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

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The manuscript Network Neuroscience and Translational Medicine for Understanding Mental Health: The example of Posttraumatic Stress Disorder by Carl Weems is a position piece indicating the advances in circuit-based interrogation of neuropsychiatric disorders, using PTSD as an example, would benefit from less emphasis on case control studies with a greater focus on prospective studies on affected individuals over time as a means to gauge disease progression and/or therapeutic efficacy of interventions.

What I liked about this report: The author provides a strong narrative underscoring the possibilities of network-based studies for determining vulnerabilities within individually affected persons in the context of PTSD. The author also state clearly that traditional 'disease' versus 'control' constructs have limited validity when trying to find out what is really the root cause. There is likely significant overlap and redundancy to corticocortical networks driving salient behaviors, such as executive function that are compromised in many brain disorders. Also, variability in patients makes finding a sole 'engram' that drives PTSD unrealistic.

What I think could use revisions:

1. Figure 1 image and text.

Figure 1 was hard to follow and read. The text box was fuzzy and barely readable (at least in the Review copy) and would benefit from a revision with higher DPI and larger text. The text rows could be culled and streamlined for ease of viewing. Also, a figure legend description is recommended. What does 'person 1' and 'person 2' refer to? This was enumerated (briefly) in the text below but would be helpful in the legend itself. The theoretical network column was also hard to follow. The author may consider adding arrowheads to the lines for each specific network that is thought to be involved. The text on the right hand panel identifying each node was also barely readable and would benefit from a larger font and higher DPI.

2. Stressor to phenotype. The author may consider adding text indicating that disorders like PTSD may fall under the umbrella of network dysfunction disorders arising from stressors leading to aberrant phenotypes that may be refractory to standard therapeutic regimens. Although somewhat new to neuropsychiatric disorder literature, this concept is becoming more prevalent in neurodegenerative disorders, such as Alzheimer's disease and Parkinson's disease, where cortical

circuits underlying memory and/or executive function (similar to what the author provides in Figure 1) are also compromised due to stressors.

3. Pitfalls and limitations. A terse pitfalls/limitations section regarding the current state of network-driven neuroscience approaches to detect and treat disorders including PTSD is suggested. Also, the author clearly points out the limitations of case control studies, but should also consider the benefits (e.g., from a molecular/cellular/functional genomics standpoint) as well as some of the limitations of prospective studies (e.g., statistical power, cost, subject attrition, confounding age-related disorders, and the requisite need to have large cohorts, among others) to round out the discussion.