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

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Abstract

Translational network neuroscience and network models have the potential to change fundamentally our understanding of the nature of mental illness. Network neuroscience suggests that mental pathology-linked systems such as emotion regulation derive from the synchronized activation of multiple, sometimes regionally disparate areas of the brain. While the methods to actualize this understanding are emerging, case (e.g., those who meet criteria for a disorder) control (e.g., “healthy” participants) methods continue to dominate the literature. The purpose of this paper is to articulate why the field of translational and network neuroscience should largely abandon case control methods to actualize this potential. The perspective is articulated by using recent research on posttraumatic stress disorder (PTSD) to illustrate the issue in replication of network neuroscience and thus the difficulty translating the research to application. I argue that the heterogeneity of diagnoses such as PTSD - just in the presentation of meeting diagnostic criteria - combined with the complexity of human brain systems suggests that a mental disorder cannot be directly mapped to any one individual region or even multiple regions. However, symptoms and symptom sets might more reliably be links to

activation patterns. Fine grained (symptom level), well-developed (psychometrically sound), continuous measures of symptom expression and intensity will be critical to actualize the potential of network neuroscience for mental disorders like PTSD.

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Network neuroscience and network models coupled with translational medicine has the potential to change fundamentally our understanding of the nature of mental illness ([1] [2] [3]). While the methods to actualize this understanding are emerging, case (e.g., those who meet criteria for a disorder) control (e.g., "healthy" participants) methods continue to dominate the literature. Here I illustrate, why the field of translational neuroscience should largely abandon case control methods to actualize this potential, and provide a perspective on the path forward using recent research and models of post-traumatic stress disorder (PTSD).

Network neuroscience suggests that mental pathology-linked systems such as emotion regulation ([4]) derive from the synchronized activation of multiple, sometimes regionally disparate areas of the brain ([5] [6]). This research aims to identify the functional co-activation of brain structures, the structural pathways and the integrity of the white matter connections. In network models, individual regions such as the amygdala or hippocampus are considered 'nodes' with each node contributing by adding, subtracting, or altering an aspect of the signal. Connectivity between nodes is assessed by the temporal correlation between node activation, and the integrity of connections among the white-matter tracts[7].

Network neuroscience has identified key functional networks that may play a role in psychopathology, such as reactions to the traumatic stress associated with abuse, war, disasters, natural and human made hazards ([8] [9] [10]). For example, the salience network is a collection of brain regions thought to be involved in detecting behaviorally relevant stimuli and coordinating neural resources in response to these stimuli. The right side of Figure 1, is adapted from Menon ([4]) and Hermanns et al. ([11]) and shows various nodes anchored in the dorsal anterior cingulate cortex and frontoinsular cortex. The central executive network is another key one in mental health and is responsible for "executive" cognitive functions such as emotion regulation, decision making, control of memory, and the control of attention anchored in the dorsolateral prefrontal cortex and dorsolateral posterior parietal cortex ([4]). PTSD may be characterized by a weak or hypoactive executive network and overactive and strongly connected salience network ([8][9][10]).

	Criteria	Person 1	Person 2	Theoretical Network
A.	Exposure to actual or threatened death, serious injury, or sexual violence.[1,2]	Y	Y	
B.	Presence of one (or more) of the following intrusion symptoms.[3]	Y	Y	
1.	Recurrent, involuntary, and intrusive distressing memories of the traumatic event(s).	Y	N	
2.	Recurrent distressing dreams in which the content and/or affect of the dream are related to the traumatic event(s).	N	N	
3.	Dissociative reactions (e.g., flashbacks) in which the individual feels or acts as if the traumatic event(s) were recurring. (Such reactions may occur on a continuum, with the most extreme expression being a complete loss of awareness of present surroundings.)	N	N	
4.	Intense or prolonged psychological distress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event(s).	N	Y	
5.	Marked physiological reactions to internal or external cues that symbolize or resemble an aspect of the traumatic event(s).	N	Y	
C.	Persistent avoidance of stimuli associated with the traumatic event as evidenced by one or both of the following:	Y	Y	
1.	Avoidance of or efforts to avoid distressing memories, thoughts, or feelings about or closely associated with the traumatic event(s).	Y	N	
2.	Avoidance of or efforts to avoid external reminders (people, places, conversations, activities, objects, situations) that arouse distressing memories, thoughts, or feelings about or closely associated with the traumatic event(s).	N	Y	
D.	Negative alterations in cognitions and mood associated with the traumatic event(s) as evidenced by two (or more) of the following:	Y	Y	
1.	Inability to remember an important aspect of the traumatic event(s).	Y	N	
2.	Persistent and exaggerated negative beliefs or expectations about oneself, others, or the world.	Y	N	
3.	Persistent, distorted cognitions about the cause or consequences of the traumatic event(s) that lead the individual to blame himself/herself or others.	N	N	
4.	Persistent negative emotional state (e.g., fear, horror, anger, guilt, or shame).	N	Y	
5.	Markedly diminished interest or participation in significant activities.	N	Y	
6.	Feelings of detachment or estrangement from others.	N	N	
7.	Persistent inability to experience positive emotions (e.g., inability to experience happiness, satisfaction, or loving feelings).	N	Y	
E.	Marked alterations in arousal and reactivity associated with the traumatic event(s) as evidenced by two (or more) of the following:	Y	Y	
1.	Irritable behavior and angry outbursts (with little or no provocation), typically expressed as verbal or physical aggression toward people or objects.	Y	N	
2.	Reckless or self-destructive behavior.	N	N	
3.	Hypervigilance.	N	Y	
4.	Exaggerated startle response.	N	Y	
5.	Problems with concentration.	Y	N	

