation between CRS-

R improvement following tDCS and this metric was identified, suggesting a linear relationship between clinical responsiveness and preservation of robust connectivity in the theta band. It is important to highlight that overall power spectra and connectivity were similar in tDCS responders and non-responders in all bandwidths. Hence, we propose that brain network properties are more sensitive for detecting cortical differences that could predict tDCS responsiveness.

Based on the present findings and previous results [5], theta band connectivity can be considered as a marker of the potential for recovery of consciousness. Preserved theta connectivity is predictive for responding to tDCS, and therefore might reflect residual potential for brain plasticity. It is worth highlighting that previous research has identified alpha band connectivity as a correlate of diagnostic state of consciousness in DOC [5]. However, here, we did not find any differences in alpha band connectivity between responders and non-responders. Following this (absence of) result in the alpha band, we can posit that tDCS may induce a spectral shift in connectivity from the theta to the alpha band, the alpha power being weak at baseline in patients with DOC. Notably, similar spectral shifts and behavioral improvements have been reported with pharmacological agents like Zolpidem [6]. As with Zolpidem, tDCS could have a direct effect on cortical activity, initiating activation of chronically underactive brain regions, as previously shown [7]. This hypothesis is supported by previous tDCS studies showing an increased cortical oscillation activity in the theta and alpha bands in healthy volunteers following anodal DLPFC tDCS [8,9]. In addition, based on neuroimaging studies, tDCS seems to influence both the activity under the stimulated area but also brain network connectivity encompassing long-distance brain areas [10]. In the context of DOC, we hypothesize that some long-distance connectivity encompassing cortical or subcortical regions may be chronically under-active, and

the action of tDCS on network connectivity and cortical activity could be to counteract such under-activation and induce clinical improvements, as recently shown in a case-report [11].

Even with the limited sample size of our preliminary study, the presented results suggest that patients could be screened before being enrolled in a tDCS protocol to assess if they are more prone to respond to the stimulation. This would help to allocate resources and could be a first step towards patients' tailored treatment. In contrast to PET and MRI acquisition, hdEEG represents a more affordable alternative, available at the bedside of DOC patients. Future studies aiming to assess the effects of tDCS on brain connectivity could easily use hdEEG before and after stimulation in this population of patients. These results should be replicated in a bigger cohort of patients, and future studies should look at both pre and post-tDCS hdEEG metrics to confirm our hypothesis.

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Legend:

Figure 1: EEG brain networks in tDCS non-responders vs. responders. The average power spectrum in responders (**B**) showed a theta peak not present in non-responders (**A**). Theta band network connectivity in responders (**D**) was higher than in non-responders (**C**). In the 3D network topographs, the colour map over the scalp depicts degrees of nodes in the network. Arcs connect pairs of nodes, and their normalised heights indicate the strength of connectivity between them. Topological modules within the network were identified by the Louvain algorithm. For visual clarity, of the strongest 30% of connections, only intra-modular connections are plotted. The colour of an arc identifies the module to which it belongs, with groups of arcs in the same colour highlighting connectivity within a module. See supplementary material for further details. Standard deviation of betweenness centrality in theta band networks was higher in responders than non-responders (**E**). There was a significant correlation between this network metric and behavioral improvement in individual patients (**F**). Difference in this network metric between responders and non-responders was evident across a range of network connection densities, and significant at 30% connection density (uncorrected) **(G)**.

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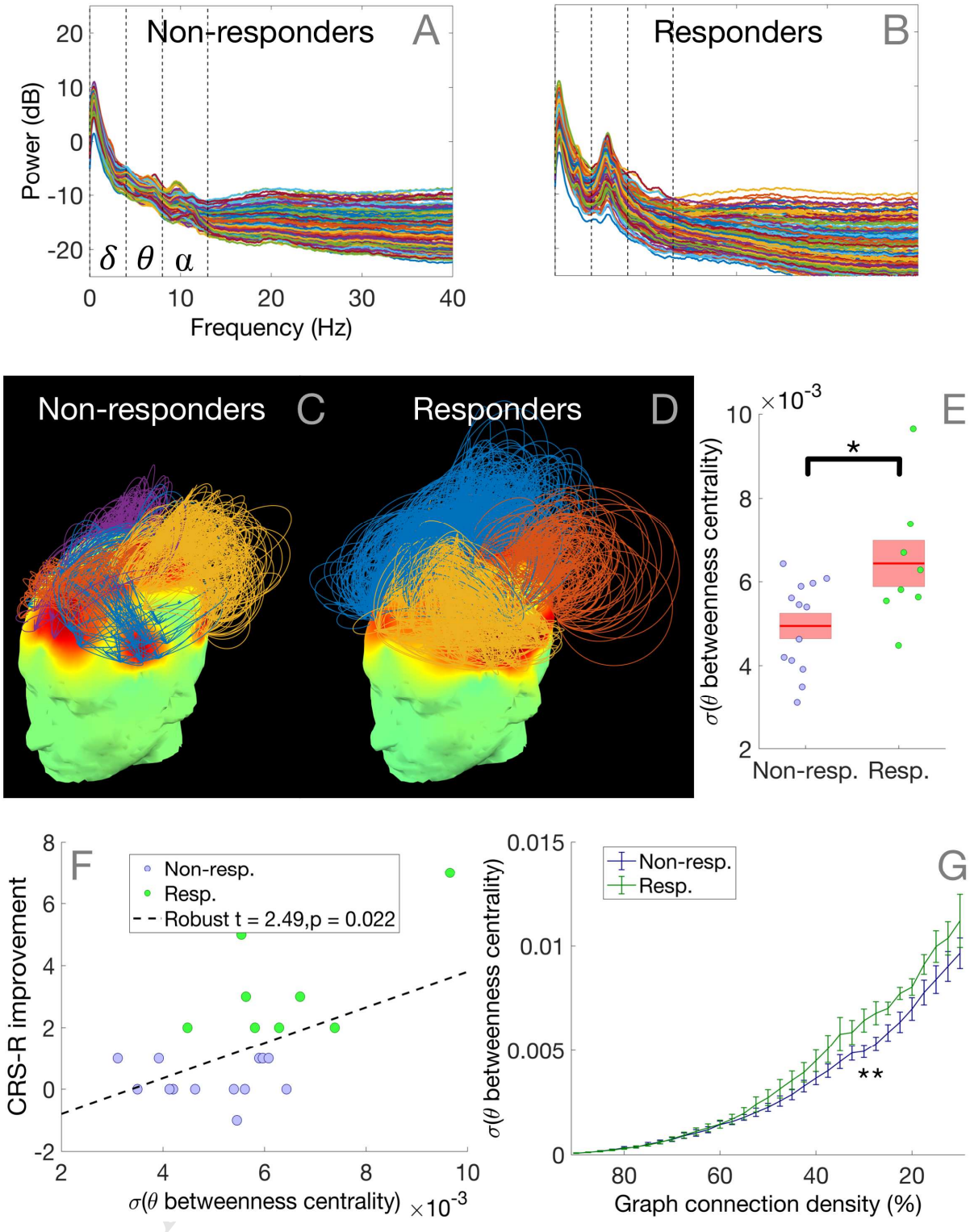
Non-responders
A
Responders
B
Power (dB)
Frequency (Hz)
δ θ α
Non-responders
C
Responders
D
E
×10-3
σ(θ betweenness centrality)
Non-resp. Resp.
F
Non-resp.
Resp.
Robust t = 2.49,p = 0.022
CRS-R improvement
σ(θ betweenness centrality) ×10-3
G
Non-resp.
Resp.
σ(θ betweenness centrality)
Graph connection density (%)