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Trauma Re-Experiencing Symptoms Modulate Topology of Intrinsic Functional Networks

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The article by Spielberg and colleagues (1) in this issue explores the large-scale topology of intrinsic functional networks in military veterans with posttraumatic stress disorder (PTSD) and mild traumatic brain injury (mTBI). The emerging approach, already applied to other neuropsychiatric disorders, begins to account for the sobering reality that neural representations of symptoms are distributed across widespread, dynamically interacting brain regions and subnetworks, which are further modulated by affective and cognitive states. Thus, the large scale of the search space under exploration requires unbiased approaches to gain the greatest flexibility and the widest possible aperture (2). By contrast, much of the prior research using resting-state functional connectivity in PTSD, while making valuable contributions to the field, has focused on the functional neural connections to specific *a priori* anatomical regions or seeds. The large repertoire of spatiotemporal patterns of activity in the brain is the basis for adaptive behavior, and uncovering disruptions in these patterns will be essential for improving our understanding of PTSD and mTBI. As such, the work of Spielberg et al. covers new ground in PTSD by using an agnostic (whole brain) approach to characterizing large-scale neural connectivity that will generate new hypotheses and spawn the discovery of the precise role that various circuits play in PTSD symptomatology.

The authors examined functional connectivity with resting-state fMRI in over 200 trauma-exposed military veterans of recent US conflicts, of whom just over half were diagnosed with PTSD and/or mTBI. Functional connectivity between automatically segmented regions was characterized using graph theoretic measures, and, subsequently, its modulation by PTSD symptoms, presence of mTBI, and functional disability was assessed. Based on evidence that mTBI aggravates the incidence and severity of PTSD, the authors posit that mTBI would exacerbate PTSD-related network disruptions. Their results show re-experiencing symptoms were associated with decoupling in two key networks. The first network decoupling produces decreased hippocampal connections to several right prefrontal cortical (PFC) structures associated with top-down control. One interpretation of this finding is a hippocampal deficit to contextualize trauma memories resulting in overgeneralization of

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these memories, which is thought to be a critical component of PTSD. It is plausible and likely that overgeneralization of memories in PTSD may enhance non-trauma memories surrounding and even preceding the traumatic event, particularly from similar semantic groups, and thereby contribute to re-experiencing symptoms. Dunsmoor and colleagues demonstrate this overgeneralization is facilitated by alterations in memory that are selectively enhanced for neutral objects if other objects from the same semantic category are subsequently paired with shock (3). This selective consolidation implicates a common neural substrate for emotional learning processes that promotes retroactive generalization of fear memories.

The second network shows re-experiencing symptoms of PTSD to be associated with decoupling of the insula within a network of basal ganglia and PFC structures. The authors propose that the role of insula in assessing salience may reflect an impairment in salience detection for currently relevant stimuli while permitting associations with prior trauma-relevant information and comorbid mTBI exacerbates this disruption in salience determination. The influence of the insula was found to be less widespread in mTBI given re-experiencing severity predicted a reduced participation coefficient (connections with different communities/modules) of the insula. The functional heterogeneity of the insula calls for future investigation of the separable role of insula sub-regions within these functional networks and their modulation by PTSD and mTBI symptoms. Abnormalities in the default mode network (DMN) function in TBI were previously shown to predict the magnitude of white matter damage in the salience network (SN) (4). Thus, the efficient regulation of activity in the DMN is predicated on the integrity of the SN and a compromise in this regulatory function produces diminished cognitive control and increased distractibility in TBI (5). Furthermore, the normal small-world architecture of the brain is disrupted by TBI that shifts the DMN and SN to a less efficient architecture. Unpacking these relationships will provide more precise information for uncovering the role of specific regions and local networks in trauma-related pathology and its interactive effects with mTBI.

Prior reports based on resting-state fMRI in PTSD focused on functional connectivity with specific seed regions such as the amygdala, amygdala subregions (6), and individual components of the DMN (7), but altogether ignored the interactive effects of PTSD and mTBI on functional connectivity. The current report extends the evidence of increased connectivity between the DMN and SN regions that was first reported by Sripada and colleagues to heighten attention to external stimuli and explain the hypervigilance and re-experiencing symptoms of PTSD (7). Amygdala connectivity in PTSD was increased with insula, reduced with the hippocampus, and had less anticorrelation with dorsal and rostral ACC. The findings are in line with the theory of diminished top-down control of the amygdala by the emotion and fear regulatory circuits (8). Focusing specifically on the basolateral amygdala (BLA) complex revealed stronger functional connectivity of the BLA complex with the ventrolateral PFC, which suggests the BLA complex could be biasing processes in target regions that support behaviors central to prevailing models of PTSD such as associative fear learning.

Magnetoencephalography has been tapped for classifying patterns of abnormal synchronous oscillations to help in the diagnosis of PTSD and investigate alterations in large-scale intrinsic network topology (9). While resting-state fMRI has hitherto not been analyzed with graph theoretical measures, application to MEG data demonstrates atypical long-range hyperconnectivity in the high-gamma-band resting-state of relevant brain regions is associated with severity of PTSD symptoms. The key finding of hyperconnectivity (increase in node degree) of the left hippocampus in patients with greater symptoms of PTSD by Dunkley et al. (9) contrasts with Spielberg's finding of right hippocampal decoupling (decrease in node degree) in patients with greater re-experiencing symptoms. Accordingly, the authors' offer divergent explanations of these findings where Spielberg concludes hippocampal decoupling reflects a failure of the hippocampus to accurately contextualize memories that leads to overgeneralization of memories (1), whereas Dunkley concludes that hippocampal hyperconnectivity might explain the disturbing mental imagery produced by re-experiencing and re-imagining of trauma memories (9). While the difference in imaging methods (MEG vs. fMRI) and symptoms used for correlation (overall vs. re-experiencing) may provide a partial explanation of the divergent findings, the role of hippocampus within the intrinsic network remains to be debated pending evidence from future studies.