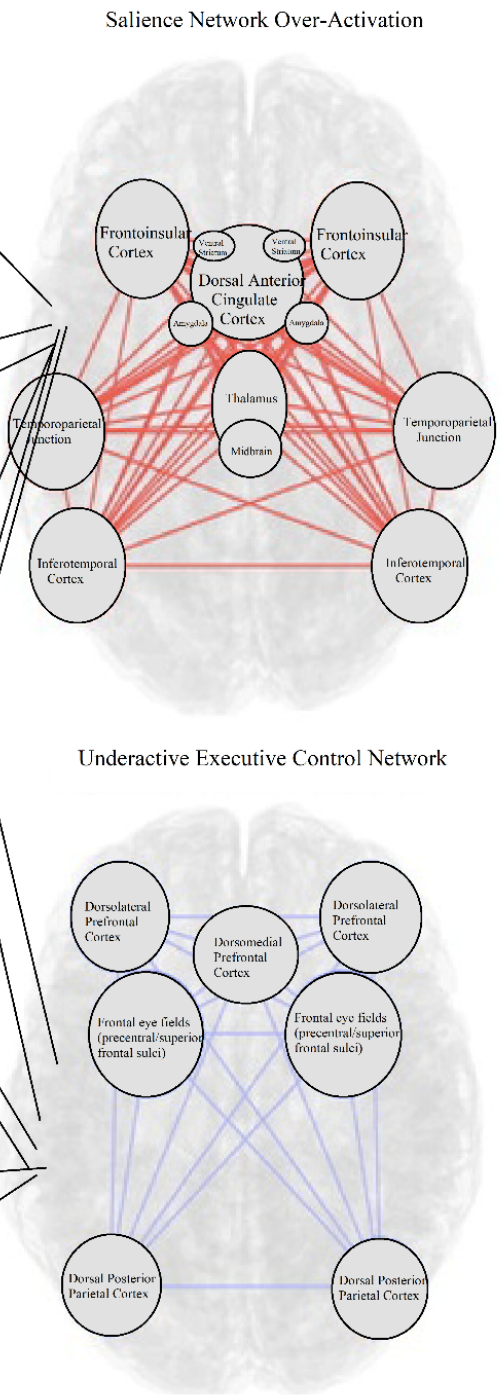

Figure 1. Schematic Illustration of Variability in Meeting DSM-5 Diagnostic Criteria for PTSD and Differential Neurobiological Network Correlates

Notes: 1. The DSM-5 criteria apply to adults, adolescents, and children older than 6 years. 2. Exposure to traumatic stress can be in one (or more) of the following ways: Directly experiencing the traumatic event(s); Witnessing, in person, the event(s) as it occurred to others; Learning that the traumatic event(s) occurred to a close family member or close friend. In cases of actual or threatened death of a family member or friend, the event(s) must have been violent or accidental; Experiencing repeated or extreme exposure to aversive details of the traumatic event(s) (e.g., first responders collecting human remains; police officers repeatedly exposed to details of child abuse). 3. For the symptoms these are “associated with the traumatic event(s), beginning after the traumatic event(s) occurred”.4. In addition, there is Criteria F. Duration of Criteria B, C, D and E is more than 1 month. G. Causes clinically significant distress or impairment in social, occupational, or other important areas of functioning. And F. is not attributable to the physiological effects of a substance (e.g., medication, alcohol) or another medical condition. Source: American. Psychiatric. Association. 2013. *Diagnostic and Statistical Manual of Mental Disorders* . Arlington, VA: Am. Psychiatric. Publishing. 5th Ed.

To illustrate, Weems et al. ([12]) summarized seven diffusion tensor imaging (DTI) which examine white matter tracts and 15 functional MRI (fMRI) studies examining functional connectivity in youth under age 18 who were exposed to traumatic stress. Among the studies that examined structural connectivity, a picture of reduced structural connectivity between limbic system structures (e.g., hippocampus, amygdala) and regions of the frontal cortex emerges—areas linked by a white matter tract known as the uncinate fasciculus. Among the functional connectivity studies in pediatric samples, as in the structural studies, a picture of differential connectivity between limbic structures and frontal cortex regions emerges. While there were some consistencies across studies there were many findings did not appear to replicate across studies([12]). Why are findings from the neuroscience of PTSD inconsistent? There may be methodological variation, sample differences, age related variation, and a related reason is variation in symptoms expression leading to wide variation within groups meeting diagnostic criteria for PTSD.

