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Connectivity-guided transcranial magnetic stimulation of the dopamine system: A proof-of-concept study

Dear Editor,

Dopamine plays an important role in many brain functions, including movement, reward and cognition. Abnormalities in dopamine function occur in brain disorders with symptoms dependent on the affected dopaminergic pathways. Although medications targeting the dopamine system can be highly effective, they lack pathway specificity, resulting in adverse effects via modulation of other dopaminergic pathways. These undesirable effects due to the lack of network-specific dopaminergic modulation are exacerbated by varying optimal dopaminergic tone across brain networks [1].

rTMS has shown the capability to modulate neurotransmitter release, including dopamine signaling [2]. In their pivotal work, Strafella and colleagues demonstrated that, in healthy volunteers, high-frequency rTMS targeted to the left dorsolateral prefrontal cortex (DLPFC) resulted in dopamine release in the ipsilateral caudate nucleus [3]; in a subsequent study, rTMS to the motor cortex resulted in dopamine release in the ipsilateral putamen [4]. The spatial topography of these findings aligns with the prevailing models of the functional organization of corticostriatal projections [5,6], suggesting that rTMS could be used to modulate dopamine function in a network-specific manner. However, there are no previous studies directly testing this hypothesis, and not all sham-controlled rTMS-PET studies have been able to replicate the rTMS-induced striatal dopamine release [2].

The aim of this study was to test functional connectivity-guided rTMS for network-specific modulation of the dopamine system. Using a within-subject design including ten healthy volunteers, we applied a single session of intermittent theta burst stimulation (iTBS) to two closely approximated prefrontal targets in separate counterbalanced sessions. Two striatal regions-of-interest (ROIs) were defined as portions of the striatum embedded in the ventral attention (ROI_{strVAN}) and default mode (ROI_{strDMN}) networks based on a pre-existing striatal 7-network parcellation [7]. The two stimulation targets were defined as the prefrontal regions exhibiting the maximal connectivity difference between the two ROIs using an external connectome derived from resting state fMRI data from 1000 healthy volunteers (Fig. 1A) [8]. Subjects underwent a brain MRI to obtain T1-weighted images for targeting and resting state fMRI to compute individual functional connectivity between the targets and striatal ROIs. Following stimulation to each target ($target_{VAN}$ and $target_{DMN}$), changes in striatal D2/D3 receptor availability were measured with [^{11}C]raclopride PET. Neuronavigated iTBS (three pulses at 50 Hz delivered at 5 Hz for 2 seconds with 8 second burst intervals; 600 pulses; 80% active motor threshold (AMT) [9]) was applied using a MagPro X100 and MCF-B65 coil. The induced electric fields (E-fields) were estimated using SimNIBS. Detailed methodological information is available in the Supplementary material.

The two TMS-PET visits were mean (s.d.) 62 (39) days apart and tracer was administered 2.2 (0.4) minutes after iTBS. There were no significant differences between the two TMS-PET visits in resting motor threshold, AMT, stimulation intensity, injected dose, or time interval between the completion of iTBS and tracer injection. The distance between the center of gravities of $target_{VAN}$ and $target_{DMN}$ in MNI space was 5.2 cm with clear differences between the induced E-fields (Fig. 1B).

We hypothesized that each stimulation target would induce dopamine release (BP_{ND} decrease) preferentially in its corresponding striatal ROI. The stimulation target × ROI interaction was not significant ($p = 0.79$), indicating no differential effect between ROIs. However, there was a significant main effect of stimulation target on BP_{ND} ($p = 0.002$), with iTBS to $target_{VAN}$ resulting in lower BP_{ND} in both ROIs compared to iTBS to $target_{DMN}$ (Fig. 1C). Importantly, these effects were confined to the *a priori* ROIs, with no significant BP_{ND} changes in the contralateral homologous subregions or in any left- or right-sided striatal subregions of the remaining five networks of the 7-network parcellation.

