Exploration of subcortical functional connectivity for therapeutic neuromodulation targeting

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Introduction

Neuromodulation of subcortical network hubs by pharmacological, electrical or ultrasonic stimulation is a promising therapeutic strategy for patients with disorders of consciousness (DoC)[1]. However, optimal targets for therapeutic stimulation have not been well established. Emerging evidence suggests that recovery of consciousness is associated with increases in network connectivity within the default mode network (DMN), as well as in cortical networks associated with higher-order cognitive tasks[2]. Therefore, identification and characterization of the subcortical nodes that are functionally connected to these networks is important for neuromodulatory therapies[1]. Here, our aim is to map and characterize the subcortical functional connectivity of the DMN and three other networks that modulate higher-order cognition: the frontoparietal network (FPN), dorsal attention network (DAN), and the salience network (SN). We also explored the functional connectivity in different networks for two subcortical regions that are frequently targeted for neurostimulation: the ventral tegmental area (VTA) in the midbrain and the central lateral nucleus (CL) in the thalamus.

Methods

168 healthy subjects with 7T resting-state fMRI (rs-fMRI) scans from the Human Connectome Project[3] were analyzed. We applied the group BrainSync + NASCAR decomposition pipeline[4–6] to the rs-fMRI data. The DMN, FPN, DAN, and SN were identified from the decomposition results by visualizing and comparing their cortical spatial maps to literature[5,7]. Then the subcortical components of each of these 4 networks were extracted and converted to a 3D volume and were overlayed on a 7T 100µm resolution *ex vivo* MRI scan for visualization[8]. Additionally, we extracted the functional connectivity of the VTA and CL by using the Harvard ascending arousal network atlas[9] and the probabilistic thalamic segmentation atlas[10]. We plotted the distributions of functional connectivity in VTA and CL using violin plots for direct comparison.

Results

Fig. 1 (A)-(D) show the functional connectivity for each of the 4 networks in the caudal midbrain, respectively. Fig. 2 (A)-(D) show the counterparts in the thalamus and basal ganglia. Panel (E) in Figs. 1 and 2 show the distributions of the functional connectivity within VTA and CL, respectively. Visually these networks have distinct functional connectivity profiles in different subcortical structures. Positive correlations to the DMN and SN were observed in the caudal midbrain, whereas the DAN shows negative correlations (i.e., anti-correlations) in this region. The thalamus shows mixed but structured connectivity patterns in all 4 networks. The putamen and globus pallidus show negative correlations to the DMN and DAN but positive correlations to the SN. Caudate correlations were positive to all four networks. With

respect to the two subcortical ROIs, the DMN and M-CIN were positively correlated for both VTA and CL. In contrast, the VTA was on average anti-correlated to the DAN, whereas the CL was on average positively correlated to this network. Conversely, the VTA has a slight positive correlation to the FPN and the CL has a strong anti-correlation to the FPN.

Conclusion

When choosing therapeutic subcortical targets for patients with DoC, it is important to consider which networks will likely be modulated. In this exploratory analysis in healthy adults, we studied the subcortical functional connectivity to networks that modulate recovery of consciousness. We found that there are substantial differences in the subcortical connectivity profiles of these networks, providing a methodological foundation for next elucidating network-based mechanisms of therapeutic efficacy in patients. Ultimately, these subcortical functional connectivity maps could be used to guide the selection of targeted neuromodulatory therapies in individual patients based on their patterns of network disruption.