Disruption in memory is a core feature of PTSD with both intrusive memories and difficulty with recall of events associated with the trauma ([13]). Network neuroscience has the potential to illuminate these difficulties with the memory systems involved in PTSD by, for example, linking the executive control network's modulation of salience network functions (e.g., emotion regulation/dysregulation via frontal control/lack f control of limbic activation). For example, Mary and colleagues ([14]) investigated if these disruptions are associated with the brain systems that normally allows control over memory among 102 individuals exposed to terrorist attacks (55 of those had PTSD symptoms and 47 who did not have any) and 73 individuals who did not experience the attacks. Functional magnetic resonance imaging focused on dorsolateral prefrontal cortex (DLPFC) a core hub of the executive control network. Among those without PTSD (both exposed and non-exposed) attempts to prevent unwanted intrusive memory into consciousness was associated with a reduction of the co-activation of control and memory systems as opposed to those with PTSD where there not a decrease in coactivation. Moreover, this effect appeared to be from the regulation of the right DLPFC directed at the hippocampus and the precuneus (both associated with episodic or traumatic memories). While this is a potentially exciting finding consistent with the neuroscience of memory, replication of such findings will remain a concern. Why?

The heterogeneity of the presentation of PTSD - just in the presentation of meeting diagnostic criteria - combined with the complexity of human brain systems suggests that a mental disorder cannot be directly mapped to any one individual region or even multiple regions consistently([4]). Figure 1 illustrates this idea using an example of two individuals both of whom have similar symptom severity (i.e., 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 do not 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]). For example, with regard to severely dysregulated emotion or self-injurious behaviors/symptoms, within a neurobiological network some brain structural or functional connections may be centrally linked while other patterns of structural and functional connections may be linked to or responsible for memory and concentration related symptoms. This type of understanding will continue to be obscured by case control designs given the aforementioned heterogeneity possible among those diagnosed with PTSD.

Network models call into question some of the fundamental assumptions underlying the conceptualization of mental disorders ([1][2][3]). Borsboom, Cramer, and Kalis ([17]) confront the ontological question of what is a mental disorder. Their point is that analogy to physical disorders such as strep throat which can be reduced to a single common cause is completely off-base for psychological constructs such as PTSD because: “symptom networks preclude the identification of a common cause of symptomatology with a neurobiological condition; in symptom networks, there is no such common cause.” (p. 1). So, unlike strep, there is not a common cause to all the symptoms or the symptoms that cause the disorder. Network neuroscience combined with network models of mental illness may foster the science of mental health by a fundamental appreciation of the heterogeneity in cause and expression ([12]). This is not to argue that network models of symptoms should be thought of in reductionist terms[18] (i.e., fundamentally reducible to brain activation([19]) ([a]). The point here about the heterogeneity of expression in meeting diagnostic criteria can reasonably be applied to learning and social models of PTSD (e.g., the complexity of observational learning as well as classical and operant conditioning processed are likely differentially related to different symptoms sets).

The specific links to the brain effects using traditional case control methods are limited in establishing even temporal associations. Thus, while the link between brain volumes differential functional connections and traumatic stress is now well-established, we do not know how much of this correlation stems from preexisting differences (e.g., poverty or other socioeconomic context effects that place someone at greater risk for experiencing trauma or developing interfering PTSD symptoms after traumatic stress). Fine grained (symptom level), well-developed (psychometrically sound), continuous measures of symptom expression and intensity are critical in this regard ([3]).

In addition to using detailed symptom measures, prospective longitudinal and intervention studies are critical for disentangling the confounding effects of factors such as poverty from traumatic stress on symptom cause and expression. Disaster research offers an opportunity to know more precisely when a traumatic event occurred and to quantify the level of exposure, both subjectively and objectively, and examine the cascade of symptoms from exposure to initial symptoms to later symptoms and how these may related to brain function. Identifying neural activation patterns that predict symptoms evolution following disasters associated with the symptoms cascades implied by network models of PTSD are needed. Changes in cortical hemodynamic activity measured with functional near-infrared spectroscopy (fNIRS) may provide a time and cost-effective option for such work ([20]) with evidence that activation patterns predicts PTSD symptoms improvements ([21]). Such data may be useful for developing interventions that target core symptoms ([22]) and thereby

promote resilience and improvement over extended difficulties following disaster for healthcare response systems ([23]).

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Footnotes

[a] While it is currently unresolved as to whether describing both symptoms and brains as networks and integrating them would be beneficial see Blanken et al., ([23]) the resolution is an empirical one, and the argument here is that such empirical study will less likely be resolved with case control methods.

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