

Mapping inter-individual functional connectivity variability in

TMS targets for major depressive disorder

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Highlights:

- E-field modelling and functional connectivity used to study TMS targets (dlPFC,OFC)
- Considerable variability in TMS target E-field patterns seen across subjects
- Large inter-subject differences in target connectivity observed and characterized
- Major functional networks targeted by dlPFC, OFC TMS were the VAN, FPN and DMN
- Insights can contribute to improved and more personalized TMS therapies in the future

Keywords:

TMS, Functional Connectivity, E-fields, Modelling, Human, Depression

Abstract

Transcranial magnetic stimulation (TMS) is an emerging alternative to existing treatments for major depressive disorder (MDD). The effects of TMS on both brain physiology and therapeutic outcomes are known to be highly variable from subject to subject, however. Proposed reasons for this variability include individual differences in neurophysiology, in cortical geometry, and in brain connectivity. Standard approaches to TMS target site definition tend to focus on coordinates or landmarks within the individual brain regions implicated in MDD, such as the dorsolateral prefrontal cortex (dlPFC) and orbitofrontal cortex (OFC). Additionally considering the network connectivity of these sites (i.e. the wider set of brain regions that may be mono- or poly-synaptically activated by TMS stimulation) has the potential to improve subject-specificity of TMS targeting and, in turn, improve treatment outcomes. In this study, we looked at the functional connectivity (FC) of dlPFC and OFC TMS targets, based on induced electrical field (E-field) maps, estimated using the SimNIBS library. We hypothesized that individual differences in spontaneous functional brain dynamics would contribute more to downstream network engagement than individual differences in cortical geometry (i.e., E-field variability). We generated individualized E-field maps on the cortical surface for 12 subjects (4 female) from the Human Connectome Project database using tetrahedral head models generated from T1-weighted MR images. F3 and Fp1 electrode positions were used to target the left dlPFC and left OFC, respectively. We analyzed inter-subject variability in the shape and location of these TMS target E-field patterns, their FC, and the major functional networks to which they belong. Our results revealed the key differences in TMS target FC between the dlPFC and OFC, and also how this connectivity varies across subjects. Three major functional networks were targeted across the dlPFC and OFC: the ventral attention, fronto-parietal and default-mode networks in the dlPFC, and the fronto-parietal and default mode networks in the OFC. Inter-subject variability in cortical geometry and in FC was high. Our analyses showed that use of normative neuroimaging reference data (group-average or representative FC and subject E-field) allow prediction of which networks are targeted, but fail to accurately quantify the relative loading of TMS targeting on each of the principal networks. Our results characterize the FC patterns of canonical therapeutic TMS targets, and the key dimensions of their variability across subjects. The high inter-individual variability in cortical geometry and FC, leading to high variability in distributions of targeted brain networks, may account for the high levels of variability in

physiological and therapeutic TMS outcomes. These insights should, we hope, prove useful as part of the broader effort by the psychiatry, neurology, and neuroimaging communities to help improve and refine TMS therapy, through a better understanding of the technology and its neurophysiological effects.

1 **Introduction**

2 *TMS stimulation therapy targets and the neurobiology of major depressive disorder*

3 A considerable number of patients with major depressive disorder (MDD) do not respond to
4 first-line therapies such as drugs or psychotherapy. People who fail two or more
5 pharmacological interventions of a sufficient dose and time are characterized as having treatment
6 resistant depression (TRD; Souery et al., 1999). Transcranial magnetic stimulation (TMS) is an
7 efficacious and cost-effective treatment for people with TRD, and is an emerging alternative to
8 existing treatments for MDD, as well as a variety of other neurological and psychiatric disorders.
9 However, the clinical utility of TMS remains limited by the large heterogeneity in its clinical
10 outcomes. One factor believed to contribute to this variable clinical response among patients is
11 individual differences in structural and functional brain connectivity (Downar and Daskalakis,
12 2013). In order to find a target site for TMS treatment, region-based approaches have focused on
13 individual brain regions implicated in MDD, such as the dorsolateral prefrontal cortex (dlPFC),
14 dorsomedial prefrontal cortex (dmPFC) and orbitofrontal cortex (OFC). On the other hand,
15 network-based approaches have shown how TMS efficacy can be improved by considering not
16 only the location of the primary stimulation site (dlPFC, OFC, etc.), but also its connectivity - i.e.
17 the wider set of distal brain regions that are mono- or poly-synaptically activated by TMS
18 stimulation (Drysdale et al., 2017; Fox et al., 2013).

19 Previous studies have shown that variability in clinical efficacy of dlPFC-targeted repetitive
20 TMS (rTMS) treatment for MDD is related to differences in the functional connectivity (FC) of
21 the specific dlPFC locations stimulated (see Fox et al., (2012), Cash et al., (2020)). These
22 observations suggest that a detailed examination of individual differences in FC patterns for
23 frontal lobe rTMS targets should prove useful in further refining TMS targeting methodologies.
24 The aim of the present study was to undertake such an examination. Specifically, we
25 characterized the FC patterns of the dlPFC and OFC, based on E-field maps generated by
26 biophysical simulations of TMS stimulation effects on the cortex (see *Methods*). Our hypothesis
27 was that individual differences in spontaneous functional brain dynamics would contribute more
28 to downstream network engagement than individual differences in cortical geometry (i.e., E-field

29 variability), which may in turn explain some of the observed heterogeneity of rTMS treatment
30 outcomes.

31 By far the most commonly targeted site in rTMS treatment of MDD is the dlPFC. That this
32 region is known to play a critical role in executive functions such as attention, planning, and
33 organization, and up-regulation of the circuits underlying these neurocognitive functions is one
34 potential explanation for its positive therapeutic effects. rTMS stimulation of the left dlPFC has
35 also been observed to regulate FC to and between the reward- and emotion-related regions of the
36 meso-cortico-limbic dopamine pathway, that have also been consistently implicated in MDD
37 (Tik et al., 2017). However, stimulation of the left dlPFC does not work for all patients, with
38 only around 46% of MDD patients achieving response, and only 31% achieving remission after a
39 standard rTMS treatment course (Fitzgerald et al., 2016). This may be due to inter-subject
40 differences in neurochemistry, in connectivity, in their specific MDD neuropathology, or a
41 variety of other potential factors. To overcome this issue of limited success with dlPFC targeting,
42 several groups have begun to explore alternative rTMS targets to treat MDD, such as the dmPFC
43 and the OFC (Downar and Daskalakis, 2013).

44 Recent research has shown that the OFC is hyperactive in MDD (Feffer et al., 2018). The OFC
45 consists of a medial (mOFC) and a lateral (lOFC) subdivision, each with unique anatomical and
46 FC profiles. The OFC has extensive cortico-cortical and cortico-striatal connections to regions
47 implicated in MDD such as the cingulate cortex, caudate, striatum, hypothalamus, amygdala,
48 hippocampus, insula, and thalamus (Zald et al., 2014). Recently, studies have begun to explore
49 the OFC as a TMS target, with the rationale being to stimulate these MDD-implicated cortico-
50 cortical and cortico-striatal loops. The OFC and its downstream connections are principal
51 contributors to reward and reversal learning (Kringelbach, 2005), predictive and fictive error
52 assessment (Boorman et al., 2013), emotional regulation, and generation of affective states
53 (Rolls, 2019). Due to the wide psychiatric implications of pathological OFC activity, this region
54 has been growing in popularity as an alternative rTMS treatment target for mental illness. For
55 example, low frequency (1Hz) rTMS of the left OFC has been shown to ameliorate symptoms in
56 patients with obsessive-compulsive disorder (OCD; Kumar et al., 2018). Relatedly, 1Hz rTMS to
57 the right OFC in a recent study saw nearly a quarter of patients suffering from MDD achieve
58 remission (Feffer et al., 2018). Importantly, these patients previously showed minimal response

59 to dmPFC-rTMS. These results point to heterogeneous mechanisms of action, and therefore
60 therapeutic effect, for dlPFC-, dmPFC-, and OFC-rTMS, possibly due to their unique
61 downstream connections.

62

63 *E-field modelling and cortical geometry*

64 TMS uses high intensity magnetic field pulses to influence neuronal activity. The TMS coil
65 produces a time-varying magnetic field, which in turn induces a focal electric field (E-field)
66 within brain (principally cortical) tissue. E-field modelling is a relatively new approach that uses
67 computationally estimated E-field maps, which can serve as a proxy to identify the region of the
68 brain that is stimulated for a given coil type, location, orientation, and (MRI scan-derived,
69 subject-specific) head and brain characteristics (Opitz et al., 2011; Thielscher et al., 2015; Weise
70 et al., 2020). These methodologies are increasingly used in clinical and basic TMS research, as a
71 means to better understand and minimize the sources of variability in TMS outcomes due to the
72 varying placement of TMS coils on the subject's scalp, and to variability in each individual's
73 skull anatomy and cortical geometry.

