Towards clinical translation of the default mode subcortical targeting for therapeutic neuromodulation

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Introduction

For patients with disorders of consciousness (DoC), functional connectivity analysis is a widely used approach to identify subcortical network hubs that could be used as therapeutic targets for neuromodulation[1]. Although the optimal therapeutic targets have not been well defined, the default mode network (DMN) is well established as a network that contributes to the modulation of consciousness[2]. We recently mapped the subcortical connectivity of the DMN using 7T resting-state fMRI (rs-fMRI) data from the Human Connectome Project (HCP)[3]. Here, our aim is to determine whether this subcortical DMN map can be reproduced, and to what degree, in data with lower signal to noise ratio (SNR), which would pave the road to clinical translation for targeted neuromodulation.

Methods

One thousand healthy subjects with 3T rs-fMRI scans from the HCP[4] were analyzed. Only the first session (1_LR) of the minimally preprocessed grayordinate rs-fMRI data were used to minimize the impact from inter-subject misalignment due to imperfect distortion correction. They were randomly split into two equal-size groups (G1 and G2), each with 500 subjects. We then applied the group BrainSync + NASCAR tensor decomposition pipeline[3,5–7] to the rs-fMRI data and the DMN was identified from the decomposition result during the post-processing, for each group independently. The cortical and subcortical components of the DMN spatial map were separated from the grayordinate representations and the subcortical fraction was converted into a 3D volume for visualization in Freeview[8]. Further, to explore the sample size effect and the potential subject selection bias, we performed the same pipeline on the same group of 84 subjects as used in the previous 7T analysis[3] (Same7T), as well as on a group of randomly selected 86 subjects who did not participate in any 7T scan (Random). The subcortical DMN connectivity results from all four

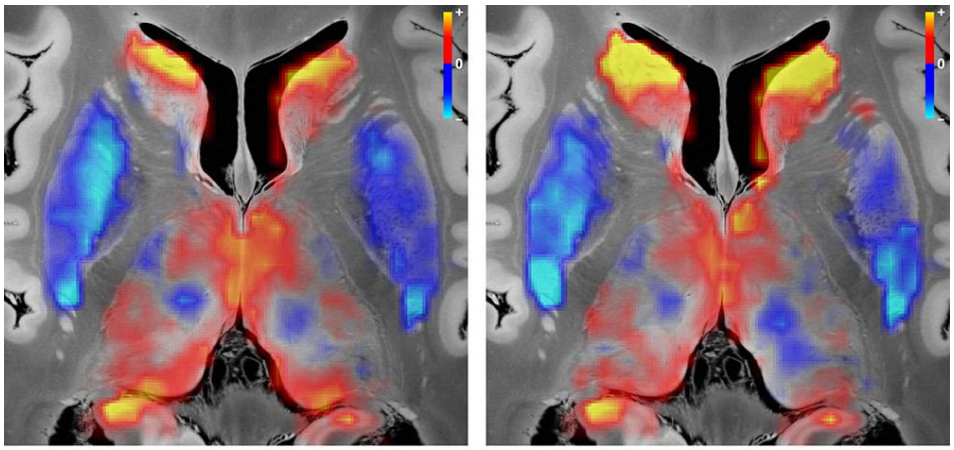
experiments (G1, G2, Same7T, and Random) were overlaid on a 7T 100 μm resolution *ex vivo* MRI dataset[9] for precise neuroanatomic analyses.