In the ventral attention network, functional connectivity from the cortical target to the corresponding striatal subregion ($target_{VAN}$-ROI_{strVAN}) correlated significantly with stimulation-induced BP_{ND} change in ROI_{strVAN} (higher connectivity associated with greater *decrease* in BP_{ND} after stimulation to $target_{VAN}$ compared to $target_{DMN}$) ($r = -0.85$, $p = 0.004$; Fig. 1D). In the default mode network, however, the correlation between the functional connectivity ($target_{DMN}$-ROI_{strDMN}) and BP_{ND} change in ROI_{strDMN} was in the opposite direction (higher connectivity associated with greater *increase* in BP_{ND} after stimulation to $target_{DMN}$ compared to $target_{VAN}$), but did not reach significance ($r = 0.57$, $p = 0.11$; difference between correlation coefficients, $p < 0.001$; Fig. 1D). The functional connectivity between these ROIs and the noncorresponding targets did not correlate with BP_{ND} change ($p > 0.7$). In exploratory analyses of factors associated with iTBS-induced dopaminergic responses, change in BP_{ND} correlated significantly with delay discounting, but not subjects' age, BMI, BIS scores, or stimulation-related parameters. More detailed results available in Supplementary material.

In this proof-of-concept study, we show that a single session of connectivity-guided iTBS to a cortical target modulates striatal synaptic dopamine levels via transsynaptic effects. We observed a significant main effect of stimulation target on BP_{ND}, with effects confined to predefined striatal ROIs and absent elsewhere in the striatum. The stimulation target × ROI interaction was not significant, however, indicating that the observed effects across ROIs did not follow the hypothesized directionality (i.e., preferential dopamine release in the ROI corresponding to the stimulation target). This limits conclusions regarding ROI-level specificity.

The results may be interpreted as iTBS to $target_{VAN}$ leading to dopamine release in both striatal ROIs or, alternatively, as iTBS to $target_{VAN}$ and $target_{DMN}$ having opposing effects on synaptic dopamine levels in the corresponding striatal subregions. Supporting the latter interpretation, ventral attention and default mode networks have

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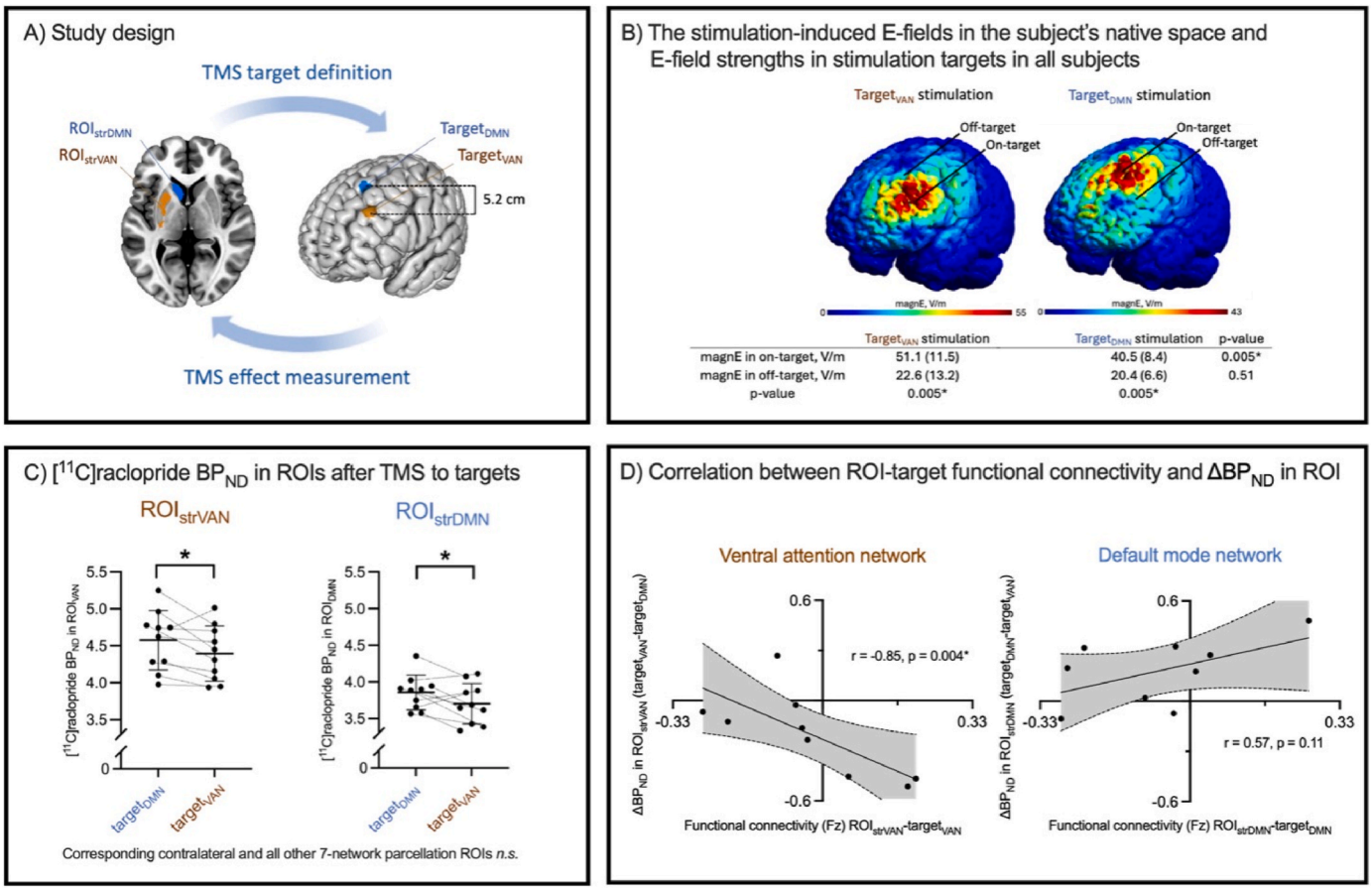

