Review of: "Network Neuroscience and Translational Medicine for Understanding Mental Health: The example of Post-traumatic Stress Disorder"

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Potential competing interests: No potential competing interests to declare.

The paper entitled 'Network Neuroscience and Translational Medicine for Understanding Mental Health: The Example of Posttraumatic Stress Disorder' deals with a relevant and currently discussed topic. I have several observations on this pre-print, which I hope will be helpful to the author.

Firstly, it is not clear what contribution the author aims to make to the existing body of research in this field.

Secondly, there are some gaps in the logic and development that I suggest rethinking and revising:

a) The connection between 'Network Neuroscience,' 'Translational Medicine,' and 'Network Models' is not clearly explained throughout the manuscript. The mention of 'Translational Medicine' is limited, and its role in the proposed development should be clarified. Regarding 'Network Neuroscience' and 'Network Models,' the author should highlight the aspects they consider to be shared, complementary, and different.

b) In several parts of the manuscript, the need to 'abandon case control methods' is indicated without a clear argument explaining this recommendation. It is worth noting that much of the cited literature, especially on page 4, is based on what could be referred to as case-control designs. Therefore, it would be beneficial to clarify why a network approach cannot be followed from a case-control design. Additionally, the relationship between the case-control design and the author's mentioned 'common cause approach to symptoms' needs further clarification.

c) On the last paragraphs of page 4, it is stated, "Figure 1 illustrates this idea using an example of two individuals, both of whom have similar symptom severity (i.e., the same number of symptoms and both meet diagnostic criteria for PTSD), but who do not share a single symptom of PTSD. Person 1's symptoms are highly characterized by cognitive concentration and memory impairment, person 2's symptoms by emotional dysregulation. These two individuals have distinct neurobiological networks taking the theoretical lead in their expression of the disorder. Case (e.g., those who meet criteria for a disorder) control (e.g., "healthy" participants) methods that compare participants with PTSD versus those who have PTSD risk continued replication failure because of this heterogeneity. A traditional view of PTSD, characterized most recently by the 5th edition of the Diagnostic and Statistical Manual (DSM- 5 [15]), is that it is a latent construct composed of latent symptom clusters (e.g., re-experiencing, hyperarousal), where these clusters are composed of observable symptoms (e.g., exaggerated startle response). A network symptoms approach emphasizes patterns of

associations between symptoms with the aim of identifying “central” symptoms and critical between/among symptom associations ([16]). In this newer framework mental illness results from a cascade of symptom associations emerging over time, leading to prolonged distress and or self-destructive behavior for some. The network approach also provides an opportunity to focus on related subgroups of symptoms (or specific central symptoms) associated with the various neurological functional and structural networks ([7]).”" It appears that there may be some confusion that needs to be clarified. A distinction should be made between theoretical models and statistical models. In the case of statistical models, it should be clearly understood that these models can be complementary and, in many cases, mathematically equivalent (e.g., comparisons between network solutions and factor models). The criticism needs to be better explained to avoid misunderstanding. It is correct to state that there is a theoretical model that explains all symptoms from a common cause, and another model that differentiates the origin for each symptom. However, equating the theoretical model (e.g., single cause) with a statistical model (e.g., latent variable or factorial approach) can lead to misinterpretation.

d) I suggest reviewing Figure 1 as the example explained on page 4 is not easily visualized based solely on the figure.

I hope these comments are relevant and useful to the author. I wish them all the best in their work.