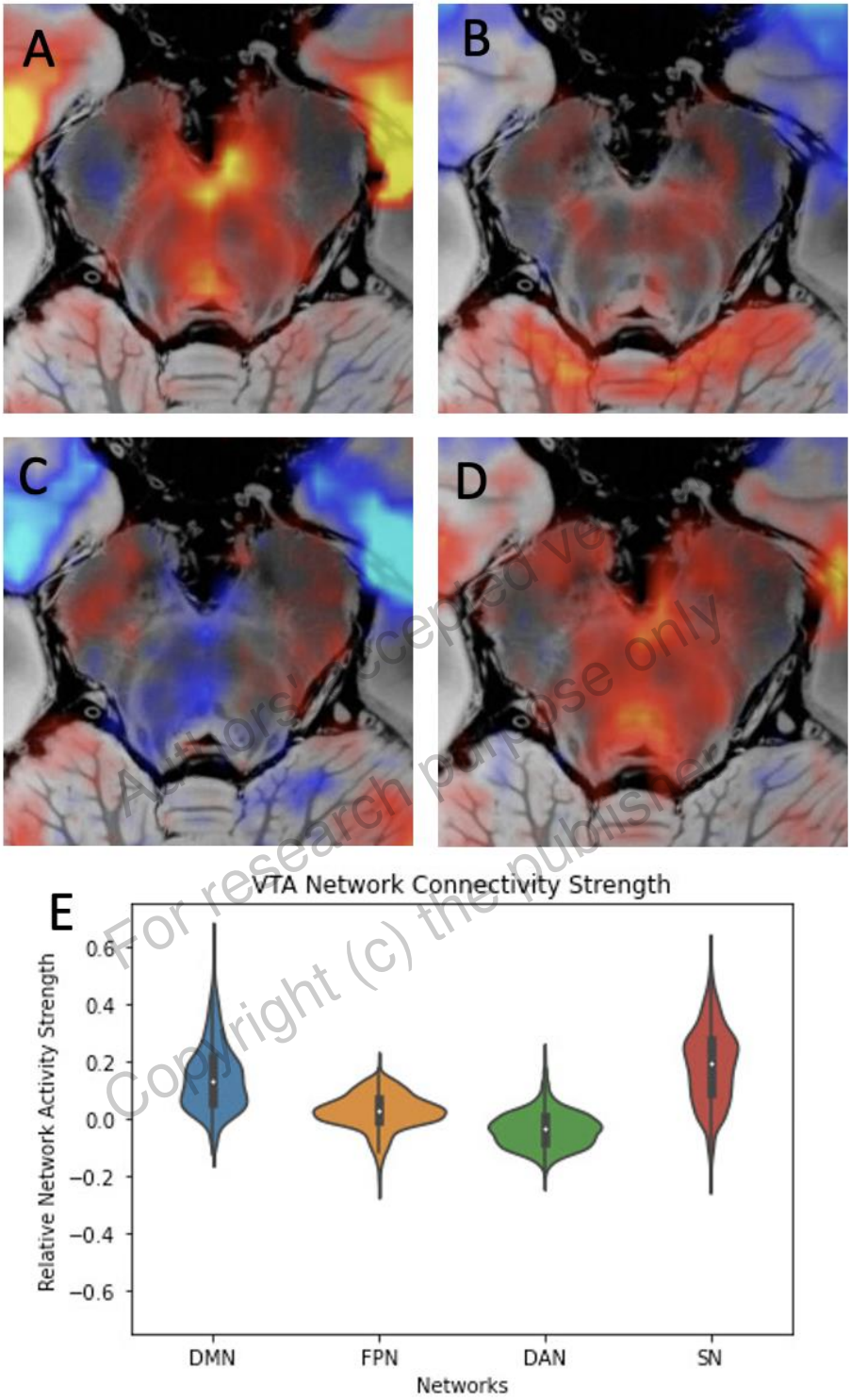

Fig 1. (A)-(D) Subcortical functional connectivity of the DMN, FPN, DAN, and SN in the caudal midbrain. (E) Violin plots of the functional connectivity within the VTA across subjects. Would it be possible to add a color bar or statement of statistical thresholding used in this plot?

