Cortical Hub Failure in Schizophrenia

Gaurav H. Patel

Schizophrenia is commonly characterized by the combination of positive, negative, and cognitive symptoms. Cognitive symptoms include problems with working memory, attention, and executive function. Integration of these cognitive processes supports many abilities, including social functioning. Impairment in this integration, then, may be a factor in disability in schizophrenia patients, preventing them from working or going to school (1). The brain networks underlying these cognitive abilities span the frontal, parietal, and temporal lobes. The networks have what is known as small-world architecture. These small-world networks consist of multiple densely connected clusters of nodes called modules or communities that are bridged by hub nodes, which are defined as nodes that connect two or more modules (2). In the brain, network nodes correspond to brain areas, and their connectivity is usually measured structurally, often with resting-state functional connectivity.

Multiple studies of brain network architecture in schizophrenia have revealed decreased modularity, increased global connectivity, and decreased numbers of hubs. These abnormalities are thought to affect the integration of information between cognitive networks (2). Others have isolated connectivity abnormalities within the default mode network, which comprises areas in the medial prefrontal and parietal cortices along with the temporoparietal junction (TPJ) (3). The default mode network may contain many of the cortical hub areas, making it the focal point for integrative processes (4), but this point remains controversial (5). The TPJ, however, by any number of criteria, appears to be a hub region and the focal point of many integrative sensory and cognitive processes (6). If the TPJ and other default mode network hub regions are preferentially affected by schizophrenia, this would translate into the network architecture abnormalities observed that lead to impaired integrative processing. However, these abnormalities have been inferred from the structural architecture of the networks rather than from any functional measures that attempt to directly measure integration of processing within and between networks.

As reported in this issue of *Biological Psychiatry*, Mäntylä *et al.* (7) make the first attempt to directly measure this functional integration in schizophrenia by studying whole-brain activity evoked by naturalistic stimuli as measured by blood oxygen level–dependent functional magnetic resonance imaging. The use of naturalistic stimuli—in this case, a 7-minute clip of the 2010 movie *Alice in Wonderland*—offers the best chance to view brain activity deficits evoked by stimuli that mimic those encountered in real life, pointing to which brain areas and networks may be the source of the behavioral deficits and symptoms that impair daily functioning. Processing these complex stimuli requires multisensory and cognitive integration, allowing researchers to test the systems responsible for information integration in ways that static sparse stimuli cannot.

However, blood oxygen level–dependent activity evoked by naturalistic stimuli can be difficult to analyze because these stimuli cannot easily be manipulated or repeated in the manner typical of event-related or block designs while still maintaining their naturalistic qualities. Using a longer movie clip allowed Mäntylä *et al.* (7) to take advantage of the intersubject correlation (ISC) method of measuring brain activity introduced by Hasson *et al.* (8). ISC measures how much the movie engages brain areas by assuming that the evoked activity in a driven brain area will be highly correlated to the activity evoked in the same brain area in another person watching the same movie. Averaged within a group, this method results in a map showing on average how engaged (correlated) each cortical brain area is by the stimulus. Critically, this map is not based on any assumptions about anatomy or cognitive processes, resulting in an unbiased whole-brain view of the areas involved in processing the movie. Contrasting ISC between first-episode psychosis patients and healthy control subjects, Mäntylä *et al.* (7) revealed deficits in engagement mostly within the default mode network.

The authors then searched for regions that showed deficient integrative processing ("hubness") of the movie in schizophrenia. They measured weighted degree centrality, which assesses the number of connections each cortical voxel has to other brain areas, weighted by strength of the connections. A voxel with less weighted degree centrality would be less able to integrate information from multiple cortical areas. The authors found a high degree of overlap of areas less engaged by the movie stimulus in schizophrenia patients, measured by ISC, with areas deficient in weighted degree centrality, again centered in the default mode network. These deficits may underlie the cognitive deficits that underlie comprehension of the movie stimuli.

