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Introduction to *JINS* Special Issue on Human Brain Connectivity in the Modern Era: Relevance to Understanding Health and Disease

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Last year (2015) commemorated the 50th anniversary of Norman Geschwind's seminal papers in *Brain* on "Disconnexion syndromes in animals and man" (Geschwind, 1965a, 1965b). In the past 50 years, huge advances have occurred in the tools and technologies available for the *in vivo* assessment of both structural and functional connectivity in the human brain, including diffusion imaging for examining structural brain connectivity, and functional magnetic resonance imaging (fMRI), electroencephalogram (EEG), and magneto-encephalogram (MEG) approaches to understanding functional brain connectivity. This has led to a dramatic increase in our understanding of the core principles of human brain connectivity and their relationship to cognitive, emotional, motor, and sensory function in health, and more recently, in clinical populations.

Facilitated by the availability of novel imaging techniques, this enhanced understanding of brain–behavior relationships reflects a fundamental conceptual shift. Basic and translational research examining task-related brain activation has been remarkably informative in terms of our understanding of the neural substrates of particular cognitive and affective processes and how these may go awry in conditions associated with impaired brain function. However, over time, it has become clear that rarely does any particular cognitive or affective process require only a single brain region, and rarely is any particular form of cognitive or behavioral dysfunction associated with disruption of only a single brain region.

Furthermore, basic neuroscience research has long made it clear that activity in any individual brain region (or any individual neuron!) is the result of inputs from and outputs to different areas of the brain. Such realizations have led to a shift in focus on neural circuits rather than on specific brain regions. More specifically, this shift has been to questions about the relationship between and among different brain regions in producing successful cognitive and affective function in health, and the ways in which abnormalities at the level of circuits contribute to the development and maintenance of specific neuropsychological impairments. The growing work on the role of brain oscillations in coordinating activity within and between neutral networks (Canavier, 2015; Ketz, Jensen, & O'Reilly, 2015; Pittman-Polletta, Kocsis, Vijayan, Whittington, & Kopell, 2015; Uhlhaas & Singer, 2015) is consistent with such hypotheses that localize neuropsychological impairments at the circuit level of function rather than within specific individual brain regions.

Aimed at highlighting this conceptual shift, this special issue has three specific goals. The first is to provide a brief overview of the current methodological and analytic tools available for understanding both normative and dysfunctional human brain connectivity. As outlined in the article by Lowe and colleagues, and to some extent in the article by Hayes and colleagues, we have seen major advances in our ability to image white matter connections in the human brain, including state-of-the art techniques that now allow researchers to follow the path of white matter connections through areas where many different fiber tracts merge, dramatically improving our ability to understand the structural basis of both short and long range communication within brain circuits.

Furthermore, as also described in the article by Lowe and colleagues, the last 30 years have also seen the emergence of methods for studying functional brain connectivity, or the covariance of spontaneous brain activity across brain regions. Originally, the concept of functional connectivity was applied to simultaneous recordings of neuronal spike trains (Gerstein & Perkel, 1969; Gerstein, Perkel, & Subramanian, 1978; Perkel, Gerstein, & Moore, 1967), which are thought to contribute to the functional connectivity observed in humans using non-invasive neuroimaging methods. A main inference of functional connectivity is that, if two regions have highly correlated neuronal activity (i.e., have high functional connectivity), then they are more likely to engage in a common set of processing mechanisms. As such, functional connectivity provides a tool for understanding what brain regions may be communicating while engaging in specific cognitive or affective processes, and therefore what brain circuits support performance and ability in different domains of cognition, emotion and/or social processing.

A major breakthrough in the development and application of functional connectivity methods for humans came in 1995, when Biswal and colleagues reported that spontaneous activity from regions in the right and left motor cortices was highly correlated even while an individual was resting (Biswal, Yetkin, Haughton, & Hyde, 1995). Of interest, this correlated activity was observed in the spontaneous low-frequency fluctuations of the BOLD signal (0.01–0.10 Hz), a frequency band that has often been discarded as noise in task-based studies, although such correlations can be seen at other frequencies as well. This work spurred a major field of exploration of what is now referred to as resting state functional connectivity. Importantly, this resting brain state activity is thought to consume a major portion of the body's energy (~20%), despite the brain only being 2% of the body's total mass (Fox & Raichle, 2007).

Furthermore, changes in metabolism due to engagement in a specific task are typically less than 5%. Thus, ongoing resting state activity may provide a rich source of pathology-related variability over and above changes observed in the context of task performance (Fox & Raichle, 2007). In addition, there is also robust work demonstrating that a large portion of the trial-to-trial variability in task-related activity reflects coherent and organized spontaneous fluctuations in brain activity (Fox, Snyder, Zacks, & Raichle, 2006), providing another piece of evidence that this is a meaningful source of variation in human brain function.

One of the key aspects of resting state functional connectivity that has spurred interest in this aspect of brain function is the realization that it reveals intrinsically organized networks of brain regions that are consistently functionally connected, even in the absence of task-induced perturbations in ongoing brain activity (Fox et al., 2005). This has been supported by numerous "network" mapping studies that have identified consistent, robust and reproducible networks of brain regions that show coordinated activity at rest (Buckner, Krienen, Castellanos, Diaz, & Yeo, 2011; Choi, Yeo, & Buckner, 2012; Craddock, James, Holtzheimer, Hu, & Mayberg, 2012; Gordon et al., 2016; Laird et al., 2011; Power et al., 2011; Smith et al., 2012; Wig et al., 2014; Yeo et al., 2011). These include the default mode network, the frontal parietal network, the cingulo-opercular network, and the dorsal attention network, to name a few.

