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HOT TOPICS

# Leveraging resting-state neurophenotypes to identify susceptibility to and heterogeneity of posttraumatic stress disorder

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Early identification of trauma-related dysfunction, such as posttraumatic stress disorder (PTSD), is necessary for effective interventions that will reduce the emotional, social, and financial burdens of trauma on survivors and society. However, these efforts have proved difficult given (a) individual variability in PTSD development after trauma exposure and (b) the wide-ranging clinical heterogeneity in potential PTSD presentations [1]. Translational neuroscience has thus begun to focus on neurophenotypes of PTSD, or brain-based measures that serve as discrete, objective markers of PTSD subgroups, to propel the development of predictive modeling for PTSD susceptibility.

Although several techniques are available for brain assessment, recent research demonstrates in-vivo assessment of the human brain's dynamic functional architecture through resting-state functional magnetic resonance imaging (rs-fMRI) may provide critical insight into neurophenotypes of trauma-related dysfunction. In contrast to task-fMRI, rs-fMRI does not place task demands on participants that may alter the basal intrinsic connectivity of brain regions. Importantly, rs-fMRI can localize canonical resting-state networks (RSNs) such as the default mode (DMN), frontoparietal control (FPCN), and salience networks. Each of these networks subserves critical cognitive and affective processes, and both these networks and processes are implicated in PTSD neurophenomenology [2].

One question is whether RSN-derived neurophenotypes provide insight into an individual trauma victim's susceptibility to posttraumatic dysfunction after trauma exposure. Our recent work highlights that the connectivity of these networks and other regions of the brain may play a role in the development of posttraumatic dysfunction [3]. In the early (i.e., 2-weeks) period after trauma, connectivity of an arousal network (e.g., amygdala, hippocampus) to the dorsolateral prefrontal and of the DMN to the inferior temporal cortex was associated with later (i.e., 3-month) PTSD symptoms and depressive symptoms. This suggests that certain RSN-derived neurophenotypes are markers of global posttraumatic dysfunction.

A second question is whether neurophenotypes identified from rs-fMRI may also be used to examine symptom heterogeneity and identify PTSD subgroups. Emergent work demonstrates RSN dynamics can accurately distinguish individuals with the "classic" form of PTSD from those with the dissociative subtype—characterized by pronounced symptoms of detachment and disconnection from one's sense of self, body, and surroundings [4]. Moreover, connectivity patterns of the DMN and FPCN differentiated adults with childhood trauma and current PTSD along a continuum of dissociation severity [5]. This work also demonstrates that PTSD neurophenotypes are sufficiently robust to permit individual-level symptom estimation based on brain function.

The emerging literature highlights the potential for rs-fMRI to facilitate identification of brain-based markers of PTSD-related dysfunction which could be translated into functional "fingerprints" of PTSD for later predictive modeling. Our work strongly implicated components of arousal networks, DMN, and FPCN as critical to these efforts. Caution and further research is needed, however, as these approaches currently cannot supplant clinical assessments in psychiatry. That said, compared to other disorders, PTSD is uniquely positioned to leverage rs-fMRI neurophenotypes *prognostically* given the antecedent for PTSD is a known environmental stressor. Furthermore, these networks point toward neural targets for treatment to prevent PTSD in both its classic and dissociative forms.

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Drafting of the paper: NGH and LAML. All authors revised the paper critically for important intellectual context and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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## ADDITIONAL INFORMATION

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