Results

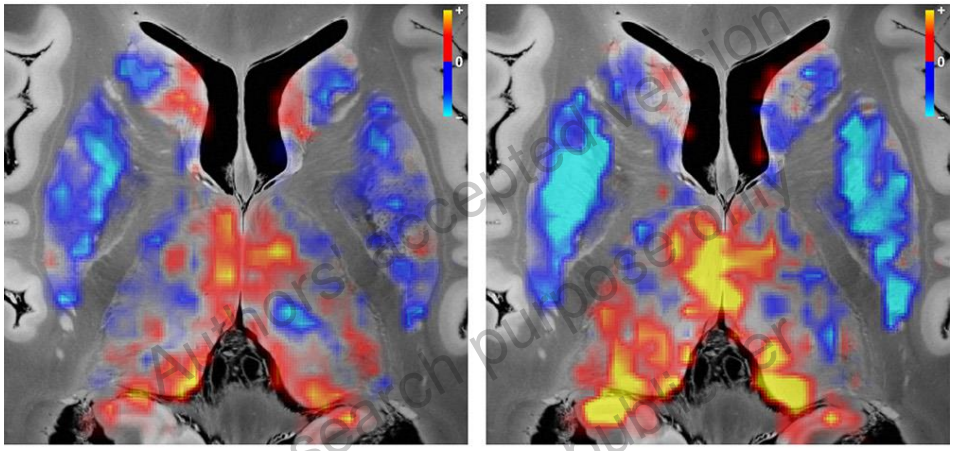
Fig. 1 (a) – (d) show the subcortical maps of the DMN in thalamus and basal ganglia for group G1, G2, Same7T, and Random, respectively; (e) shows the overall axial slice of the 7T result[3] and (f) shows the zoom-in version of (e) with anatomical labels for easy comparison. Overall, highly reproducible functional connectivity patterns were observed from the two 500-subject groups, Fig. 1 (a, b). The medial thalamic regions (e.g., the central laterial nucleus) showed positive correlations, the globus pallidus and putamen showed negative correlations, which are all consistent with our previous findings from the 7T dataset[3] and supportive of the proposed "mesocircuit" model[10]. Similar connecitivty patterns were also observed from the two 84-subject groups but with less clear boundaries between spatially contiguous regions and lower reproducibility, Fig. 1 (c, d). Fig. 2 shows the counterparts to Fig. 1 in the caudal midbrain. The ventral tegmental area and the dorsal and median raphe showed strong positive association with the DMN that was consistent between the two 500-subject groups, although with slightly less clear connectivity patterns compared to the 7T results, Fig. 2 (a, b). In contrast, intermingled positive and negative correlations were observed when only 84 subjects were used, Fig 2 (c, d), regardless of the selection of the subjects.

Conclusion

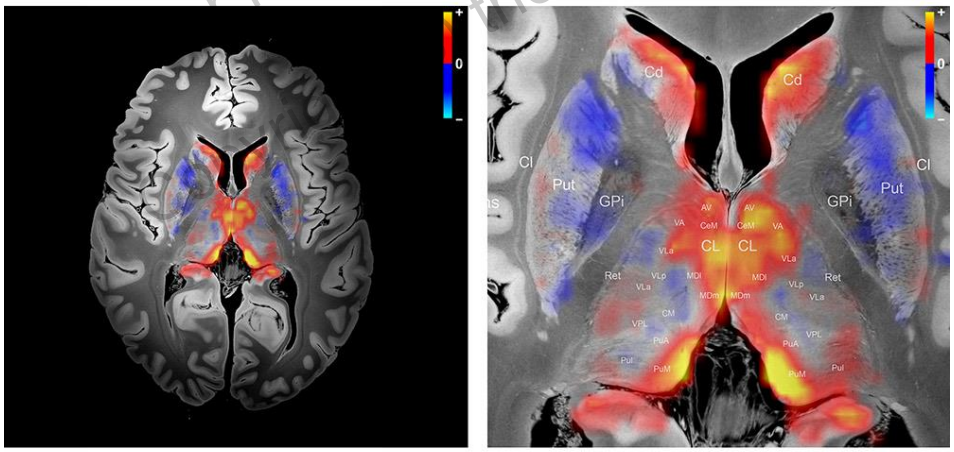
The subcortical DMN functional connectivity can be reproduced from 3T healthy control data. However, this reproducibility requires a substantially larger dataset than that used in the 7T study (500 subjects versus 84 subjects) to compensate for the lower SNR in the 3T scans. These findings suggest that clinical translation of the subcortical DMN functional connectivity to individual patients will require development of novel methods.



