Review of: "Network Neuroscience and Translational Medicine: A Case for Abandoning Case Controlled Studies of Posttraumatic Stress Disorder"

Md Abdur Rahaman[1]

1 Center for Translational Research in Neuroimaging and Data Science

Potential competing interests: No potential competing interests to declare.

The article opts to provide a different perspective on neuropsychiatric disorder studies. The author suggested exploring more network neuroscience potentials for describing the underlying mechanism of disorders like PTSD. The author criticized the conventional case-control setup for analyzing the brain's structural, functional, and connectivity aberrations due to a physical condition (PTSD, Schizophrenia). I appreciate the author brought up the subject's heterogeneity constraint - prevalent but a bottleneck in biological populations. Computational neuroscientists often must control these variations to ensure the analytical outcomes are induced from the disease-oriented deficits. Researchers handle these disparities before testing a hypothesis to validate that identified differences/similarities haven't resulted from the factors out of consideration. As such, researchers have already incorporated ideas like clustering the subjects into smaller subgroups by maximizing the homogeneity to mediate an apple-to-apple comparison. Studies have shown that clustering distinct dimensions matches the confounding factors and adds more reliability to the case-control comparison (Rahaman, Damaraju, et al. 2022; Rahaman et al. 2020; Gupta et al. 2017).

I agree that even if the two individuals are diagnosed with the same disorder, they might be completely different in their expression, and behavioral symptoms - regulated by disparate brain networks. So, diverting from a whole-group/group-average analysis is intuitive. However, still, we need the case-control comparison to understand the differences and direct the analysis toward a targeted domain. The author doesn't shed significant light on how the issues mentioned can be addressed using network neuroscience.

The brain is a complex system with non-linear, convoluted processing hubs and disorders might not be able to map on a single or a set of networks. Yet, studying the relevant networks and finding the salient patterns is a step toward solving the subproblem. Studies synthesize both healthy and case brains and find reproducible biomarkers across multiple neurodegenerative diseases (Salgado-Pineda et al. 2011; Stegmayer et al. 2014; Du et al. 2020). These brain networks explain diseased-linked alterations. The focus should be on developing more smart ways to compare and assess to handle these inherent logical artifacts (subject variability) in biological acquisitions.

The author mentioned 'There is not a common cause to all the symptoms or the symptoms that cause the disorder.' How 'network neuroscience' is possibly complementing heterogeneity and tackling this evasiveness is not clear. Nevertheless, the narrative describes a crucial characteristic of neural disorders which needs more perspectives, analogies, and

knowledge to understand these symptoms. Integrating information from multiple physiologies might help us better understand the phenomena. Multi-modal studies (Dolci et al. 2022; Rahaman et al. 2021; Rahaman, Garg, et al. 2022) for leveraging multiple biological sources are being popular in this direction.

I believe the article initiates multiple crucial questions for the neuroscience community but has been less successful in connecting the solution to network neuroscience. Sticking the explanation for network connectivity into PTSD could be more useful. Besides, running more PTSD-focused experiments on described connections, their strength, and stability would be more interesting to incorporate.

References:

Dolci, Giorgio, Md Abdur Rahaman, Jiayu Chen, Kuaikuai Duan, Zening Fu, Anees Abrol, Gloria Menegaz, and Vince D Calhoun. 2022. "A deep generative multimodal imaging genomics framework for Alzheimer's disease prediction." In *2022 IEEE 22nd International Conference on Bioinformatics and Bioengineering (BIBE)*, 41-44. IEEE.

Du, Yuhui, Zening Fu, Jing Sui, Shuang Gao, Ying Xing, Dongdong Lin, Mustafa Salman, Anees Abrol, Md Abdur Rahaman, and Jiayu Chen. 2020. 'NeuroMark: An automated and adaptive ICA based pipeline to identify reproducible fMRI markers of brain disorders', *NeuroImage: Clinical*, 28: 102375.

Gupta, Cota Navin, Eduardo Castro, Srinivas Rachkonda, Theo GM van Erp, Steven Potkin, Judith M Ford, Daniel Mathalon, Hyo Jong Lee, Bryon A Mueller, and Douglas N Greve. 2017. 'Biclustered independent component analysis for complex biomarker and subtype identification from structural magnetic resonance images in schizophrenia', *Frontiers in psychiatry*, 8: 179.

Rahaman, M. A., J. Chen, Z. Fu, N. Lewis, A. Iraji, and V. D. Calhoun. 2021. "Multi-modal deep learning of functional and structural neuroimaging and genomic data to predict mental illness." In *2021 43rd Annual International Conference of the IEEE Engineering in Medicine & Biology Society (EMBC)*, 3267-72.

Rahaman, M. A., J. A. Turner, C. N. Gupta, S. Rachakonda, J. Chen, J. Liu, T. G. M. van Erp, S. Potkin, J. Ford, D. Mathalon, H. J. Lee, W. Jiang, B. A. Mueller, O. Andreassen, I. Agartz, S. R. Sponheim, A. R. Mayer, J. Stephen, R. E. Jung, J. Canive, J. Bustillo, and V. D. Calhoun. 2020. 'N-BiC: A Method for Multi-Component and Symptom Biclustering of Structural MRI Data: Application to Schizophrenia', *IEEE Trans Biomed Eng*, 67: 110-21.

Rahaman, Md Abdur, Eswar Damaraju, Jessica A Turner, Theo GM van Erp, Daniel Mathalon, Jatin Vaidya, Bryon Muller, Godfrey Pearlson, and Vince D Calhoun. 2022. 'Tri-clustering dynamic functional network connectivity identifies significant schizophrenia effects across multiple states in distinct subgroups of individuals', *Brain Connectivity*, 12: 61-73.

Rahaman, Md Abdur, Yash Garg, Armin Iraj, Zening Fu, Jiayu Chen, and Vince Calhoun. 2022. "Two-Dimensional Attentive Fusion for Multi-Modal Learning of Neuroimaging and Genomics Data." In *2022 IEEE 32nd International Workshop on Machine Learning for Signal Processing (MLSP)*, 1-6. IEEE.

Salgado-Pineda, P, E Fakra, P Delaveau, PJ McKenna, E Pomarol-Clotet, and O Blin. 2011. 'Correlated structural and

functional brain abnormalities in the default mode network in schizophrenia patients', *Schizophrenia research*, 125: 101-09.

Stegmayer, K., H. Horn, A. Federspiel, N. Razavi, T. Bracht, K. Laimböck, W. Strik, T. Dierks, R. Wiest, T. J. Müller, and S. Walther. 2014. 'Supplementary motor area (SMA) volume is associated with psychotic aberrant motor behaviour of patients with schizophrenia', *Psychiatry Res*, 223: 49-51.