74 Approaches to TMS coil placement include the '5cm-rule', 10-20 EEG electrode locations,
75 MRI-guided anatomical targeting, and the more recent fMRI FC-guided targeting. However,
76 there is a considerable amount of variability in the 'ideal' TMS coil placement to optimally
77 stimulate a specific target. For example, the F3 10-20 electrode position may result in different
78 parts of the dlPFC being stimulated in different individuals. Moreover, previous research has
79 shown that differences in the complex neuroanatomy of each individual human skull and brain
80 (i.e., brain size, gyri and sulci differences) results in E-fields of varying shapes, sizes and depths
81 (Thielscher et al., 2011). The combined effect of TMS coil placements and subject-specific
82 differences in skull anatomy and cortical geometry leads to an inter-subject variation in E-field
83 patterns across patients/subjects, and is a potential explanation for some of the high variability in
84 rTMS therapy outcomes. Furthermore, the interaction between these cortical geometry-driven
85 variability in TMS induced E-fields and variability in intrinsic FC patterns, despite receiving
86 some attention from researchers previously (Opitz et al., 2016), remains poorly understood.

87

88 ***Present study***

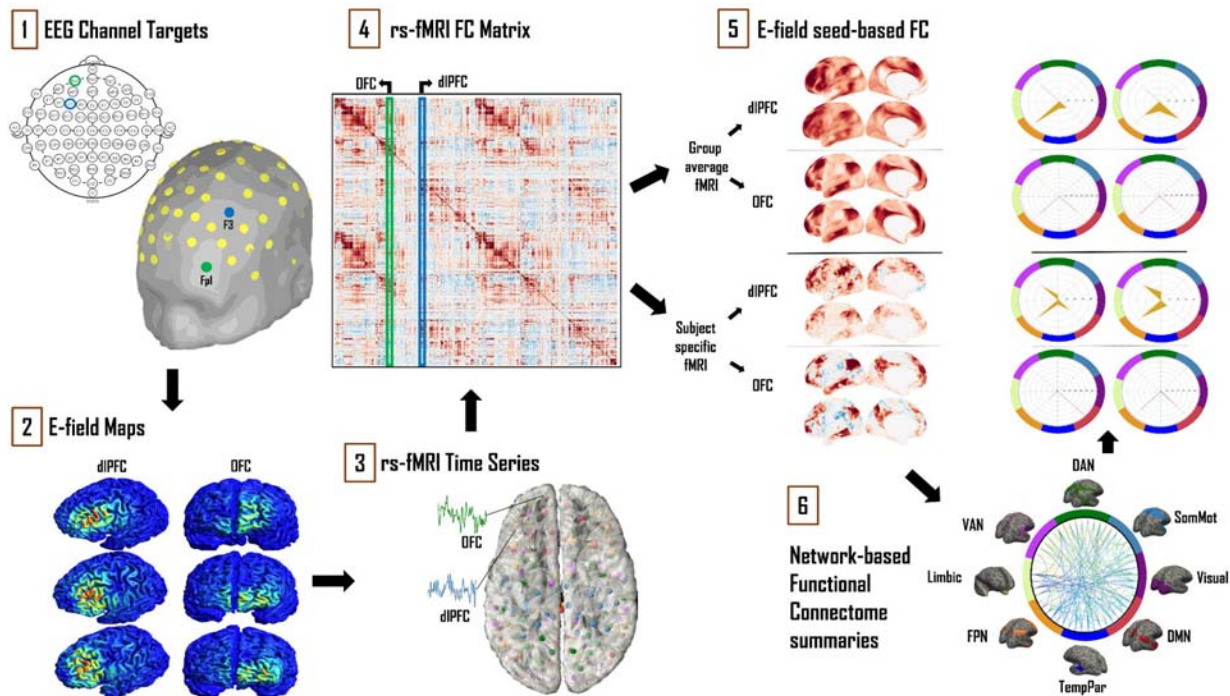
89 It is likely that the dlPFC and OFC have unique functional connections, through which they each
90 exert their differential therapeutic effects following rTMS treatment (Vila-Rodriguez and
91 Frangou, 2021). The patterns of these connections likely vary considerably across subjects, and
92 very little is currently known about the relative contributions of these variability sources to TMS
93 treatment outcomes. In the present study, we therefore sought to address part of this knowledge
94 deficit, by systematically examining E-field and FC patterns for dlPFC and OFC TMS target
95 sites, using structural and functional neuroimaging scans in a group of healthy control subjects.
96 We computed simulated TMS E-fields centered at the dlPFC and OFC, and studied their FC
97 patterns using both individual and group averaged resting-state fMRI data. We found specific
98 networks being targeted as a result of dlPFC or OFC TMS. While the same major networks were
99 targeted consistently across our subject cohort, substantial inter-individual differences in each
100 subject's specific relation to these networks were also observed. Comparing individual subject
101 and group-average FC patterns for a consistent E-field-defined seed region allowed us to assess
102 the contribution of inter-individual variability in FC patterns, independently of variability in
103 cortical geometry. Conversely, comparing FC patterns for a single group-level E-field seed to
104 those for subject-specific E-field seeds allowed us to quantify variability in TMS target
105 connectivity due purely to skull and cortical geometry variation. Our results highlight the inter-
106 individual differences in dlPFC and OFC TMS FC, potentially paving the way for personalized
107 rTMS therapy in the future.

108

109 **Methods**

110 Analysis of T1-weighted anatomical MRI (for E-fields) and fMRI (for FC) data was conducted
111 for 12 randomly selected subjects from the human connectome project (HCP) database, looking
112 specifically at FC patterns related to dlPFC and OFC TMS stimulation. We computed TMS E-
113 fields using the SimNIBS software package, and focused on the cortical surface component of
114 the stimulated tissue. The group average and individual subject HCP CIFTI dense connectomes

115 were used to determine the FC of TMS targets to the rest of the brain; and we used the standard
116 Yeo/Schaefer parcellations to summarize the downstream connections of the dlPFC and OFC.
117 Finally, we defined a framework for assessing contributions to overall variability from cortical
118 geometry, FC, and from a combination of these two sources. Each of these steps are detailed
119 below.



121 **Figure 1: Schematic of the analytical approach.** 1) Left dlPFC and OFC 10-20 EEG electrode locations were
122 identified as F3 and Fp1, respectively. 2) SimNIBS simulations were run using these electrode locations as TMS coil
123 placements, with the main output of interest being cortical surface E-field maps. 3) Resting state fMRI time series
124 for 12 subjects from the HCP database were averaged and converted into ‘dense connectome’ FC matrices. 4) The
125 connectivity patterns of each subject’s E-field were determined using these dense connectomes. 5) FC maps of the
126 resulting E-fields were thus obtained with group-averaged and subject-specific resting-state fMRI data. 6) These
127 maps were further analyzed and summarized in terms of connectivity to the canonical multi-network parcellation
128 templates of Yeo et al., (2011). The most prominent networks targeted by dlPFC and OFC TMS are reported. Spider
129 plot visualizations in this example and later figures show the networks being targeted as a percentage (area of orange
130 polygon) of the suprathreshold E-field vertices.

131

132 **Determining the TMS E-field**

133 The TMS-induced electric field was modelled using tools from the SimNIBS software library
134 (Thielscher et al., 2015). A tetrahedral surface mesh head model (.msh file) was created from T1-
135 weighted MR images and Freesurfer tissue segmentations for twelve subjects (4 female) from the
136 HCP database. This mesh consisted of five tissue types: white matter (WM), grey matter (GM),
137 cerebro-spinal fluid (CSF), skull, and scalp. The assigned conductivity values were fixed, as per
138 the SimNIBS defaults: 0.126 S/m (WM), 0.275 S/m (GM), 1.654 S/m (CSF), 0.01 S/m (skull),
139 and 0.465 S/m (scalp). In order to investigate possible effects due to head geometry, two head
140 mesh types were used as part of the SimNIBS analysis pipeline. The first were each subject's
141 unique head meshes, as derived from that subject's own neuroanatomical MRI scans. The second
142 was the general template head mesh, 'ernie.msh', which is distributed as a part of SimNIBS. The
143 EEG 10-20 system F3 electrode was selected to target the left dlPFC, for two reasons: First: EEG
144 F3 is in our experience currently the most commonly used left dlPFC targeting method in clinical
145 rTMS practices. Second: it has been reported that TMS targeting approaches based on the 10-20
146 EEG system account better for variability across different skull shapes and sizes than scalp-based
147 measurements such as the '5cm rule' (Cash et al., 2020). With regards to the OFC, previous
148 work has shown that targeting right OFC via the Fp2 electrode led to remission in MDD patients
149 unresponsive to dlPFC- and dmPFC-rTMS (Fettes, 2020). Given the high level of anatomical
150 symmetry between hemispheric homologues, here we used the Fp1 electrode (left-side
151 homologue of Fp2, thus targeting left OFC), so as to keep both TMS targets in the left
152 hemisphere. This approach enabled us to make more direct comparisons between dlPFC and
153 OFC, minimizing extraneous methodological differences. We strongly expect our left OFC
154 results to generalize well to right OFC targets, although we leave the full demonstration of this
155 for future work. The left dlPFC has been used as a target for rTMS therapy almost since the
156 technique's inception (George et al., 1995), and while there are heterogenous outcomes
157 associated with left dlPFC rTMS, it is still one of the most widely used rTMS targets for MDD
158 (Cash et al., 2020; Pascual-Leone et al., 1996). The use of the OFC as a TMS target to treat
159 psychiatric disorders, while still a novel and largely underexplored idea, has recently gained
160 traction - with OFC rTMS showing promise in treating MDD (right OFC; Feffer et al., 2018) and
161 OCD (left OFC; Kumar et al., 2018).