One of the brain regions demonstrating the largest differences in ISC and weighted degree centrality was the TPJ. Like the prefrontal cortex, the TPJ is not only massively expanded in humans versus nonhuman primates, such as macaques, but is also one of the last to fully develop, maturing in early adulthood around the typical time of the onset of schizophrenia. This region has been identified by others (4,5) as a hub that is ideally situated for the integration of information from multiple cognitive networks, with nodes from the default mode, attention, memory, and face-processing networks. Among other abilities, the TPJ has been implicated in playing a critical role in social functioning (9). This region has also been substantially reorganized in humans versus macaques (10), suggesting that the TPJ underlies social abilities that are unique to humans. Deficits affecting integrative processing in this region then may have dire consequences for social functioning in individuals suffering from schizophrenia.

SEE CORRESPONDING ARTICLE ON PAGE 655

https://doi.org/10.1016/j.biopsych.2018.08.007
ISSN: 0006-3223

The Mäntylä *et al.* (7) study represents the first step in understanding how deficits in the connectivity of and integrative processing in the TPJ and other cortical areas and networks leads to deficits in real-world functioning. Future studies building on these results can take advantage of new high-resolution sequences to explore how failures of integration affect the dynamics of the interactions of these brain networks during the processing of naturalistic stimuli, as well as linking these deficits to symptoms and behavioral deficits in comprehension of social situations. This and future studies will then serve as a bridge between basic behavioral and neuroscience studies of brain functioning and the symptoms that schizophrenia patients experience in the real world.

Acknowledgments and Disclosures

Early Career Investigator Commentaries are solicited in partnership with the Education Committee of the Society of Biological Psychiatry. As part of the educational mission of the Society, all authors of such commentaries are mentored by a senior investigator. This work was mentored by Daniel C. Javitt, M.D., Ph.D.

This work was supported by National Institute of Mental Health Grant No. K23MH108711, the Brain and Behavior Research Foundation, the American Psychiatric Foundation, and the Sydney J. Baer Foundation.

GHP receives income and equity from Pfizer, Inc. through family.

Article Information

From Columbia University Medical Center and the New York State Psychiatric Institute, New York, New York

Address correspondence to Gaurav H. Patel, M.D., Ph.D., New York State Psychiatric Institute, 1051 Riverside Dr., Unit 21, New York, NY 10032; E-mail: ghp2114@cumc.columbia.edu.

Received Aug 6, 2018; accepted Aug 14, 2018.

References

1. Nuechterlein KH, Subotnik KL, Green MF, Ventura J, Asarnow RF, Gitlin MJ, *et al.* (2011): Neurocognitive predictors of work outcome in recent-onset schizophrenia. Schizophr Bull 37(suppl 2): S33–S40.
2. Bullmore ET, Sporns O (2012): The economy of brain network organization. Nat Rev Neurosci 13:336–349.
3. Whitfield-Gabrieli S, Thermenos HW, Milanovic S, Tsuang MT, Faraone SV, McCarley RW, *et al.* (2009): Hyperactivity and hyperconnectivity of the default network in schizophrenia and in first-degree relatives of persons with schizophrenia. Proc Natl Acad Sci U S A 106:1279–1284.
4. Buckner RL, Sepulcre J, Talukdar T, Krienen FM, Liu H, Hedden T, *et al.* (2009): Cortical hubs revealed by intrinsic functional connectivity: Mapping, assessment of stability, and relation to Alzheimer's disease. J Neurosci 29:1860–1873.
5. Power JD, Schlaggar BL, Lessov-Schlaggar CN, Petersen SE (2013): Evidence for hubs in human functional brain networks. Neuron 79: 798–813.
6. Corbetta M, Patel GH, Shulman GL (2008): The reorienting system of the human brain: From environment to theory of mind. Neuron 58: 306–324.
7. Mäntylä T, Nummenmaa L, Rikandi E, Lindgren M, Kieseppä T, Hari R, *et al.* (2018): Aberrant cortical integration in first-episode psychosis during natural audiovisual processing. Biol Psychiatry 84:655–664.
8. Hasson U, Nir Y, Levy I, Fuhrmann G, Malach R (2004): Intersubject synchronization of cortical activity during natural vision. Science 303:1634–1640.
9. Green MF, Horan WP, Lee J (2015): Social cognition in schizophrenia. Nat Rev Neurosci 16:620–631.
10. Patel GH, Yang D, Jamerson EC, Snyder LH, Corbetta M, Ferrera VP (2015): Functional evolution of new and expanded attention networks in humans. Proc Natl Acad Sci U S A 112:9454–9459.