

Connectome predictive modelling of PTSD symptom severity

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Methodological Issue Being Addressed The FDA has not approved a new drug for PTSD in over two decades. Early phase clinical trials have designed treatments on the basis of findings from seed-based or region-of-interest approaches, but many fail in Phase III. In part, this may be because pathology in PTSD extends beyond individual brain regions to interactions and connections between networks. With the identification of new networks previously not implicated in PTSD using data-driven approaches, we may optimize therapies in which localization of functional regions is critical, for instance by targeting overall connectivity or regions typically considered to be more peripheral.

Introduction We advance this research by conducting a comprehensive evaluation of whole-brain functional dynamics using predictive models (i.e. the whole-brain resting state functional connectome signature) of PTSD symptoms to allow the examination additional functional networks in an agnostic, unbiased manner. This approach can also help us to identify treatments for patients with PTSD who have shared connectivity profiles. We use connectome-based predictive modelling (CPM), a multivariate data-driven predictive mapping of resting whole-brain functional connections. This approach has successfully identified biomarkers for novel therapeutics and trauma exposure, overcomes the need to limit the analysis to a few seeds, and boosts the reliability of resting state functional connectivity mitigating the overfitting and inherent increase in Type 1 error associated with univariate multiple comparisons.

Methods Fifty-four United States Veterans completed functional magnetic resonance imaging (fMRI) (64% male, mean age=44, SD=14). All participants had a clinical diagnosis of PTSD as measured by the Clinician Administered Interview for DSM-5 (CAPS-5) (i.e. moderate to severe). The PTSD Checklist for DSM-5 (PCL-5) was used as a continuous measure of PTSD symptom severity to derive the predictive models. We generated a network restricted strength predictive model (NRS-PM) by taking a pairwise average connectivity of all modules as AA-50 (hierarchical connectivity at 50 modules). 1000 iterations of tenfold cross-validation were conducted to ensure statistical significance. After identifying the PCL connectome network, we extracted the network (average connectivity in each participant) to generate AA-50.

Results The connectome predictive model significantly predicted PTSD symptom severity on PCL-5 ($r=0.28$, $p=0.006$). Pervasive hypoconnectivity with every major network was observed. Higher PCL score was associated with lower functional connectivity between default mode and visual nodes, default mode and dorsal salience nodes, and visual and sensorimotor nodes. PCL severity was also associated with higher functional connectivity between central executive and visual nodes, default mode with ventral salience and subcortical nodes, and higher within network connectivity in

visual nodes.

Conclusion We identified a cross-validated connectome predictive model of PTSD symptoms. Overall, global dysconnectivity was observed, a factor that would not be observable with seed-based univariate methodology. Reduced connectivity between the default mode and central executive network dominated the PTSD signature. Increased connectivity centered around the ventral salience, dorsal salience, and visual nodes. Our findings suggest that the visual network deserves greater consideration in models of PTSD, particularly given relevant roles in processing visual imagery and generating autobiographical memories, potentially related to hypervigilance and flashbacks. This knowledge may translate to more successful clinical trials. For instance, there is potential for TMS to be applied to manipulate brain connectivity within these specific networks and to induce global changes in brain connectivity. Though the dorsolateral prefrontal cortex and ventromedial prefrontal cortex are typically targeted in TMS for PTSD, clinical trials should also test the impact of neuromodulation of visual regions and their connections with other nodes and whether changes in specific PTSD symptom clusters are observed. If our findings are replicated, they may also address the problem of diagnostic heterogeneity in clinical trials, with the potential to enrich for a more biologically homogenous subject population based on this connectome signature to obtain a better efficacy signal with less noise.

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Guidelines I have read and understand the Poster Guidelines

Disclosures LAA has served as a consultant, speaker and/or advisory board member for Guidepoint, Transcend Therapeutics, Source Research Foundation, Reason for Hope, Beönd, The Cohen Foundation, and is owner of NPSYT, PLLC. CGA has served as a consultant and/or on advisory boards for Freedom Biosciences, Aptinyx, Genentech, Janssen, Psilocybin Labs, Lundbeck, Guidepoint, and FSV7, and as editor of Chronic Stress for Sage Publications, Inc. He also filed a patent for using mTORC1 inhibitors to augment the effects of antidepressants (Aug 20, 2018).

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