In the future, the methods applied to resting state fMRI by Spielberg and colleagues will inevitably undergo refinement to more accurately identify the fluctuating subjective states experienced by participants during the resting-state by retrospectively querying participants about the thoughts and emotions dominating their consciousness. This data could be incorporated to better account for the noise associated with neural dynamics at rest, given there is considerable heterogeneity in predominant mood states across participants that are further modulating large-scale neural topology. As the authors point out, trained pattern classifiers could identify patterns of synchronous activity associated with various mood states. Taken a step further, comparing the network alterations in PTSD with other disorders such as depression, generalized anxiety, social phobia, specific phobias, and other anxiety disorders would be informative. In keeping with RDoC, the network organization might be examined in relation to specific symptoms (e.g. hypervigilance) across disorders.

The authors keenly cite the implication that resting-state scans lack a goal-directed task that engages attention networks and may by their very nature highlight network topologic changes associated with re-experiencing symptoms, which are frequently dominated by intrusive thoughts when attentional systems are not engaged by “distracting” activity. Attention-demanding goal-directed activities are an effective strategy for managing anxiety and re-experiencing symptoms in patients with PTSD. Clinical observation confirms that abrupt increases in trauma-related thoughts and memories frequently coincide with life transitions that decrease goal-directed activity such as job loss or retirement. Future research that compares connectivity differences between rest and distraction may offer insights into neural systems involved in holding symptoms of intrusive thoughts and memories at bay through intentional or guided engagement in salient goal-directed activities. The interplay between task-positive and task-negative networks supports the expectation that re-experiencing symptoms are more prominent during task-negative states when the functional connections within the task-negative networks such as the DMN are stronger. Task-positive networks such as the SN or the dorsal attention network may be weakly modulated by re-

experiencing symptoms and more strongly influenced by other symptoms of PTSD. The reciprocal relationship between task-positive and task-negative network architecture and the differential modulation of specific PTSD symptoms needs to be compared within a single study as Daniels and colleagues conducted in a small PTSD sample using seed-based psychophysiological interaction analyses (10). However, it would be important to expand this comparison of task-positive and task-negative networks to a large sample that employs graph theoretical measures and tests network modulation by PTSD symptom clusters.

The work by Spielberg and colleagues makes an important contribution to understanding disruptions in intrinsic network topology. This understanding will be vital to developing future treatments for PTSD and mTBI, particularly therapies such as transcranial direct current stimulation and others that aim to intervene at the level of correcting disruptions in network topology.

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References

1. Spielberg JM, McGlinchey RE, Milberg WP, Salat DH. Brain network disturbance related to posttraumatic stress and traumatic brain injury. *Biol Psychiatry*. 2015 In Press.
2. Turk-Browne NB. Functional interactions as big data in the human brain. *Science*. 2013; 342:580–4. [PubMed: 24179218]
3. Dunsmoor JE, Murty VP, Davachi L, Phelps EA. Emotional learning selectively and retroactively strengthens memories for related events. *Nature*. 2015; 520:345–8. [PubMed: 25607357]
4. Sripada RK, King AP, Welsh RC, Garfinkel SN, Wang X, Sripada CS, et al. Neural dysregulation in posttraumatic stress disorder: Evidence for disrupted equilibrium between salience and default mode brain networks. *Psychosomatic Medicine*. 2012; 74:904–11. [PubMed: 23115342]
5. Bonnelle V, Ham TE, Leech R, Kinnunen KM, Mehta MA, Greenwood RJ, et al. Salience network integrity predicts default mode network function after traumatic brain injury. *Proc Natl Acad Sci U S A*. 2012; 109:4690–5. [PubMed: 22393019]
6. Mayer AR, Mannell MV, Ling J, Gasparovic C, Yeo RA. Functional connectivity in mild traumatic brain injury. *Hum Brain Mapp*. 2011; 32:1825–35. [PubMed: 21259381]
7. Brown VM, Labar KS, Haswell CC, Gold AL, McCarthy G, Morey RA, et al. Altered resting-state functional connectivity of basolateral and centromedial amygdala complexes in posttraumatic stress disorder. *Neuropsychopharmacology*. 2014; 39:351–9. [PubMed: 23929546]
8. Sripada RK, King AP, Garfinkel SN, Wang X, Sripada CS, Welsh RC, et al. Altered resting-state amygdala functional connectivity in men with posttraumatic stress disorder. *J Psychiatry Neurosci*. 2012; 37:241–9. [PubMed: 22313617]
9. Dunkley BT, Doesburg SM, Sedge PA, Grodecki RJ, Shek PN, Pang EW, et al. Resting-state hippocampal connectivity correlates with symptom severity in post-traumatic stress disorder. *Neuroimage-Clin*. 2014; 5:377–84. [PubMed: 25180157]
10. Daniels JK, McFarlane AC, Bluhm RL, Moores KA, Clark CR, Shaw ME, et al. Switching between executive and default mode networks in posttraumatic stress disorder: Alterations in functional connectivity. *J Psychiatry Neurosci*. 2010; 35:258–66. [PubMed: 20569651]