162 At both coil centres (F3, Fp1), the coils were positioned using the standard orientation to ensure
163 that the resulting E-field is directed perpendicularly into the cortex. Previous studies have shown

164 that this standard orientation is able to achieve the highest perpendicular E-field values (Janssen
165 et al., 2015). This is done by pointing the coil handle away from the midline of the cortex. The y-
166 direction position values for the dlPFC (F3) and OFC (Fp1) are therefore F5 and AF7,
167 respectively. Of the various coil models available in SimNIBS, we used the Magstim 70mm
168 Figure-8 coil, which is the most common coil type in both clinical and research settings. To keep
169 our focus primarily around the target regions (dlPFC, OFC), we used a threshold of 0.9
170 Volt/meter (V/m) to limit the size of the E-field obtained (Romero et al., 2019). We report the E-
171 field sizes in terms of ‘number of vertices’, where the vertices in question are from the left
172 hemisphere surface portion of CIFTI-space dense connectomes that consist of 32,000 vertices
173 per hemisphere. The average face area (and therefore approximate E-field physical unit size) for
174 these CIFTI 32K surfaces is 0.05 mm².

175

176 *Functional Connectivity*

177 Resting-state fMRI data of the 12 HCP subjects was used to study the FC of TMS target regions.
178 For full details on the HCP acquisition protocols and related information, see (Glasser et al.,
179 2013; Uğurbil et al., 2013; Van Essen et al., 2013, 2012).

180 For subject-specific FC analyses, the FC for the CIFTI format time series for each HCP subject’s
181 four resting-state fMRI scans were averaged and converted into ‘dense connectome’ (Pearson
182 correlation) FC matrices, each containing 91,282 rows and columns (corresponding to ~64,000
183 cortical surface vertices, and ~27,000 sub-cortical voxels). For group-level FC analyses, the
184 HCP_S1200_GroupAvg_v1 (1003 subjects) dense connectome was used instead of individual-
185 subject data. The FC of a given E-field was determined by taking the average FC, over all the
186 vertices within that E-field, to every other node in the dense connectome FC matrix. Note that in
187 this study we only studied connectivity within the stimulated (i.e. the left) hemisphere. In order
188 to summarize which downstream regions were functionally connected to the stimulated areas, we
189 grouped the connectivity profiles of dlPFC and OFC stimulation target sites according to the
190 canonical functional network parcellation of Yeo et al. (2011) and Schaefer et al. (2018). These
191 canonical networks consisted of the visual (Vis), somato-motor (SomMot), dorsal attention
192 (DAN), ventral attention (VAN), limbic, fronto-parietal (FPN), temporo-parietal (TempPar) and

193 default-mode (DMN) networks (Yeo et al., (2011), Schaefer et al., (2018)). These canonical
194 Yeo/Schaefer network summaries give a useful low-dimensional complement to the high-
195 dimensional (E-field seed column-averaged) FC dense connectome columns, helping us to gain a
196 better understanding of which functional networks might be stimulated by TMS, and how the
197 pattern of stimulated areas varied between target sites (dlPFC, OFC) and across subjects. Here,
198 the individual units of a Yeo/Schaefer parcellation-based functional connectome are the brain
199 regions identified by Schaefer et al. (2018), and serve as building blocks for functional brain
200 anatomy. In the context of network analysis, each parcel represents a single node within a whole
201 brain network. In the following, we therefore refer to these individual Yeo/Schaefer parcels as
202 network ‘nodes’. In all subjects, we analyzed E-field variability, FC patterns, and the major
203 nodes of the most common functional networks and the FC maps they created.

204 To explore the impact of individual brain features on the variability of TMS target connectivity,
205 we delineated a two-level FC analysis framework. At the first level (1a, 1b), the two most likely
206 main sources of TMS FC variability are analyzed separately, and at the second level (2) they are
207 analyzed in combination:

208 *1a. Influence of individual head, skull, and cortical geometry on TMS target connectivity*
209 *patterns.* To examine this we computed the variability shown in the E-fields by holding
210 the FC constant. To do this, we used each subject’s unique head mesh to determine their
211 individualized E-field map. As described above, the connectivity of each subject’s
212 specific E-field to the canonical HCP_S1200_GroupAvg_v1 resting-state FC matrix was
213 studied.

214 *1b. Inter-subject differences in TMS target connectivity due purely to each subject’s*
215 *unique functional connectivity profile.* This line of analysis involved using the same E-
216 field across all subjects, but combining it with individualized FC. The SimNIBS general
217 template head mesh (‘ernie.msh’) was used to generate a fixed E-field pattern for all
218 subjects, for each of the two TMS targets. The connectivity patterns of this fixed E-field
219 to the rest of the brain was calculated using each subject’s individual FC matrix, derived
220 from their four resting-state fMRI scans. This approach allowed us to measure the effect
221 of individual spatial FC fingerprints on TMS target connectivity.

222 **2. Combined influence of individual cortical geometry and individual functional**
223 *connectivity structure on TMS target connectivity patterns.* To represent the ‘real-world’
224 scenario, where individual characteristics of both cortical geometry and FC jointly
225 contribute to TMS target connectivity patterns, we combined the approaches in 1a and 1b
226 above, and studied patterns using both each subject’s unique head mesh and their specific
227 FC matrices.

228

229 ***Statistical Analysis***

230 To evaluate statistically the hypothesis that, for each of the two TMS target regions, there was
231 differential loading across downstream brain networks, connectivity scores were compared
232 separately for dlPFC and OFC using repeated-measures one-way ANOVA, with the (within-
233 subjects) factor “NETWORK” (8 levels for the 8 functional networks: Vis, SomMot, DAN,
234 VAN, Limbic, FPN, TempPar, DMN). Subsequent pairwise post-hoc comparisons were
235 performed to determine significant differences between NETWORK levels. The critical p-value
236 was then adjusted using Tukey correction to account for multiple comparisons (**.05; Tukey
237 corrected; *.05 uncorrected).

238

239 ***Code and Data Availability***

240 All analyses reported in this paper were conducted on CentOS linux compute servers running
241 Python 3.7.3, using the standard scientific computing stack and several open-source
242 neuroimaging software tools - principally SimNIBS (E-field simulations; Thielscher et al., 2015),
243 Nibabel (neuroimaging data I/O; Brett et al., 2020) and Nilearn (neuroimaging data
244 visualizations; Abraham et al., 2014). All code and analysis results are openly available at
245 github.com/griffithslab/HaritaEtAl2021_tms-efield-fc.

246

247 **Results**

248 *Influence of individual cortical geometry on TMS target connectivity patterns*

249 *E-field variability*

250 There was considerable variability across the subject group in the estimated amount of activated
251 tissue in the vicinity of each TMS target location, as defined by the spatial extent of the
252 thresholded E-field surface maps. At the dlPFC, E-field size ranged from 415 to 1037 vertices
253 (663.2 ± 199.8). The OFC on the other hand was smaller in terms of overall E-field size, ranging
254 from 106 to 300 vertices (162.3 ± 57.0). The E-field sizes varied to a greater extent for dlPFC
255 stimulation (scalp position F3) than for OFC stimulation (scalp position Fp1) (Fig. 2 - **Panel A**).
256 (See *Methods* for information on the threshold value chosen and on physical dimensions of
257 surface units).