(a) G1: 500 Subjects (b) G2: 500 Subjects



(c) Same7T: 84 Subjects (d) Random: 84 Subjects



(e) (f)

Fig. 1. The subcortical functional connectivity of the DMN in thalamus and basal ganglia. (a) 500-subject results from group 1 (G1); (b) 500 subject result from group 2 (G2); (c) 84-subject result from the same set of subjects as used in the previous 7T study; (d) 84-subject result from a random set of subjects who did not participate in the 7T study; (e) Overview of the axial slice with the result from the previous 7T study; (f) Zoom-in version of (e) with anatomical labels. (e) and (f) was adapted from Li, *et al.* NeuroImage, 2021.

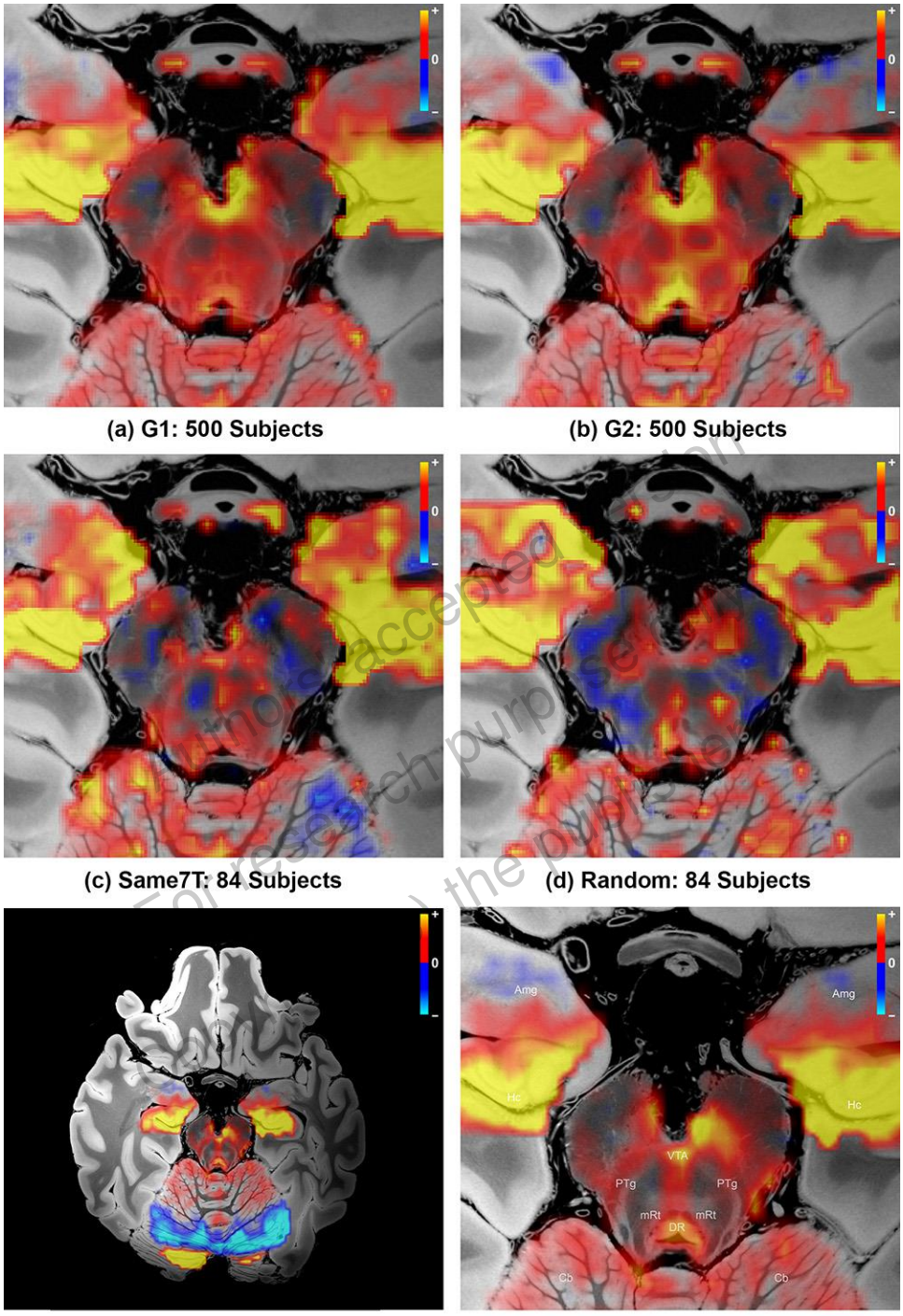


Fig. 2. The subcortical functional connectivity of the DMN in caudal midbrain. See Fig. 1 for the captions and the group information of the subfigures.

References

1. B. L. Edlow, et al., "Personalized connectome mapping to guide targeted therapy and promote recovery of consciousness in the intensive care unit", *Neurocrit Care*, vol. 33, no. 2, pp. 364–375, 2020. DOI: 10.1007/s12028-020-01062-7.
2. B. L. Edlow, J. Claassen, N. D. Schiff, D. M. Greer, "Recovery from disorders of consciousness: mechanisms, prognosis and emerging therapies", *Nat Rev Neurol*, vol. 17, no. 3, pp. 135–156, 2021. DOI: 10.1038/s41582-020-00428-x.
