Long-standing hypotheses about schizophrenia as a “dysconnection” syndrome are consistent with the idea that mental illness arises in part from brain circuit disruptions, with impairments in cognition and behavior occurring because of a failure of coordinated action across multiple brain regions. One such theory, put forth by Andreasen and colleagues, suggested that schizophrenia involves a disruption in the integration of cortical—striatal—thalamic—cerebellar circuits. Anatomical work in primates has shown that the thalamus is topographically organized into parallel pathways connecting specific thalamic nuclei to different regions of cortex. The medial dorsal and anterior nuclei of the thalamus project to the dorsolateral prefrontal cortex (dLPC), whereas the lateral nuclei project more to sensorimotor regions, with similar findings in functional brain connectivity studies in humans. A large body of evidence has shown reduced connectivity from bilateral thalamic regions, medial dorsal, and anterior nuclei in particular, to the bilateral dLPC, dorsal anterior cingulate, parts of the striatum, and bilateral cerebellum in schizophrenia. This is often coupled increased connectivity between the thalamus, lateral nuclei in particular, and motor, visual, and/or auditory sensory regions.

Such altered thalamocortical connectivity has been found in individuals at both clinical and genetic high risk for schizophrenia, and even to some extent in other disorders characterized by psychosis, such as bipolar disorder. Furthermore, among individuals at clinical high risk, altered thalamic connectivity was most pronounced among those who subsequently converted to a psychosis diagnosis. These robust findings across studies are consistent with the idea that coordination among these brain regions is disrupted in individuals with schizophrenia spectrum disorders. Furthermore, the relationship of this impaired thalamic connectivity with cognitive function is consistent with the idea that thalamocortical networks are critical for organizing brain oscillations important for effective cognitive function.

The work by Zhang and colleagues adds significantly to this literature on thalamocortical connectivity dysfunction in psychosis in important ways. This work focused on adolescents with early-onset psychosis, a population for which there have been questions about continuity in etiology with populations whose psychosis onsets later in adolescence and adulthood. Zhang et al. demonstrate disrupted connectivity of the thalamus to a number of areas across the cortex in a large sample of such adolescents, including, importantly, a large subset of medication-naive individuals. Consistent with the clinical high-risk and adult psychosis literature, the authors find evidence for hyperconnectivity of lateral and, to some extent, medial—dorsal, thalamic nuclei to a range of cortical regions. However, less consistent with the adult literature, they do not find evidence of hypo-connectivity of the thalamus to the dLPC.

These data provide evidence consistent with the idea that early-onset schizophrenia is on the same spectrum with psychosis that emerges later in the course of development, and provides further support for the critical role of disrupted thalamocortical connectivity in psychosis. However, there are several aspects of their work that require further discussion, and some directions for new approaches to examining functional connectivity that may help clarify findings in the field. Zhang et al. interpret some of the hyperconnectivity that they found as evidence for increased connectivity between the thalamus and regions of the Salience Network, a brain network thought to be important for monitoring the relevance of external stimuli in the environment. However, examination of the location of regions in Figure 2 and Table 2 of their paper suggests that the insula region that they found is posterior to the insula regions that are typically part of the Salience Network, and the anterior cingulate region that they found is very anterior and much more consistent with anterior prefrontal regions found in the default mode network. Furthermore, Zhang et al. state that they did not find evidence of reduced thalamic connectivity with the dLPC. However,
examination of Figure 2 and Table 2 again suggests that they actually did see reduced connectivity from the caudal thalamus to the bilateral dIPFC. Admittedly, this is not the thalamic region for which they predicted reduced connectivity to the dIPFC, but it is nonetheless an important observation. Relatedly, Zhang et al. argue that their findings suggest that reduced thalamic-to-dorsolateral prefrontal cortex connectivity may emerge later in development. Specifically, they suggest that work in the NAPLS 1 clinical high-risk cohort found that the most prominent alteration in those who later converted to psychosis was increased sensorimotor—thalamic connectivity, and that subsequent work in the NAPLS 2 cohort found that only thalamocortical hyperconnectivity predicted conversion. However, the NAPLS 1 work found that both hypo-connectivity of the thalamus to the dIPFC and hyper-connectivity to sensori-motor regions predicted conversion to psychosis (see Figure 1 of Anticevic et al.\(^3\)). Furthermore, in the NAPLS 2 report, the authors took a whole-brain approach and found hyperconnectivity across many different networks in an analysis that aggregated data across tasks and resting state functional connectivity. When Cao et al. examined resting state functional connectivity (rsFC) in isolation, they did not find any connectivity that predicted conversion to psychosis. Thus, the question of whether hypo-connectivity of the thalamus to the dIPFC emerges only later in the course of illness or development is still an open question.

A key question is what the field can do going forward to help clarify patterns of disrupted thalamocortical connectivity across populations. First, it is important to demonstrate the overall patterns of connectivity found in the controls. In the Zhang et al. study, it is not clear whether the controls showed the expected patterns of connectivity between medial dorsal regions of the thalamus and the dIPFC, and/or whether they showed unexpected patterns of connectivity from other nuclei to the dIPFC. This information would provide important context in which to interpret any unexpected findings in patients. Second, a potentially fruitful direction is to focus on parcellations of the thalamus that reflect functional boundaries.\(^9\) Although there are clearly similarities in boundaries based on anatomical versus functional connectivity features, if our goal is examine functional circuits, matching parcellation sources to the scientific questions of interest may help hone in on the best regions to examine and help enhance replication across studies. Third, another potentially fruitful direction is to move toward individually defined parcellations of the thalamus in identifying seed regions, an approach that has broad applicability across brain regions.

There are reliable individual differences in the specific subregions of subcortical and cerebellar structures, including the thalamus, that show rsFC with cortical networks.\(^{10}\) Thus, the use of group-level parcellations may be missing key individual differences that could be clouding replication across studies and reducing the precision of our estimates. The downside of such individual-specific approaches is that they do require more data to be reliable, and would not be possible with the small amount of data historically acquired in human studies (eg, Zhang et al. had only 6—9 minutes of resting state data for participants, which is on the low side for reliability results even with group-average parcellation). However, advances in technology, pulse sequences, and post-processing techniques that enhance rsFC data quality are hopefully making the examination of individual level parcellations feasible, and could significantly enhance our understanding of thalamocortical connectivity in psychosis, given the emerging evidence, including that provided by Zhang et al., of its importance in understanding the evolution of psychosis.

**REFERENCES**

6. Murray JD, Anticevic A. Toward understanding thalamocortical dysfunction in schizophrenia through computational models of neural circuit dynamics. Schizophr Res. 2017;180:70-77.