From Connectivity to Clinical Translation: A Brain Network Model

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Impaired functional connectivity within and between large-scale brain networks has been linked to diverse forms of psychiatric illness (1). Despite converging evidence supporting a model of network dysfunction for psychopathology, additional work is needed before this knowledge can be applied translationally. In the current issue of *Biological Psychiatry: Global Open Science*, we consider Perino et al.’s (2) resting-state functional connectivity study of pediatric anxiety disorders in the context of large-scale network models of psychopathology [e.g., (3)] and provide an outline of the steps needed to overcome the current barriers to clinical translation.

Pediatric anxiety disorders are highly prevalent and predict the development of further mental health problems in adulthood (4). While traditionally conceptualized as disorders of excessive fear, models of anxiety now propose that basic cognitive processes may be affected in anxiety pathology as well. For example, there is evidence to support that increased attention toward salient stimuli coupled with deficient cognitive control may drive anxiety symptoms (5), and that these abnormalities are present from young ages in those who are predisposed to anxiety (6). These cognitive processes are thought to be subserved by distinct functional neural networks, including the ventral attention network (VAN), the cingulo-opercular network (CON), and the frontoparietal network, which are involved in rapid orienting toward novel stimuli, detecting the need for cognitive control, and implementing cognitive control, respectively (7). These canonical networks have been related to cognition in healthy and clinical populations, though they have been understudied in those with pediatric anxiety. Linking anxiety-associated cognitive processes to underlying neural networks may guide the targeting of novel interventions for pediatric anxiety.

Perino et al. (2) provide insight into how alterations of attention functioning, as well as resting-state brain networks, may be related to anxiety symptoms in children. In their previous work, Perino et al. (8) reported that anxiety symptoms measured dimensionally were associated with greater involuntary attention capture of nonaffective cues, as well as greater activation of the inferior frontal gyrus, a key node of the VAN. In the current study, Perino et al. (2) extend this work by showing that both pediatric anxiety and attention capture are associated with greater CON–VAN connectivity at rest. The authors suggest that enhanced CON–VAN connectivity in pediatric anxiety may stem from a history of excessive coactivation during which greater VAN sensitivity to attention capture is communicated to the CON. Interestingly, the authors also report that anxiety is associated with alterations within the CON, as well as between the CON, visual network, and default mode network. Given that the CON may serve as a switch between networks underlying externally oriented attention (e.g., visual) as well as internally oriented processing [e.g., the default mode network (3)], altered resting-state functional connectivity of CON with these networks may relate to altered use of salient stimuli to guide both internally and externally focused processes in anxious children.

Building from models suggesting alterations of both internal/affective and external/cognitive processes in anxiety, the present work suggests that anxiety may be linked not only with vigilance toward threat but also with heightened attention toward salient stimuli more generally. Evolutionarily, faster orienting toward novel stimuli may confer a survival benefit, but in anxiety, faster orienting is observed alongside slower disengagement from salient stimuli, which may confer a disadvantage (i.e., reduced attentional flexibility). Perino et al.’s (2) findings align with the notion that greater CON–VAN connectivity may underlie less flexibility in shifting attention away from stimuli that are no longer relevant and toward new stimuli that have become relevant. This model of network connectivity implies that in anxiety, increased attentional capture occurs in the absence of a specific threat, and instead reflects a general, externally oriented disposition. From a phenomenological perspective, this model could help explain the persistence of fears, worries, and avoidance in pediatric anxiety disorders despite the presence of safety cues such as parental reassurance and even a child’s own insight that their anxiety is excessive.

Notably, Perino et al. (2) observe best practices for resting-state data collection and processing in their study, an especially important step toward making advances in neuroimaging studies of child anxiety. Resting-state functional connectivity analysis is particularly sensitive to motion artifacts. Moreover, age is inversely correlated with motion, making it more challenging to study canonical networks in children. By using a 20-minute resting-state functional magnetic resonance imaging protocol, Perino et al. (2) were able to censor frames with excessive motion and still retain at least 8.04 minutes of resting-state data from each child participant. As collecting this amount of data may not be feasible for all studies, it will be important for future investigators to consider the tradeoff between data retention and data quality. Ensuring that other research groups collect high-quality data and use processing pipelines that reduce the effects of motion will improve the likelihood of replication.