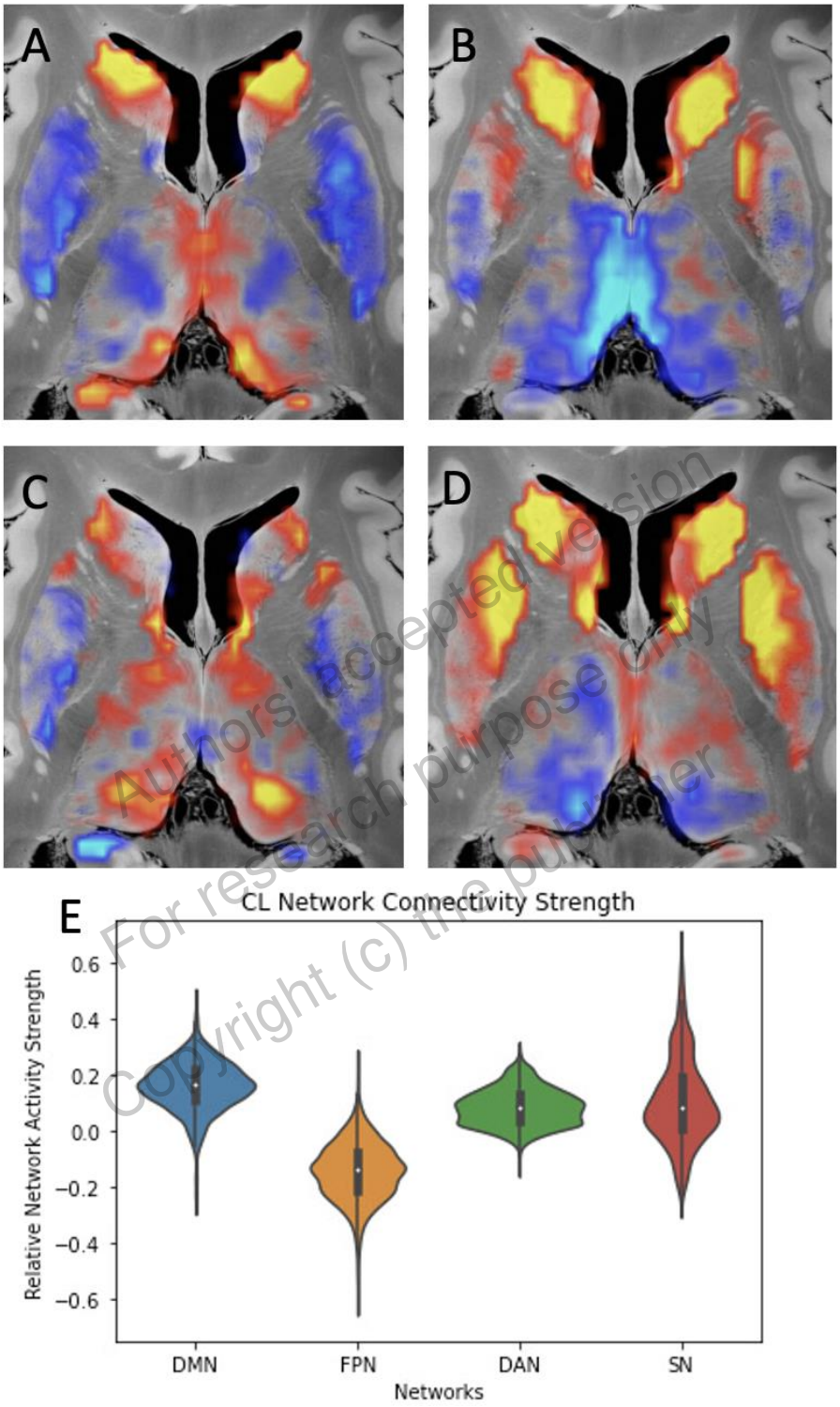

Fig 2. (A)-(D) Subcortical functional connectivity of the DMN, FPN, DAN, and SN in the thalamus and basal ganglia. (E) Violin plots of the functional connectivity within the CL across subjects.

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. Y. Bodien, C. Chatelle, B. Edlow, "Functional networks in disorders of consciousness", *Semin Neurol*, vol. 37, no. 05, pp. 485–502, 2017. DOI: 10.1055/s-0037-1607310.

3. 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.

4. 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.

5. J. Li, Y. Liu, J. L. Wisnowski, R. M. Leahy, The intrinsic spatiotemporal organization of the human brain - A multi-dimensional functional network atlas (preprint). bioRxiv. DOI: 10.1101/2021.12.09.472035.

6. 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.

7. L. Q. Uddin, B. T. T. Yeo, R. N. Spreng, "Towards a universal taxonomy of macro-scale functional human brain networks", *Brain Topogr*, vol. 32, no. 6, pp. 926–942, 2019. DOI: 10.1007/s10548-019-00744-6.

8. 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.

9. B. L. Edlow, et al., "Neuroanatomic connectivity of the human ascending arousal system critical to consciousness and its disorders", *J Neuropathol Exp Neurol*, vol. 71, no. 6, pp. 531–546, 2012. DOI: 10.1097/NEN.0b013e3182588293.

10. J. E. Iglesias, et al., "A probabilistic atlas of the human thalamic nuclei combining ex vivo MRI and histology", *NeuroImage*, vol. 183, pp. 314–326, 2018. DOI: 10.1016/j.neuroimage.2018.08.012. PMCID: PMC6215335.