258

259 *Functional network connectivity based on subject-specific E-fields*

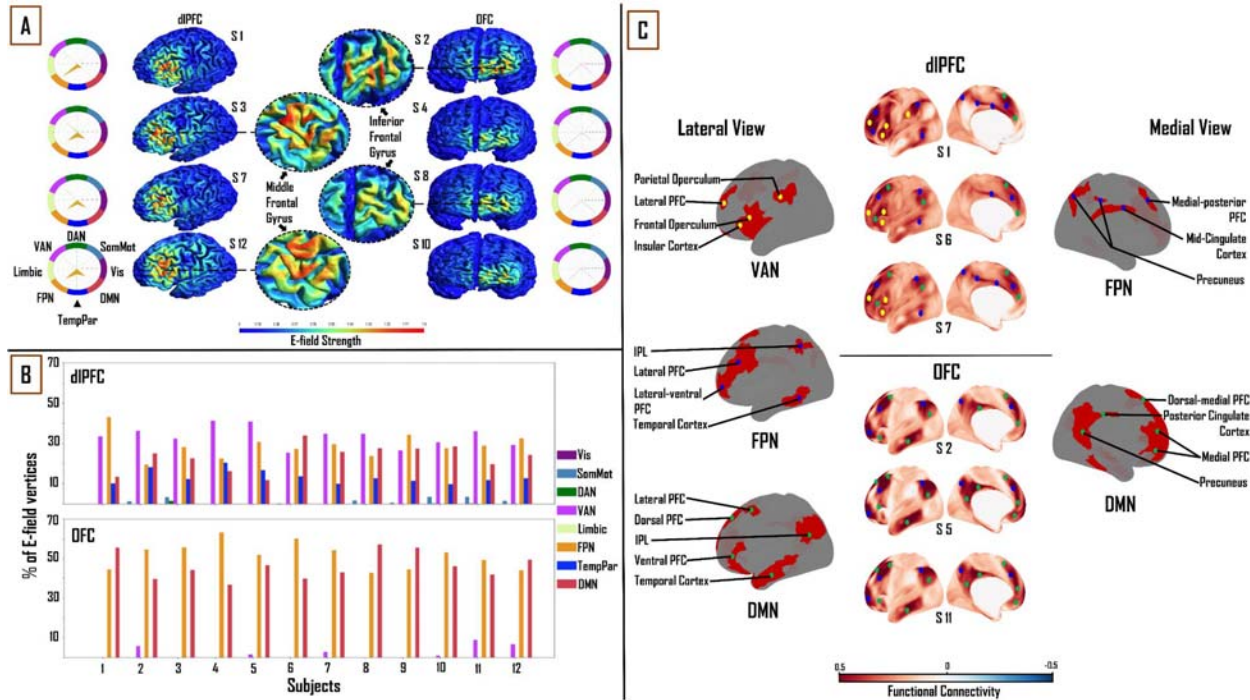
260 We analyzed connectivity strength within each subject's E-field maps by comparing maximum
261 FC values. A significant main effect of "NETWORK" was found at the dlPFC ($F_{(1,7)} = 141.66$, p
262 < 0.0001 , $\eta^2 = 0.93$) and OFC ($F_{(1,7)} = 424.64$, $p < 0.0001$, $\eta^2 = 0.97$). Across all subjects, three
263 networks from the Yeo et al. (2011) functional network parcellations had maximum FC to
264 vertices in the dlPFC and OFC E-fields. In the dlPFC, the VAN ($33.4 \pm 4.7\%$), FPN ($28.9 \pm$
265 5.8%) and DMN ($22.9 \pm 6.3\%$) accounted for an average of 85% of the E-field vertices. In the
266 OFC, the FPN ($51.5 \pm 6.4\%$) and DMN ($46.4 \pm 6.5\%$) accounted for 98% of the E-Field vertices.
267 In addition to the above, other functional parcels with FC to the E-field vertices include the
268 somato-motor and temporo-parietal networks. (Fig. 2 - **Panel B**).

269

270 *Relationship between TMS targets and downstream brain regions in subject-specific E-fields*

271 After summarizing the overall structure of TMS target connectivity to the rest of the brain in
272 terms of E-field vertex FC to the eight canonical Yeo networks, we examined more closely the
273 spatial topographies of these FC patterns. Specifically, we studied the seed-based FC maps
274 (where the seed is the entire thresholded E-field, and the maps are averaged over vertices within

275 the seed) for each subject and target site, and identified through extensive manual inspection the
276 dominant and consistent sub-patterns within those maps. Specific brain regions in the VAN, FPN
277 and DMN were highlighted with dIPFC-TMS stimulation. On the lateral cortical surface, key
278 nodes within the VAN included the frontal and parietal opercula, lateral prefrontal cortex (PFC),
279 and insular cortex. The main lateral FPN nodes were the posterior part of the middle and inferior
280 temporal gyri, inferior parietal lobule (IPL) and the lateral-ventral and lateral PFC. Medial FPN
281 nodes included the precuneus, mid-cingulate cortex and medial-posterior PFC. Within the DMN,
282 we observed the IPL, the lateral and ventral PFC on the lateral cortical surface; while the dorsal-
283 medial and medial PFC constituted the medial DMN nodes. On the medial surface of the cortex,
284 we observed FPN and DMN nodes, however, there were no specific VAN nodes (Fig. 2 - *Panel*
285 *C [top]*). With regards to the OFC, specific regions in the FPN and DMN were highlighted.
286 Within the FPN, laterally, we observed several of the same nodes noted above, including the
287 lateral-ventral, lateral PFC and IPL. Medial FPN nodes included the medial-posterior PFC and
288 precuneus. In the DMN, the IPL and lateral PFC were seen once again as key nodes laterally.
289 Medial DMN nodes included the dorsal-medial, medial PFC, and precuneus. DMN nodes
290 specific to the OFC included the dorsal PFC and the anterior portion of the middle and inferior
291 temporal gyri on the lateral cortical surface; and the posterior cingulate cortex (PCC) on the
292 medial cortical surface (Fig. 2 - *Panel C [bottom]*). Critically, similar key nodes within different
293 functional networks showed markedly different FC patterns between the two TMS target sites.



294
295 **Figure 2: Influence of individual cortical geometry on TMS target connectivity.** **A)** Individual subject E-fields for
296 a subset of subjects highlighting anatomical differences between dIPFC and OFC E-fields. Spider plots on either
297 side show functional network connectivity (expressed as a percentage of E-field vertices), based on the group-
298 average FC matrix. E-field unit = V/m. **B)** Maximum FC of each functional network parcellation, represented as a
299 percentage of E-field vertices, for all subjects. Top: VAN, FPN and DMN accounted for 85% of E-field vertices in
300 the dIPFC. Bottom: FPN and DMN accounted for ~98% of the E-field in OFC. **C)** *Top:* Lateral and medial view of
301 dIPFC FC maps in subjects 1, 6 and 7, highlighting the key regions that are functionally connected across VAN,
302 FPN and DMN. These regions lie mainly in frontal, parietal and temporal cortices. *Bottom:* Lateral and medial view
303 of OFC FC maps in subjects 2, 5 and 11, highlighting key regions that are functionally connected across FPN and
304 DMN. These regions lie mainly in medial-frontal, cingulate and posterior parietal cortices. VAN = ventral attention
305 network, FPN = fronto-parietal network, DMN = default-mode network.

306

307 ***Influence of connectivity structure on TMS target connectivity patterns***

308 In the previous section we held the FC matrix fixed, allowing us to characterize inter-subject
309 differences in (putative) TMS target connectivity resulting purely from variation in head, skull,
310 and brain anatomy and geometry. We now examine the reverse scenario: inter-subject
311 differences in TMS target connectivity due purely to the individualized FC, but using a single
312 fixed E-field map for all subjects.

313

314 *E-field Variability*

315 The size of the constant E-field at the dlPFC was 310 vertices and at the OFC was 63 vertices
316 (Fig. 3 - *Panel A*).

317

318 *Functional network connectivity based on constant E-fields*

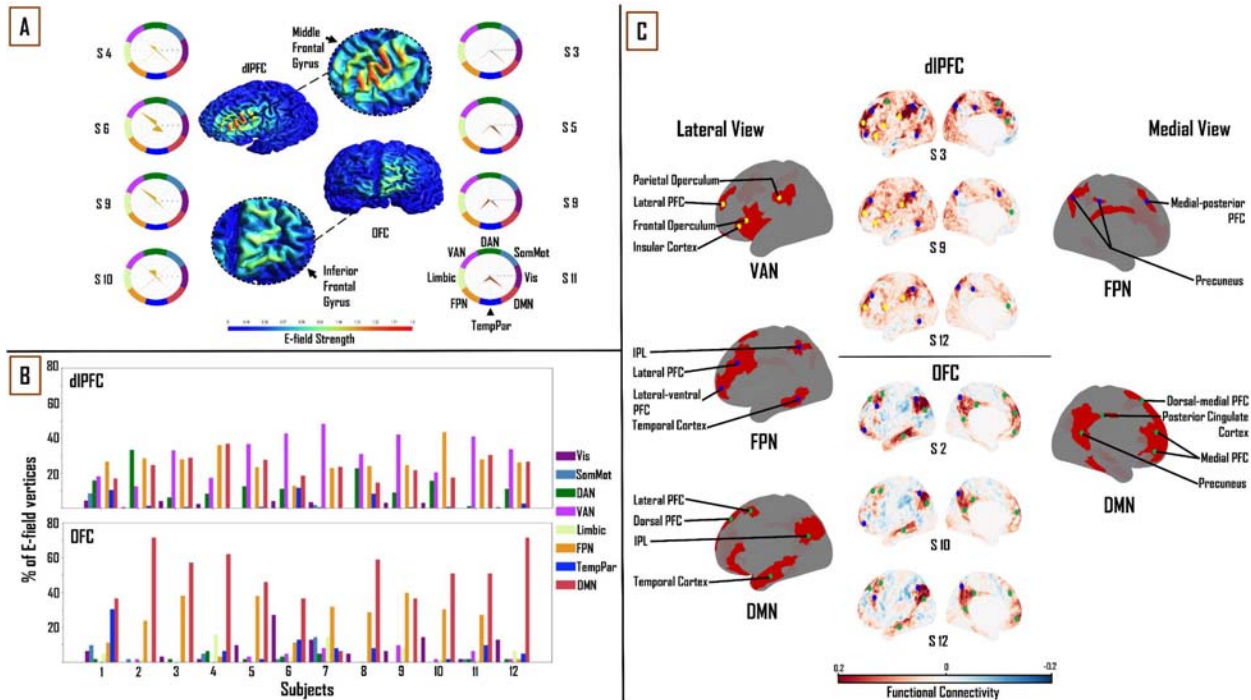
319 One-way ANOVA identified a significant main effect of “NETWORK” for both dlPFC ($F_{(1,7)}=$
320 41.12 , $p < 0.0001$, $\eta^2= 0.79$) and OFC ($F_{(1,7)}= 31.06$, $p < 0.0001$, $\eta^2 = 0.74$). The same three
321 functional networks from the subject-specific analysis were seen to have maximum FC to
322 vertices in the constant E-field across subjects. In the dlPFC, dominant connectivity to the VAN
323 (31.3 ± 11.2 %), FPN (26.9 ± 7.1 %) and DMN (23.9 ± 6.2 %) together accounted for 82% of E-
324 field vertices. In the OFC, the FPN (23.7 ± 13 %) and DMN (48.7 ± 17.4 %) together accounted
325 for 72% of the E-Field vertices (Fig. 3 - *Panel B*).