3. J. Li, W. H. Curley, B. Guerin, D. D. Dougherty, A. V. Dalca, B. Fischl, A. Horn, B. L. Edlow, "Mapping the subcortical connectivity of the human default mode network", *NeuroImage*, vol. 245, p. 118758, 2021. DOI: 10.1016/j.neuroimage.2021.118758.
4. D. C. Van Essen, et al., "The Human Connectome Project: A data acquisition perspective", *NeuroImage*, vol. 62, no. 4, pp. 2222–2231, 2012. DOI: 10.1016/j.neuroimage.2012.02.018.
5. J. Li, J. L. Wisnowski, A. A. Joshi, R. M. Leahy, "Robust brain network identification from multi-subject asynchronous fMRI data", *NeuroImage*, vol. 227, p. 117615, 2021. DOI: 10.1016/j.neuroimage.2020.117615.
6. H. Akrami, A. A. Joshi, J. Li, R. M. Leahy, "Group-wise alignment of resting fMRI in space and time", *Medical Imaging 2019: Image Processing*, San Diego, United States, Mar. 2019, p. 103. DOI: 10.1117/12.2512564.
7. A. A. Joshi, M. Chong, J. Li, S. Choi, R. M. Leahy, "Are you thinking what I'm thinking? Synchronization of resting fMRI time-series across subjects", *NeuroImage*, vol. 172, pp. 740–752, 2018. DOI: 10.1016/j.neuroimage.2018.01.058.
8. B. Fischl, "FreeSurfer", *NeuroImage*, vol. 62, no. 2, pp. 774–781, 2012. DOI: 10.1016/j.neuroimage.2012.01.021.
9. B. L. Edlow, et al., "7 Tesla MRI of the ex vivo human brain at 100 micron resolution", *Sci Data*, vol. 6, no. 1, p. 244, 2019. DOI: 10.1038/s41597-019-0254-8.
10. N. D. Schiff, "Recovery of consciousness after brain injury: a mesocircuit hypothesis", *Trends in Neurosciences*, vol. 33, no. 1, pp. 1–9, 2010. DOI: 10.1016/j.tins.2009.11.002.