Spotlight

Cell PRESS

Special Issue: The Connectome

Brain network interactions in health and disease

Deanna M. Barch

Departments of Psychology, Psychiatry, and Radiology, Washington University in St. Louis, St. Louis, MO, USA

Understanding how brain systems interact to produce complex behaviors is a central goal of cognitive neuroscience. Palaniyappan and colleagues enhance our understanding of how interactions among brain systems contribute to individual differences in function and psychopathology by examining causal interactions among the salience and central executive systems in schizophrenia.

A growing body of research has identified the presence of multiple brain networks supporting human behavior. These networks include a salience network involving dorsal anterior cingulate and anterior insula regions thought to be relevant to attending to survival-relevant events in the environment; a central executive network (CEN) consisting of regions in the middle and inferior prefrontal and parietal cortices engaged by many higher level cognitive tasks and thought to be involved in adaptive cognitive control; and a default mode network (DMN) consisting of regions in medial frontal cortex and posterior cingulate, among others, that reliably reduce their activity during active cognitive demands and which may be involved in attention to internal emotional states or self-referential processing [1].

Palaniyappan *et al.* [2] examined how deficits in the reciprocal causal interactions between two of these brain networks – the salience system and CEN – may be impaired in schizophrenia and contribute to deficits in symptoms and cognition. Palaniyappan *et al.* focused on the insula, a key node in the salience system, and the dorsolateral prefrontal cortex (DLPFC), a key CEN node. They report impairments in the excitatory causal outlow of the anterior insula to the DLPFC, as well as deficits in the inhibitory feedback of the DLPFC on the anterior insula and the dorsal anterior cingulate (another putative node in the salience network). Further, they found that the severity of deficits in the interactions between the salience and CEN systems predicted the degree of impairment in a factor reflecting symptom severity and processing speed.

It is absolutely critical to the field of psychopathology to move towards examining interactions between systems, as the complexity and range of impairments present in disorders such as schizophrenia are highly unlikely to be due to impairments in a single system, let alone a single brain region. Researchers have long thought of schizophrenia as a 'dysconnection' syndrome, where impairments in cognition and behavior occur because of a failure of coordinated action across multiple brain regions [3]. Palaniyappan and colleagues help to make such hypotheses concrete, by linking disturbances in the interactions between brain systems to function in schizophrenia. Moreover, their results are consistent with prior work showing that deficits in functional connectivity among brain systems such as the CEN, the cingular-opercular network (related to the salience network), and a cerebellar error network contribute to the severity of cognitive dysfunction in schizophrenia [4].

However, importantly, the work of Palaniyappan and colleagues goes beyond prior research by looking at potential causal influences using Granger causality. Granger causality can provide information about the causal influences of one brain region/system on another by identifying when brain activity in one region(s) precedes and predicts activity in another region. Although criticisms have been raised about the ability of Granger causality to identify causal influences [5], Palaniyappan and colleagues do an excellent job of examining and ruling out such confounds, providing greater confidence that they have identified potential causal interactions between the salience and CEN systems.

The article by Palaniyappan *et al.* also raises a major methodological concern for connectivity research in psychopathology, namely, the confounding influence of increased movement. Increased movement can lead to spurious changes in connectivity, particularly reduced long-range and/or increased short range connectivity. Simply removing individuals with movement above a certain level and/or using movement parameters as regressors is insufficient to address these confounds [6,7], as there may still be significant group differences in movement. Palaniyappan *et al.* report excluding individuals who moved more than 3 mm and used movement regressors as a nuisance covariate. Furthermore, they report using ArtRepair to correct motion artifacts. However, they did not report whether any of the movement parameters differed across groups before or after correction. Given that the vast majority of the differences between groups were in the direction of reductions in connectivity in schizophrenia, this leaves open the concern that some of these findings might reflect movement artifacts. One might argue that the obtained associations with illness severity help to rule out such a concern, but one would first need to show that illness severity was not correlated with movement. The explosion of research on functional connectivity in relationship to psychopathology means that the field needs to pay much more attention to such potential confounds.

Corresponding author: Barch, D.M. (dbarch@artsci.wustl.edu).

A second intriguing issued raised by Palaniyappan and colleagues is the potential role of DMN impairments in schizophrenia. The authors relate their findings to the DMN through the idea that the anterior insula may influence the relationship between the CEN and DMN systems, and that this may contribute to difficulties in 'switching off' the DMN in schizophrenia. The challenge to this idea is that there is no systematic evidence that schizophrenia is associated with a failure to suppress the DMN. There are reports of such findings in the literature, but the available meta-analyses of neural alterations during cognitive function in schizophrenia do not provide evidence for consistent failures to suppress DMN activity during working memory, executive function, or long term memory (e.g., [8,9]). One might argue that such meta-analyses could be biased against finding evidence for altered DMN activity in schizophrenia if the contributing studies failed to examine regions showing deactivation, even though at least some did so. As such, a key direction for future research will be to use meta-analytic techniques that allow us to better understand the degree to which abnormalities in DMN function or connectivity contribute to specific dimensions of psychopathology.

It is also important to highlight that by examining interactions between the salience system and the CEN, Palaniyappan and colleagues begin to link deficits in cognitive control to potential deficits in attention to 'salient' events in the environment. This helps to bring the work on the function of the CEN in schizophrenia out of the purely 'cognitive' domain, providing a bridge to an understanding of how cognitive control deficits might interact with and be influenced by real world events in the environment. Further, it is important that the authors examined a dimensional measure of function and cognition, instead of focusing only on diagnostic group differences. The field has increasingly recognized that there is great heterogeneity within disorders, as well as commonalities across disorders. Thus, examination of dimensions of psychopathology in relationship to interactions between brain networks is consistent with the Research Diagnostic Criteria Initiative [10] of identifying core brain–behavior systems that drive variation in human function.

References

1 Power, J.D. *et al.* (2011) Functional network organization of the human brain. *Neuron* 72, 665–678
2 Palaniyappan, L. *et al.* (2013) Neural primacy of the salience processing system in schizophrenia. *Neuron* 79, 814–828
3 Andreasen, N.C. *et al.* (1998) 'Cognitive dysmetria' as an integrative theory of schizophrenia: a dysfunction in cortical-subcortical-cerebellar circuitry? *Schizophr. Bull.* 24, 203–218
4 Repovs, G. *et al.* (2011) Brain network connectivity in individuals with schizophrenia and their siblings. *Biol. Psychiatry* 69, 967–973
5 Smith, S.M. *et al.* (2011) Network modelling methods for FMRI. *Neuroimage* 54, 875–891
6 Satterthwaite, T.D. *et al.* (2013) An improved framework for confound regression and filtering for control of motion artifact in the preprocessing of resting-state functional connectivity data. *Neuroimage* 64, 240–256
7 Power, J.D. *et al.* (2013) Methods to detect, characterize, and remove motion artifact in resting state fMRI. *Neuroimage* http://dx.doi.org/10.1016/j.neuroimage.2013.08.048
8 Minzenberg, M.J. *et al.* (2009) Meta-analysis of 41 functional neuroimaging studies of executive function in schizophrenia. *Arch. Gen. Psychiatry* 66, 811–822
9 Ragland, J.D. *et al.* (2009) Prefrontal activation deficits during episodic memory in schizophrenia. *Am. J. Psychiatry* 166, 863–874
10 Insel, T. *et al.* (2010) Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. *Am. J. Psychiatry* 167, 748–751

1364-6613/$ – see front matter © 2013 Published by Elsevier Ltd.
http://dx.doi.org/10.1016/j.tics.2013.09.004 Trends in Cognitive Sciences xx (2013) 1–2