326

327 *The relation between TMS targets and downstream brain regions in constant E-fields*

328 Turning again to a detailed inspection of the seed-based FC maps, specific brain regions in the
329 VAN, FPN and DMN were highlighted with dlPFC-TMS, and within the FPN and DMN in
330 OFC-TMS. Within the VAN, similar to our findings in the previous section, the lateral PFC,
331 frontal and parietal opercula, and the IPL were the key nodes observed on the lateral cortical
332 surface. The lateral FPN nodes included the posterior regions of the middle and inferior temporal
333 gyri, the IPL and the lateral-ventral and lateral PFC. We noted the precuneus and medial-
334 posterior PFC as the main medial FPN nodes. Key DMN nodes included the lateral PFC and the
335 dorso-medial and medial PFC. Again, as in the previous section, on the medial surface of the
336 cortex, we observed FPN and DMN nodes, but no specific VAN nodes were seen (Fig. 3 - *Panel*
337 *C [top]*). At the OFC, on the lateral left cortical surface, the FPN included some of the same
338 nodes noted above such as the lateral-ventral and lateral PFC, and the IPL. The main lateral
339 DMN nodes included the IPL, the anterior portion of the middle and inferior temporal gyri, and

340 the dorsolateral PFC. On the medial left cortical surface, the DMN nodes included the dorsal-
 341 medial PFC, medial PFC, precuneus and PCC (Fig. 3 - **Panel C [bottom]**). It is important to
 342 clarify here that, while similar brain regions were seen appearing as key nodes within the
 343 different functional networks, the FC patterns were markedly different between the two TMS
 344 targets and across different subjects.



345 **Figure 3: Influence of individual subject FC on TMS target connectivity.** **A)** constant (ernie-based) dIPFC and
 346 OFC E-fields, from F3 and Fp1 TMS targets, are 310 and 63 vertices in size, respectively. Spider plots on either side
 347 show functional network connectivity (expressed as a percentage of E-field vertices), based on subject-specific FC
 348 matrices. E-field strength unit = V/m. **B)** Maximum FC of each functional network represented as a percentage of
 349 the E-field vertices of each subject. *Top:* VAN, FPN and DMN accounted for 82% of E-field vertices in dIPFC.
 350 *Bottom:* FPN and DMN accounted for 72% of E-field vertices in OFC. **C)** *Top:* Lateral and medial view of dIPFC
 351 FC maps in subjects 3, 9 and 12, highlighting the key regions that are functionally connected across the VAN, FPN
 352 and DMN. These regions lie mainly in frontal, parietal and temporal cortices. *Bottom:* lateral and medial views of
 353 OFC FC maps in subjects 2, 10 and 12, highlighting key regions that are functionally connected across the FPN and
 354 DMN. These regions lie mainly in medial-frontal, cingulate, and posterior parietal cortices (bottom). VAN = ventral
 355 attention network, FPN = fronto-parietal network, DMN = default-mode network.

357

358 **Combined influence of individual cortical geometry and individual connectivity structure on**
 359 **TMS target connectivity patterns**

360 In order to evaluate the similarity of the network engagement in the dlPFC and OFC (when using
361 subject-specific E-fields) between the group average FC matrix and subject-specific FC matrices,
362 we studied the Pearson correlation between the percentage of E-field vertices (Figs 2, 4 - **Panel**
363 **B**) for the VAN, FPN and DMN, across all subjects, for these two FC matrix variants. For dlPFC
364 targets, the group average and subject-specific FC matrices showed a high correlation in the
365 percentage E-field vertices that maximally correlated with the DMN ($r=0.67$), but this was not
366 the case for the VAN and FPN ($r=0.07$ and $r=0.03$, respectively). We found the opposite to be
367 true in the OFC. Here, we observed that there was a higher correlation between the percentage of
368 E-field vertices preferentially correlated with FPN ($r=0.52$) than with DMN ($r=0.2$), when
369 comparing group average and subject-specific FC matrices.

370 Similarly, to determine the similarity of the network engagement in the dlPFC and OFC (when
371 using subject-specific FC matrices) between the fixed ('ernie') E-field and subject-specific E-
372 field, we looked at the Pearson correlation between the percentage of E-field vertices, for the
373 VAN, FPN and DMN, across all subjects, for the two E-field variants. In the dlPFC, the fixed
374 and subject-specific E-fields showed a much higher degree of correlation in proportion of
375 vertices in each subject's specific FC matrix maximally targeting the VAN and FPN ($r=0.82$ and
376 $r=0.76$, respectively), than the DMN ($r=-0.05$). In the OFC, we noticed the reverse to be true.
377 The fixed and subject-specific E-field showed a higher correlation in proportion of vertices
378 correlated with the DMN ($r=0.7$), than with the FPN ($r=0.4$). A comparison of the differences in
379 patterns of FC between the fixed E-field and the subject-specific E-field can be found in Fig. 4 -
380 **Panel A**. Taken together, these analyses indicate that the average E-field and group-average FC
381 data are able to predict which networks are targeted, for some networks, but cannot necessarily
382 tell the degree to which each individual network is specifically targeted across subjects.

383

384 *Functional network connectivity based on subject-specific E-fields and subject-specific*
385 *functional connectivity matrices.*

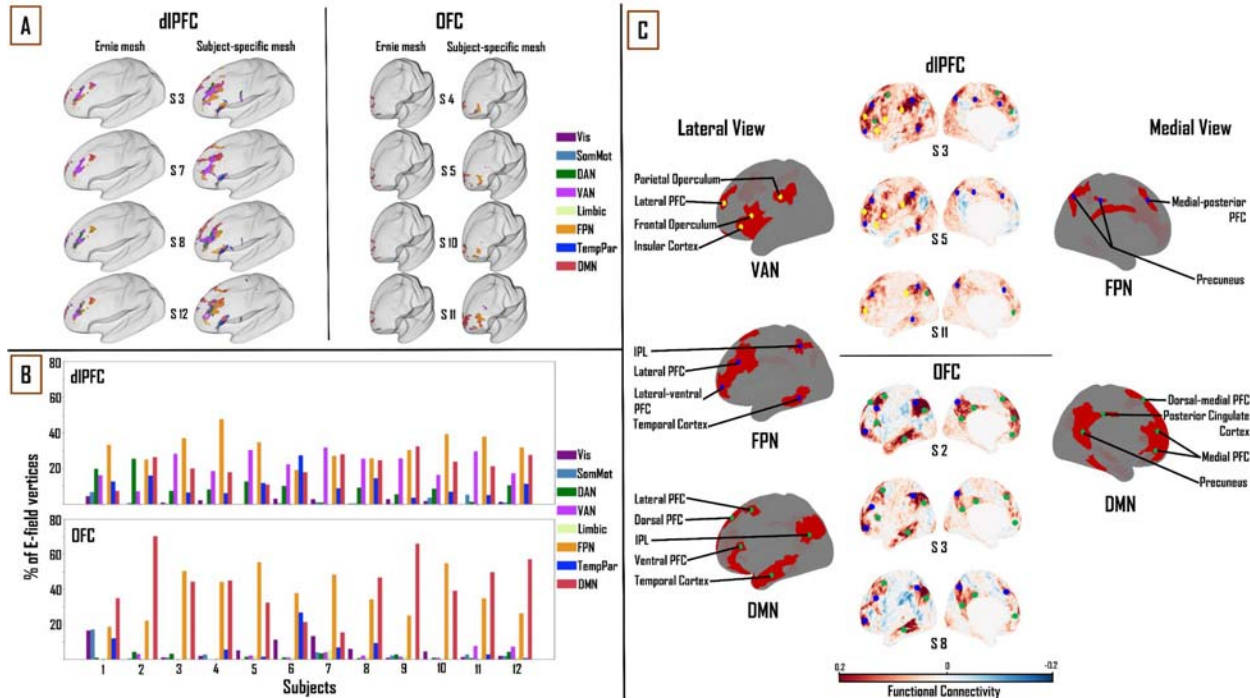
386 Again, one-way ANOVA showed a significant main effect of "NETWORK" for dlPFC ($F_{(1,7)} =$
387 44.33 , $p < 0.0001$, $\eta^2 = 0.80$) and OFC ($F_{(1,7)} = 45.48$, $p < 0.0001$, $\eta^2 = 0.81$). In the dlPFC, VAN
388 ($22.3 \pm 7.1\%$), FPN ($32.4 \pm 7.4\%$) and DMN ($21.4 \pm 7\%$) were seen to account for 76% of the E-

389 field vertices. FPN ($37.6 \pm 12.4\%$) and DMN ($43.5 \pm 15.8\%$) accounted for 81% of the E-field
390 vertices in the OFC. (Fig. 4 - **Panel B**).