Increasing the reliability of imaging methods is crucial for clinical translation. In contrast to the previous neuroimaging literature in pediatric anxiety that has focused on a priori regions of interest, Perino et al. (2) use network-level analysis to examine the connectivity of previously defined cortical

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networks across the whole brain. This approach appropriately limits multiple comparisons and increases power to detect meaningful effects. As divergent findings can arise from the use of different network parcellations, processing streams, and task design (for behavioral and task-based analyses), standardization of methods remains a major challenge for the field. For example, the key finding of the present study focused on CON–VAN connectivity; however, previous work has used the “salience network” synonymously with both the CON and the VAN. To move forward toward replication and clinical translation, the field will need to settle on common network definitions. An additional challenge for the study of resting-state connectivity–defined networks in children is that publicly available network atlases, such as the one used by Perino et al. (2), may not accurately capture network organization in children. Connectivity and cognitive processes mature rapidly during childhood and adolescence, and best practices for studying the brain at different ages are still under development (5).

In addition, moving beyond categorical diagnoses of anxiety to examine the association of anxiety and behavior dimensionally, Perino et al.’s (2) study is consistent with Research Domain Criteria framework (6). For clinical translation of neuroscience findings, it will be important for the field to understand how the normal to abnormal range of clinical phenomena map onto brain and behavior. Including individuals with subclinical symptoms may identify patterns of connectivity that associate with risk for developing an anxiety disorder and provide a cut point for healthy connectivity that could be targeted as an objective measure of treatment success. A Research Domain Criteria perspective to study the constructs underlying anxiety will also allow for the consideration of comorbid symptoms. Although the Perino et al. (2) findings remain significant after controlling for comorbidities, CON dysfunction has been implicated across many forms of psychopathology. Thus, future work is needed to further examine the specificity of CON alterations with anxiety.

The present study has important implications for the treatment of pediatric anxiety. For example, could cognitive training be designed to modify attentional capture to treat anxiety? As attentional capture reflects both faster orienting toward novel stimuli and slower disengagement from these stimuli, training could focus on reducing hypersensitivity to salient cues or improving flexibility of attention shifting by pairing invalid targets with rewards. Alternatively, existing attention bias modification paradigms could be modified to include nonemotional stimuli. It is possible that the focus on threat biases over more general attentional orienting is one reason that attention bias modification has shown to be less effective than initially promised. In addition, the findings of the present study suggest that specific neural network pairs could be modulated directly via transcranial magnetic stimulation to determine how VAN–CON connectivity relates to anxiety severity (Figure 1).

Perino et al. (2) provide an excellent foundation for the translation of clinical neuroscience findings into practice in pediatric anxiety. However, full clinical translation will require us, as a field, to move beyond group comparisons and correlations across individuals within a group to examine how changes in connectivity associate with changes in behavior and anxiety symptoms within individuals over time. To do so, we need to establish objective, mechanistically relevant biomarkers that track with fluctuations in anxiety severity in a given child over time. As the present study focused on children between 7 and 13 years of age, it will also be important to examine if the relationship between anxiety, connectivity, and behavior varies across development. Furthermore, larger longitudinal and neuromodulatory studies are needed to assess causal relationships between CON–VAN connectivity, behavior, and symptoms.

Perino et al. (2) show that alterations of CON are associated with anxiety in children and that CON–VAN connectivity, specifically, is also associated with involuntary attention capture to nonaffective cues. This work provides important groundwork for future translational neuroimaging studies and provides specific behavioral and network findings that could be tested as novel treatment targets for pediatric anxiety.

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Article Information

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