Fig. 1. Connectivity-guided transcranial magnetic stimulation of striatal dopamine function

A) *A priori* selected striatal regions-of-interest (ROIs) defined as portions of the striatum embedded in the ventral attention (ROI_{strVAN}) and default mode (ROI_{strDMN}) networks based on the striatal network parcellations by Choi et al. (2012) [7]. The corresponding cortical stimulation targets were derived based on maximal functional connectivity difference from the striatal ROIs. The resulting MNI coordinates for target center of gravities were −38, 44, 32 for $target_{VAN}$ and −22, 34, 50 for $target_{DMN}$. The effects of the stimulation on striatal dopamine function were investigated by measuring changes in [^{11}C]raclopride non-displaceable binding potential (BP_{ND}) in the *a priori* ROIs. B) Stimulation-induced E-fields in a subject's native space with median (IQR) electric field strengths at the on-target (i.e., target that was stimulated) and off-target (i.e., target that was not stimulated) in the two stimulation conditions in the whole sample. C) [^{11}C]raclopride BP_{ND} was significantly lower after iTBS to $target_{VAN}$ compared to iTBS to $target_{DMN}$ in both ROI_{strVAN} [mean (s.d.) 4.57 (0.40) vs. 4.39 (0.37); corresponding to 3.8% (95% C.I. 0.3-7.3) relative reduction in BP_{ND}] and ROI_{strDMN} [3.85 (0.24) vs. 3.70 (0.28); corresponding to 3.9% (95% C.I. 0.1-7.6) relative reduction in BP_{ND}]. The mean (95% C.I.) peak voxelwise BP_{ND} change was 15.5% (8.3-22.7%) in the ipsilateral caudate nucleus (supplementary material). D) Correlations between stimulation-induced ΔBP_{ND} and subjects' individual functional connectivity between the stimulated cortical target and striatal ROI (ROI-target connectivity) in the ventral attention network (VAN) and default mode network (DMN). ΔBP_{ND} for each ROI was calculated by subtracting BP_{ND} after stimulation to the off-target (i.e., the target corresponding to the other ROI) from BP_{ND} after stimulation to the on-target (i.e., the target corresponding to the studied ROI). Thus, increased stimulation-induced increase in synaptic dopamine levels after on-target compared to off-target stimulation would be reflected as negative ΔBP_{ND}. *p < 0.05; *n. s.* = not significant.

previously been shown to have opposing local brain metabolic responses to high-frequency rTMS compared to sham stimulation [10]. In addition, the magnitude of iTBS-induced dopaminergic effect correlated with the strength of individual functional connectivity between the cortical target and striatal ROI (significant in the ventral attention network but not in the default mode network), suggesting that individual connectivity-based targeting, rather than normative connectomes may be required to optimize dopaminergic effects.

The limitations of this study include lack of an inactive sham condition, small sample size, possible E-field overlap between nearby targets and investigating effects approaching [^{11}C]raclopride test-retest variability. Together, these findings suggest that connectivity-guided stimulation can modulate the dopaminergic system in a spatially constrained manner, although the direction of effects may not be fully predictable from normative connectivity alone.