391

392 *The relation between TMS targets and downstream brain regions*

393 At the dlPFC, on the lateral left cortical surface, the IPL, frontal and parietal opercula, and lateral
394 PFC were the major VAN nodes. Lateral FPN nodes included the IPL, the lateral-ventral and
395 lateral PFC, and the posterior region of the middle and inferior temporal gyri. Medially, the FPN
396 nodes consisted of the medial-posterior PFC and the precuneus. The lateral DMN nodes included
397 the lateral PFC, ventral PFC and IPL. Medially, the DMN nodes included the dorsal-medial and
398 medial PFC. Once again, similar to the previous sections, no VAN nodes were observed on the
399 medial cortical surface (Fig. 4 - **Panel C [top]**). At the OFC, on the lateral cortical surface, the
400 FPN nodes included the IPL, lateral-ventral and lateral PFC. Medial FPN nodes included the
401 precuneus and medial-posterior PFC. Within the DMN, the IPL, lateral and dorsal PFCs and the
402 anterior region of the middle and inferior temporal gyri were noted as the main lateral nodes.
403 Medially, the precuneus, PCC, dorsal-medial and medial PFC made up the DMN nodes (Fig. 4 -
404 **Panel C [bottom]**).



405
 406 **Figure 4: Combined influence of individual cortical geometry and individual FC on TMS target connectivity. A)**
 407 Differences in patterns of FC between fixed ('ernie') and subject-specific E-fields. **B)** The maximum FC of each
 408 functional network is shown, represented as a percentage of the thresholded E-field vertices for each subject. *Top:*
 409 VAN, FPN and DMN accounted for 76% of the E-field vertices in dIPFC. *Bottom:* FPN and DMN accounted for
 410 81% of the E-field in OFC. **C)** *Top:* lateral and medial views of dIPFC FC maps in subjects 3, 5 and 11, highlighting
 411 the key regions that are functionally connected across the VAN, FPN and DMN. These regions lie mainly in the
 412 frontal, parietal and temporal cortices. *Bottom:* lateral and medial views of OFC FC maps in subjects 2, 3 and 8,
 413 highlighting the key regions that are functionally connected across FPN and DMN. These regions lie mainly in
 414 medial-frontal, cingulate, and posterior parietal cortices. VAN = ventral attention network, FPN = fronto-parietal
 415 network, DMN = default-mode network.

416

417 Discussion

418 In this study, we sought to characterize comprehensively two major therapeutic TMS target sites,
 419 the dIPFC and the OFC, in terms of a) their patterns of FC to other regions and canonical brain
 420 networks, and b) the level and sources of inter-subject variability in those connectivity patterns,
 421 using a combination of E-field modelling and analyses of resting state fMRI data in a group of
 422 healthy subjects. With respect to the first of these, our chief conclusion was that three major
 423 functional networks were targeted across the dIPFC and OFC: VAN, FPN and DMN in the

424 dIPFC, and FPN and DMN in the OFC. Furthermore, while these major networks consistently
425 appeared across all subjects, the relative connectivity strengths between the networks, as well as
426 the downstream nodes within each network, varied considerably on a subject-wise basis. This is
427 consistent with previous observations in both animals (Bergmann et al., 2020) and humans
428 (Mueller et al., 2013). With respect to the question of the level and sources of variability, our
429 approach was to separate, and study both independently and in combination, the effects of
430 variability in skull anatomy and cortical geometry (as encapsulated in subject-specific E-field
431 maps), and of variability in subject-specific FC maps. These analyses showed that the average E-
432 field and group-average FC data are able to predict which networks are targeted, for some
433 networks, but cannot necessarily tell the degree to which each individual network is specifically
434 targeted across subjects. In the following we discuss the key components of these findings, their
435 interpretation in relation to previous work, and highlight important caveats and limitations.

436

437 *Connectivity of TMS targets*

438 Regions showing strong FC with TMS targets give us some insight into the potential functional
439 effects of TMS stimulation. The results of our study revealed the VAN, FPN and DMN as the
440 major functional networks targeted by dIPFC TMS, and the FPN and DMN as the major
441 networks targeted by OFC TMS. Specific network nodes within each of these networks were
442 observed. Some network nodes such as the lateral PFC (VAN, FPN, DMN) and precuneus (FPN,
443 DMN) were seen across all subjects and in multiple networks. On the other hand, certain
444 networks and nodes were specific to dIPFC TMS or OFC TMS. For example, the connectivity to
445 the VAN is seen in dIPFC TMS, but not in OFC TMS. At the level of individual network nodes,
446 the PCC is a DMN-specific node in E-field FC patterns for OFC TMS targets, but not dIPFC
447 TMS targets. Furthermore, while many similar nodes occur across these networks in multiple
448 subjects, the overall pattern of FC observed varies from subject to subject. The relevance and
449 important functions of the three major functional networks highlighted in these results (FPN,
450 DMN and VAN) are outlined below.

451 The FPN is a system implicated in cognitive control for regulating goal-driven behaviour. This
452 network is believed to play a key role in problem solving, as well as actively preserving and

453 editing the information stored in working memory (Uddin et al., 2019). The DMN is active
454 during resting wakefulness, when an individual is not actively engaged with external stimuli
455 (Fox et al., 2005). The DMN is also involved in ruminative processes, specifically with thoughts
456 concerning oneself, their past or future events (Andrews-Hanna, 2012). The VAN, sometimes
457 called the salience network, keeps track of salient events (triggered by sensory stimuli) and plays
458 a role in response inhibition or selection (Menon and Uddin, 2010). The VAN is crucial for
459 spontaneous cognitive control, where it helps switch between the DMN's ruminative/self-
460 reflective functions to the FPN's task-based/externally driven functions (Menon, 2011; Menon
461 and Uddin, 2010). Neuroimaging studies have shown that the heterogeneous nature of MDD and
462 its subtypes may emerge as a result of unique patterns of disruption in these networks' dynamics
463 (Feffer et al., 2018). Indeed, multiple research groups have begun to utilize abnormal FC patterns
464 to characterize MDD subtypes (Peng et al., 2012), showing how differences in spontaneous
465 dynamics might potentially lead to different clinical outcomes (Fox et al., 2012). In line with this
466 evidence, our results suggest that a connectivity-based targeting strategy for optimizing network
467 engagement on a per-subject basis may be beneficial for optimizing clinical responses.

468

469 *Implications for rTMS therapy*

470 A systematic review of 25 neuroimaging studies of MDD summarized that hypoconnectivity
471 occurs within the FPN and VAN, while regions that were a part of the DMN exhibited
472 hyperconnectivity (Kaiser et al., 2015). There are multiple inhibitory and excitatory rTMS
473 protocols used for inducing region-specific changes in neural activity. Excitatory paradigms
474 include intermittent theta burst stimulation (iTBS) and high-frequency (10-20Hz) rTMS, whereas
475 prevalent inhibitory paradigms are continuous theta burst stimulation (cTBS) and low frequency
476 (~1Hz) rTMS (Downar and Daskalakis, 2013; Huang et al., 2005). The implications from our
477 results may further enhance rTMS targeting practices by informing not only region but type of
478 paradigm to use as well. In our study, 10 subjects had a higher number of vertices targeting the
479 FPN or VAN than DMN, in the dlPFC (Figure 4 - **Panel B [top]**). Therefore, one way of
480 understanding the positive therapeutic effects of applying iTBS or high frequency rTMS at the
481 dlPFC in MDD patients may be that this intervention could result in an excitation - and perhaps

482 renormalization - of the VAN and FPN networks, which show hypoconnectivity in MDD (Kaiser
483 et al., 2015). At the OFC, our results show that 7 out of 12 subjects have a higher number of
484 vertices targeting the DMN than the FPN (Figure 4 - **Panel B [bottom]**). In this case, applying
485 cTBS or low-frequency rTMS may be expected to inhibit the DMN, and again potentially
486 achieve a renormalization of DMN hyperconnectivity in MDD. Targeting specific networks with
487 unique rTMS paradigms in this way may alleviate depressive symptoms more efficiently. In the
488 future, this line of research may be further explored to identify which networks are affected in a
489 given patient, and selectively targeting them, thereby potentially personalizing rTMS therapy for
490 individuals with MDD.

