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Invited commentary

Global network disorganization underlying psychosis high risk states

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Heterogeneity in connectivity patterns across the brain is well known to be the norm rather than the exception. Some brain regions, called hubs, are more densely connected than other nodes. In addition, hubs connect more densely with other hubs (Sporns et al., 2007) than with other nodes, thereby forming dense cores of connectivity. Such "rich club" organization mediates the majority of information flow (Misic et al., 2014) and the integration of complex information flow among segregated communities of nodes (Gomez-Gardenes et al., 2010). As such, rich-club connections constitute the majority of wiring cost (van den Heuvel et al., 2012), are metabolically demanding (Bullmore and Sporns, 2012) and are vulnerable to disruption by targeted attacks and consequent interference on the neural traffic (van den Heuvel and Sporns, 2013). Such hub connectivity is reported to be under genetic control with a distinct transcriptional signature (Fulcher and Fornito, 2016). Hub neurons are found to appear early in the development of *C. elegans* (Towlson et al., 2013) and in neuronal cultures (Schroeter et al., 2015). To further support developmentally early origins of rich club neurons and genetic control, rich club organization has been shown at 30-week gestation (Ball et al., 2014; van den Heuvel et al., 2015). This convergent data is relevant for the investigation of certain aspects of topological network characteristics underlying schizophrenia and high-risk states.

Schizophrenia is proposed to be a disorder of dysconnection and of neurodevelopment. Persons with schizophrenia show abnormalities in global and local network organization that are associated with cognitive impairments and severity of psychotic symptoms. As schizophrenia research has been shifting to earlier phases of the illness to focus on reducing long-term morbidity and developing preventative efforts, more attention is now being dedicated to examining network topology among persons with higher risk for developing psychoses. While familial high risk requires schizophrenia in a first-degree relative, clinical high risk requires psychopathological manifestations and functional deficits in addition. For this reason, the genetic underpinnings of hubs, the neurodevelopmental basis for hub neuron development, and the importance of neurodevelopmental underpinnings of network topology appear to be relevant in the investigation of risk states for schizophrenia.

A few studies have begun to systematically address the aforementioned considerations. Collin et al. (2017) reported reduced rich club connectivity in offspring of schizophrenia parents compared to controls as well as offspring of bipolar disorder parents suggesting that rich club organization is affected in persons at elevated risk for schizophrenia even before they manifested the illness. The findings also supported that there was relative specificity to schizophrenia familial risk compared to familial risk for bipolar disorder. Schmidt et al. (2017) reported reduced rich club index in persons with at-risk mental states. Although rich club organization was noted in both controls and persons with at-risk mental states, rich club regime was narrower in clinical high risk (CHR) individuals and lower tendency for having strongest connections among hubs. Rich club regime is a range of richness of connections in weighted rich club examination (Colizza et al., 2006). Further, rich club connectivity correlated with severity of negative symptoms supporting clinical importance of these findings.

The study by Hua et al., (In this issue) comparing persons with CHR, early schizophrenia and controls differs from the above studies in that it reports no difference in the rich club organization among this group, but early schizophrenia persons had fewer rich club network connections compared to both CHR and controls. Further, reduced connections were more localized to rich club organization but not generalized reductions in connections. The differences were of modest effect sizes. However, CHR converters showed reduced rich club organization with large effect sizes compared to CHR non-converters when these groups included only those CHR who were followed up for 2 years. Correlations with prodromal psychopathology were not significant making its clinical importance unclear in this sample. Compared to Schmidt et al. (2017),

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Hua et al. had larger sample size and subjects were relatively younger, and eligibility criteria for CHR were somewhat different between the two studies. To further characterize global network organization, its importance to the biology of risk, and its potential for prediction of conversion to psychosis, more studies with larger samples are needed. Despite differences in findings between the studies, such efforts are important to characterize network topology among different phases of the illness.

Another pattern of connectivity that is consistent within the rich-club pattern is small-world organization which has also been described in schizophrenia (Liu et al., 2008). Small world networks show substantially higher clustering coefficients compared to random networks while having comparable path lengths, possibly indicative of their higher resilience to potential network disruptions (Bassett and Bullmore, 2006) in contrast to rich club networks. A recent study reported reduced small world properties of a network built using electrophysiological data collected during working memory task in subjects with first-episode schizophrenia and high-risk persons that positively correlated with global cognitive measures (Jhung et al., 2013). However, small world organization of white matter network did not differ among persons with schizophrenia, their relatives, and controls (Yan et al., 2015).

Currently, no consistently replicated patterns of global brain organization are identified as being associated with the risk states. Existing studies point to different regions in the brain as being involved in rich club or small world organization. More often, methodological approaches including the parcellation scheme, network construction, thresholding, and subsequent analyses appear to be contributing to the heterogeneity of findings. Some studies that show differences between groups suggest reduced rich club and small world organization that can potentially make the network of high-risk persons less resilient to pathological processes. There are no prospective longitudinal studies to examine the nature of progression, if any. If the progression of this pattern of network organization is confirmed among persons at elevated risk for schizophrenia, then discerning the nature of changes in the network organization and factors that affect such changes may be the key to identify susceptible parts of the network and design novel treatments.

CRediT authorship contribution statement

KMP conceived the manuscript and took a lead in drafting the commentary. JR, JC, and SI participated in critical discussion on this topic and edited the manuscript.

Declaration of competing interest

None of the authors have conflict interest.

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