CRediT authorship contribution statement

Mikael Eklund: Data curation, Formal analysis, Investigation, Project administration, Visualization, Writing – original draft, Writing – review & editing. **Mark C. Eldaief:** Conceptualization, Writing – review & editing. **Lauri Tuominen:** Conceptualization, Writing – review & editing. **Kalle J. Niemi:** Data curation, Formal analysis, Writing – review & editing. **Juho Aaltonen:** Data curation, Writing – review & editing. **Virva Saunavaara:** Writing – review & editing. **Jussi Hirvonen:** Writing – review & editing. **Semi Helin:** Writing – review & editing. **Christin Y. Sander:** Writing – review & editing. **Bruce Rosen:** Writing – review & editing, Conceptualization. **Alvaro Pascual-Leone:** Writing – review & editing, Conceptualization. **Michael D. Fox:** Conceptualization, Writing – review & editing. **Aapo Nummenmaa:** Conceptualization, Funding acquisition, Methodology, Supervision, Writing – review & editing. **Juho Joutsa:** Conceptualization, Funding acquisition, Methodology, Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal

relationships which may be considered as potential competing interests: Mikael Eklund reports financial support was provided by The Finnish Parkinson Foundation, The Finnish Medical Foundation, Maire Taponen Foundation, The Finnish Brain Foundation, Orion Research Foundation, Turku University Hospital and National Institutes of Health. Kalle J Niemi reports financial support was provided by Finnish Parkinson Foundation, the Finnish Cultural Foundation (Pertteli Aaltonen Fund), Sigrid Juselius Foundation, the Finnish Neurological Society, the University of Turku, the Turku University Foundation, Turku University Hospital and TYKS Foundation. Alvaro Pascual-Leone reports was provided by Healthy Aging Initiative, the Eleanor and Herbert Bearak Memory Wellness for Life Program, Diane and Mark Goldman, and grants from the National Institutes of Health, Jack Satter Foundation, and BrightFocus Foundation. Michael D. Fox reports financial support was provided by The National Institutes of Health, the Kaye Family Research Endowment, the Ellison Baszucki Family Foundation, the Once Upon a Time Foundation, The BD2 Foundation, the Manley Family, the May Family Autism Research Fund, and Chuck and Kerri Bean. Aapo Nummenmaa reports financial support was provided by National Institutes of Health. Juho Joutsa reports financial support was provided by Sakari Sohlberg Foundation, Signe & Ane Gyllenberg Foundation, and Turku University Hospital. Kalle J. Niemi reports a relationship with The Finnish Parkinson Foundation, the Finnish Neurological Society, the Finnish Society of Nuclear Medicine, the Finnish Cultural Foundation (Pertteli Aaltonen Fund), Turku University Hospital, and the University of Turku, and Merck that includes: funding grants and travel reimbursement. Alvaro Pascual-Leone reports a relationship with Neuroelectrics, TetraNeuron, Bitbrain, Zeta Surgical, and AscenZion that includes: board membership. Michael D. Fox reports a relationship with Magnus Medical, Soterix, Abbott, Boston Scientific, Tal Medical, MDC Venture Capital that includes: consulting or advisory. Michael D. Fox reports a relationship with Salma Health that includes: consulting or advisory. Michael D. Fox reports a relationship with Neuronetics and Boston Scientific that includes: funding grants. Juho Joutsa reports a relationship with Addiktum, Lunbeck, Novartis and Nordic Infucare that includes: speaking and lecture fees. Juho Joutsa reports a relationship with Adamant Health, Insightec and Summaryx that includes: consulting or advisory. Juho Joutsa reports a relationship with Insightec, Abbvie and Abbott that includes: travel reimbursement. Juho Joutsa reports a relationship with Teva Finland that includes: board membership and consulting or advisory. Alvaro Pascual-Leone has patent licensed to APL is listed as an inventor on several issued and pending patents on the real-time integration of transcranial magnetic stimulation with electroencephalography and magnetic resonance imaging, and applications of noninvasive brain stimulation in various neurological disorders; as well as digital biomarkers of cognition and digital assessments for early diagnosis of dementia. Michael D. Fox has patent issued to MDF has intellectual property on the use of brain connectivity imaging to analyze lesions and guide brain stimulation. - If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2026.103109.

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