491

492 ***Functional Connectivity Variability***

493 We calculated the Pearson correlation coefficient between the percentage of E-field vertices for
494 the VAN, FPN and DMN, across all subjects, for the group average FC matrix and the subject-
495 specific FC matrix. The group average FC matrices were able to predict inter-individual
496 differences in how networks were targeted from the dlPFC and OFC, to a certain extent. In the
497 dlPFC, we observed that the 1003-subject HCP average FC matrix was able to predict what
498 DMN connectivity would be with the subject-specific FC matrices ($r=0.67$). This was not the
499 case with the VAN ($r=0.07$) and FPN connectivity ($r=0.03$). However, this observation was
500 reversed in the OFC. Here, the average FC matrix was able to predict what FPN connectivity
501 would be with subject-specific FC matrices ($r=0.52$) but not with the DMN ($r=0.2$). One
502 explanation for this finding is that DMN has a more consistent spatial pattern across subjects
503 than the VAN or FPN, such that subject-level and group-level patterns are relatively more
504 similar than for other networks. However, this line of reasoning does not explain why a pattern
505 reversal occurs at the OFC. In summary, our results confirm the general intuition that using an
506 average FC matrix provides a gross estimate of what the targeted networks might be, but precise
507 targeting requires each subject's specific FC data.

508

509 ***E-field Variability***

510 We observed the mean subject-specific thresholded E-field size to be 663 and 162 vertices, in the
511 dlPFC and OFC, respectively. However, the E-field size varied considerably across subjects,
512 with a standard deviation of ± 200 vertices in the dlPFC and ± 56 vertices in the OFC. This high
513 intersubject variability of dlPFC and OFC E-fields can be attributed to variability in subject-
514 specific cortical geometry. Consistent with this, the boundaries between the five main tissue
515 types have been shown to affect E-field distributions. These include the skin, skull, CSF, white
516 matter, and gray matter (Thielscher et al., 2011), and are highly variable across subjects.
517 Furthermore, this E-field variability had a knock-on effect on variability in the connectivity of
518 the dlPFC and OFC stimulation targets to downstream functional networks. In the dlPFC, the
519 normative template E-field (from the ‘ernie’ brain) and subject-specific E-fields showed a similar
520 pattern of targeting to the VAN and FPN in each subject’s specific FC matrix ($r=0.82$ and 0.76 ,
521 respectively). However, this was not the case with the DMN ($r=-0.05$). In the OFC, the opposite
522 was found to be true. The normative template E-field and subject-specific E-field showed a
523 similar pattern of targeting to the DMN ($r=0.7$), but not so much with the FPN ($r=0.4$). A
524 potential reason for this observation is the large difference in size between the template E-field
525 and the subject-specific E-fields. In the dlPFC, the subject-specific E-fields are twice as large
526 (mean = 663 vertices) as the template E-field (310 vertices). The difference is greater in the
527 OFC, with the subject-specific E-fields (mean=162) being over two and half times the size of the
528 template E-field (63 vertices). The additional vertices in each subjects’ specific E-field tend to
529 target the VAN and FPN in the dlPFC, as the E-field vertices here are predominantly present on
530 the ventral/lateral surface of the prefrontal cortex. The DMN, being more medially located
531 overall, therefore has much lower connectivity to dlPFC when the template E-field is used than
532 when subject-specific E-fields are used (Figure 4 - **Panel A [left]**). Furthermore, this line of
533 reasoning can be extended to account for the pattern reversal observed in the OFC, where the
534 template E-field does not account for the additional vertices in the subject-specific E-fields
535 which are spread more laterally, targeting the FPN (Figure 4 - **Panel A [right]**), and hence shows
536 a pattern targeting the DMN but not the FPN.

537

538 ***Caveats and Limitations***

539 While the results of this study are promising, there are some important caveats and limitations to
540 highlight.

541 One important limitation is the fact that we only use the left hemisphere to study TMS target
542 connectivity. The reason for this choice was in part practical (simplifying surface-based
543 analysis), but also reflected the fact that as a rule we expect FC patterns to the two TMS target
544 zones to be dominated by intrahemispheric connections, with the obvious exception of the
545 contralateral homologue (i.e., right dlPFC and right OFC). By using FC data from only one
546 hemisphere, we are therefore potentially missing some important differences between subjects
547 and TMS targets in their connectivity to the contralateral homologues. However, given that our
548 focus here is on patterns of FC to distal cortical regions that are outside of either the primary
549 target area or its hemispheric homologue, we feel this approach is justified.

550 Another important limitation is the E-field threshold, and its effect on resultant FC calculations.
551 In this study, the E-field threshold was set to 0.9 V/m, which is slightly lower than that used by
552 (Romero et al., 2019). Our justification for this choice is that higher thresholds (i.e., above 0.9
553 V/m) shrink the E-field sizes, especially in the OFC, and hamper FC calculations. The problem
554 remains however that in the field of TMS more broadly, it is not yet clear what a 'correct' E-field
555 threshold should be. Often this is conceived as the minimum induced current necessary to
556 depolarize neuronal membranes and cause them to fire. Subthreshold effects (i.e. ones not
557 resulting from action potential induction at the primary stimulation site) may nevertheless
558 potentially have an important role in TMS responses; for example by facilitating the occurrence
559 and frequency of suprathreshold events. Spatially, the question of E-field thresholding relates
560 quite closely to the question of E-Field size and extent (since high thresholds usually 'trim' the
561 edges of activated areas, eliminating vertices around the penumbra first).

562 A further, related, limitation is that interpretation of our results, and those from related work (e.g.
563 Opitz et al., 2016) rests heavily on the notion that FC can serve as a reliable indicator of which
564 downstream brain regions, distal to the TMS target site, would themselves be 'activated', or
565 otherwise affected, by TMS administration. In defense of this principle, multiple studies have
566 shown experimentally that neuronal activation as a result of TMS is not limited to the cortical
567 circuits closest to the scalp (Bergmann et al., 2021; Hawco et al., 2018; Siebner et al., 2009;

568 Solomon-Harris et al., 2016). These studies show that initial local neuronal activation spreads
569 across cortical and subcortical regions to neighbouring and distant parts of the brain. In other
570 words, it appears to be impossible to stimulate a single region of the brain with TMS without
571 affecting a large number of downstream network nodes. While further studies are required to
572 decipher the precise pathways taken to activate these downstream nodes, FC maps offer a
573 plausible proxy for assessing which networks are being engaged for a given TMS target region.

574 We note that the sample size used in the present study is a further potential limitation. Our
575 reasoning here was that by focusing on a relatively small number of subjects, we could conduct
576 an in-depth analysis of downstream TMS target connectivity, with extensive visual comparisons.
577 Our detailed study of how E-field sizes affect TMS target connectivity, and our close look at FC
578 maps highlighting key downstream nodes within major functional networks, justifies, we believe,
579 the moderate sample size for this specific investigation.

580 Importantly, the subjects chosen for this study are from a normative, healthy sample (from the
581 HCP database). However, MDD patients may have different/altered connectivity patterns that the
582 healthy subject patterns may not be representative of. While previous research has looked at
583 connectivity-based targeting in MDD patients with promising results (Weigand et al., 2018), a
584 full-fledged clinical trial evaluating this method is yet to be undertaken (Cash et al., 2020).

585 One potential improvement to the methodology used here that may be considered for future work
586 is to evaluate alternative TMS coil options. Here, we have chosen to use the Magstim 70mm
587 Figure-8 coil to run our TMS simulations in SimNIBS. Used in both clinical and research
588 settings, it has been shown that Figure-8 coils allow for a more focused stimulation of the target
589 site (Thielscher and Kammer, 2004) than other design options. We used the Figure-8 coil type to
590 run our simulations for both the dlPFC and OFC. However, the thresholded E-field size
591 difference between these two TMS targets in our analyses is likely due mainly to their
592 anatomical locations, and distance from the stimulating coil. The dlPFC is located at the frontal
593 lobe and lies on the lateral and dorsal surface of the medial convexity, fairly close to the scalp
594 surface. The OFC, on the other hand, is a large gray matter shelf located on the ventral surface of
595 the frontal lobes, above the orbit of the skull. As a result, a large portion of the OFC is not
596 accessible via the Fp1 electrode position on the scalp (which is more frontal in location than

597 ventral). Thus, a typical Figure-8 coil cannot target the OFC as effectively as it can the dlPFC,
598 owing to the inconsistency of the targeting surface. To address this issue, alternate coil designs
599 have been proposed, such as crown-shaped coils, C-shaped coils (Deng et al., 2008) and H-
600 shaped coils (Levkovitz et al., 2009), which have been developed to target deeper cortical
601 regions. It will be valuable to analyze the resulting E-fields produced by these coils with our
602 current methodology, to better establish the effects of TMS with all potentially available coil
603 configurations on novel treatment sites, such as the ventral OFC and regions of the medial PFC.

604

605 *Conclusions and Future Directions*

606 We have presented data characterizing the FC patterns of canonical therapeutic TMS targets and
607 the key dimensions of their variability across subjects. Our hope is that these insights prove
608 useful as part of the broader effort by the psychiatry, neurology, and neuroimaging communities
609 to help improve and refine TMS therapy, through a better understanding of the technology and
610 its neurophysiological effects. Further work shall be needed to evaluate the predictive and
611 clinical utility of the TMS target fMRI FC profiles, through both prospective and retrospective
612 clinical neuroimaging studies in MDD patients. Progress on the neurobiological question of what
613 are the network-level effects of TMS stimulation, however, necessitates an integrative approach
614 combining various neuroimaging and physiological modalities, and various quantitative
615 techniques. In particular, characterization of the structural connectivity between TMS targets and
616 their downstream networks using diffusion-weighted MRI tractography analyses, which can
617 serve as a useful proxy for axonal connectivity between various brain regions, shall be an
618 important area of investigation that should complement the results reported in the present study.
619 How do target region connectivity profiles from tractography connectivity compare to their FC
620 analogues? How should discrepancies and convergences between structure and function be
621 interpreted in relation to expected TMS effects? Ultimately the best-known general strategy for
622 reconciling such questions (and one that we are currently pursuing intensively) is to develop
623 validated and predictively accurate computational models of brain stimulation responses, that
624 include relevant biological detail but are also sufficiently scalable to allow whole-brain activity
625 simulations. In future work, our aim is to use mechanistic modelling approaches to formalize and

626 test hypotheses around synaptic-, local circuit-, and network-level mechanisms in brains
627 receiving noninvasive stimulation, and to use the insights obtained to help improve the efficacy
628 of TMS in the clinic.

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633 Writing - Review & Editing, Visualization; JDG: Conceptualization, Methodology, Writing -
634 Review & Editing, Supervision, Funding acquisition; DM: Writing - Review & Editing,
635 Visualization; FM: Writing - Review & Editing.

636

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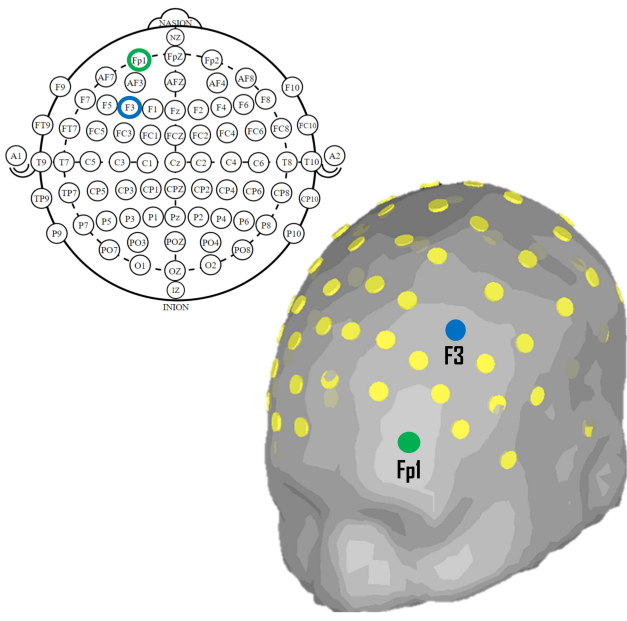
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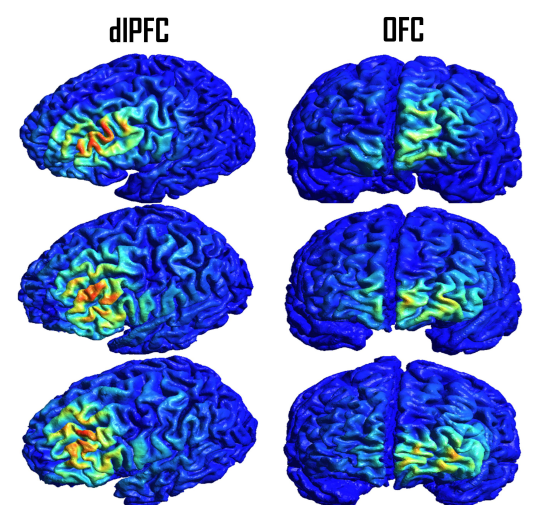
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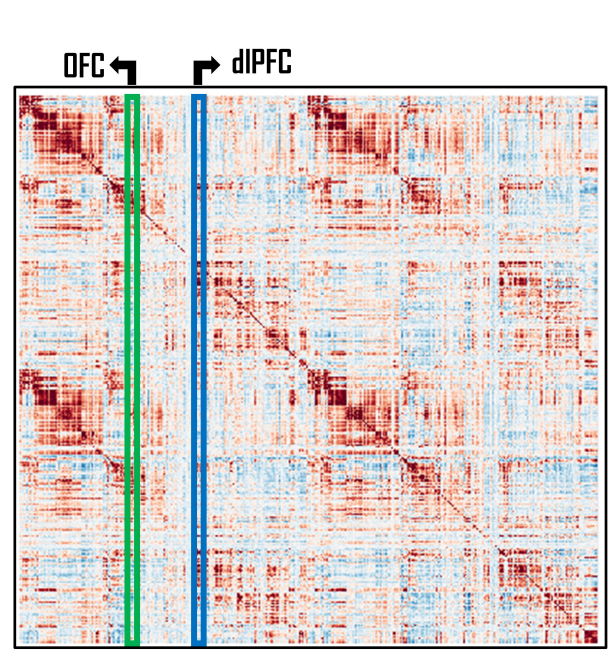
1 EEG Channel Targets



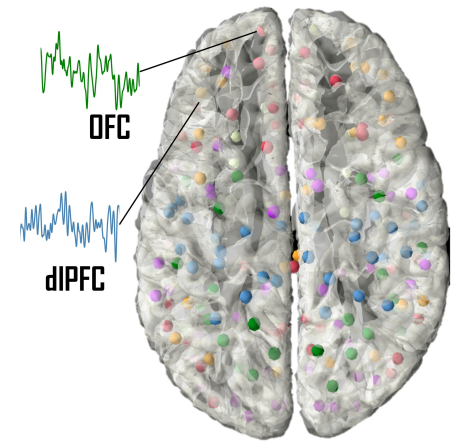
2 E-field Maps



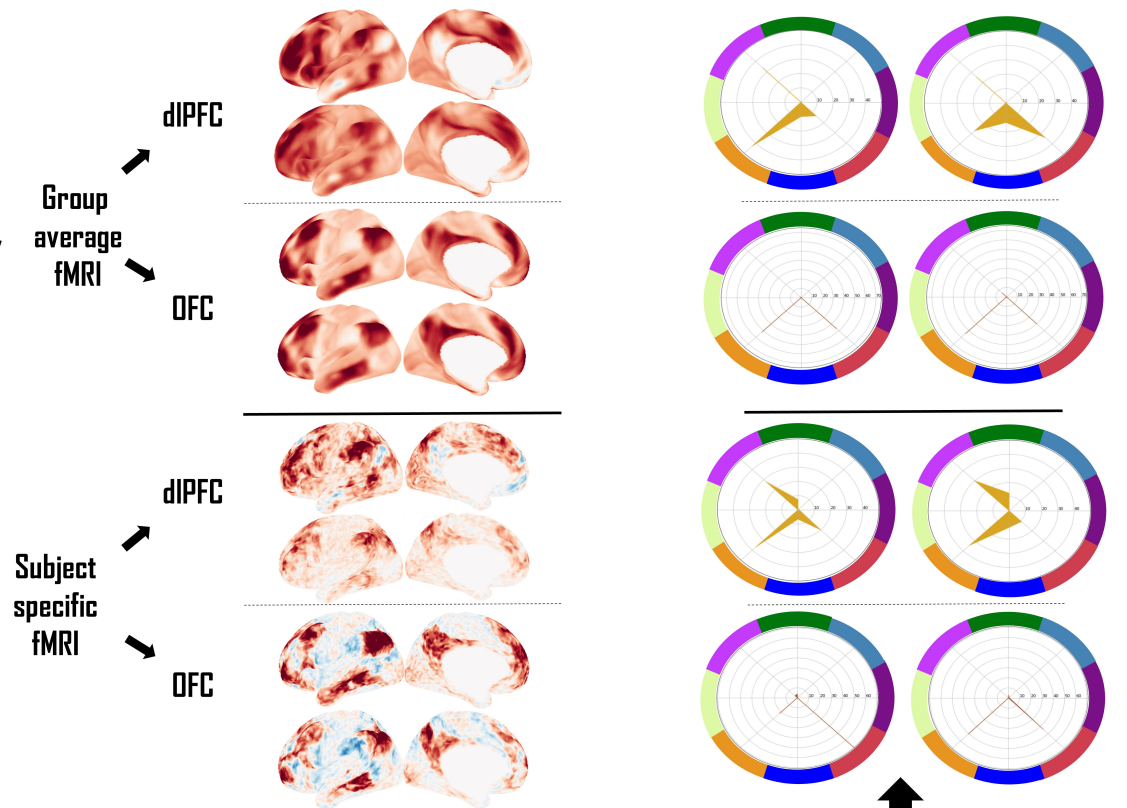
4 rs-fMRI FC Matrix



3 rs-fMRI Time Series



5 E-field seed-based FC



6

Network-based Functional Connectome summaries