Importantly, many of these networks map closely or at least partially, to networks that have been identified in task-based studies, providing validation to the functional meaningfulness of this coordinated activity (Laird et al., 2011). Such functional connectivity networks have their basis in part in structural connectivity (Betzel et al., 2014; Hermundstad et al., 2013; Horn & Blankenburg, 2015; Horn, Ostwald, Reisert, & Blankenburg, 2014; Messe, Rudrauf, Giron, & Marrelec, 2015; Miranda-Dominguez et al., 2014), but are not isomorphic with regions that show direct structural connectivity. As such, the mapping of resting state networks to known task networks has led to the hypothesis that resting state networks reflect in part organized interactions that arise from a history of co-activation over development (Power et al., 2011). Such networks are now frequently referred to as "intrinsic" connectivity networks, given that they are not dependent on performance of a particular task for identification, are present even at rest and are relatively consistent across task and environmental states. Many of the articles in this special issue focus on these networks to understand the source of pathology in various forms of brain dysfunction.

A second goal of this special issue is to provide integrative and synthetic summaries of the state-of-the field in our current understanding of brain connectivity impairments associated with both neurological and neuropsychiatric disorders. As such, the article by Hayes and colleagues reviews the current state of the literature on understanding traumatic brain injury (TBI) as a disorder of brain connectivity. Much of the work on TBI has long focused on the impairments in white matter that may occur as a result of the different traumas that can lead to TBI, with the recognition that damage to white matter connections may be occurring even when focal lesions are not found. The article by Hayes et al. provides evidence that TBI is indeed associated with white matter damage. The corpus callosum seems to be particularly vulnerable to the forces that lead to TBI, but the existing evidence suggest that the damage associated with TBI can be quite diffuse and present in many different tracts, perhaps dependent on the nature and severity of the causal trauma. This white matter damage persists even into chronic phases of TBI and has been associated with cognitive and functional impairments. Furthermore, TBI is also associated with alterations in functional connectivity, with several studies highlighting disrupted connectivity of the default mode network and its contribution to post concussion symptoms and impairments in attention focus.

The review article by Teipel and colleagues highlights the potentially important roles of both structural and functional connectivity in the evolution of Alzheimer's disease (AD). As described in this review article, there are now numerous cross-sectional and longitudinal studies relevant to AD documenting impairments in white matter, including abnormalities in limbic tracts such as the fornix, the uncinate fasciculus and the posterior and parahippocampal fibers of the cingulum. Furthermore, there is growing evidence of abnormalities in resting state connectivity, with several studies demonstrating abnormalities of the default mode network. Abnormalities in connectivity have also been documented using coherence measures in EEG. Importantly, there is increasing evidence of links between structural and functional connectivity impairments in the default mode network in AD. As noted by Teipel et al., these findings are helping us to understand the potential etiological mechanisms of AD relevant pathology, as well as the longitudinal evolution of the disease. However, more work is needed for such findings to have direct clinical application. On the opposite end of the life span, Koyama and colleagues also argue for the importance of connectivity in understanding the developmental trajectory of children who may be at risk for the development of a range of disorders that impact brain function.

The third goal of this special issue is to present cutting-edge empirical findings on the nature and role of connectivity impairments in understanding variations in cognitive and emotional function, as well as in a range of clinical populations. To this end, the special issue includes several novel empirical findings on ways in which either structural or functional connectivity contributes to cognitive and affective function in both health and disease. Several papers provide data on the relationships between behavior and brain connectivity in healthy individuals, providing evidence for the functional significance of individual variation in brain connectivity. For example, Unger and colleagues demonstrate that individual differences in the integrity of the inferior longitudinal fasciculus (ILF) and the inferior fronto-occipital fasciculus (IFOF) predict emotion recognition performance as well as memory for emotional faces. Ly and colleagues provide evidence for a relationship between the microstructure of the fornix and both task-related connectivity and performance during episodic recognition in healthy aging, providing an interesting model of potential pathways to individual differences in memory.

The other empirical papers in this special issue demonstrate how abnormalities in structural and or functional connectivity may contribute to behavioral and affective impairments in various forms of brain pathology. For example, Putcha and colleagues provide intriguing evidence that altered coupling of the salience and default mode networks relates to cognitive function in both healthy individuals and those with Parkinson's disease. The salience and default mode networks are typically "anti-correlated," and it is thought that the ability to down-regulate activity of the default mode network during cognitive tasks is important for effective performance. The finding by Putcha et al. that a lack of anti-correlation was associated with impaired function in executive, memory, and psychomotor speed domains is consistent with this hypothesis.

Relatedly, Dobryakova and colleagues provide evidence that altered connectivity among frontal-parietal regions predicts impaired processing speed in multiple sclerosis. Rao and colleagues examined connectivity of hippocampus to both fronto-temporal and fronto-parietal regions among individuals with remitted major depression compared to controls during semantically cued episodic memory performance. They found evidence for impaired memory performance and altered hippocampal connectivity among the previously depressed individuals, along with evidence for disrupted relationships between hippocampal connectivity and memory.

Finally, three articles bring to bear a graph theoretic approach to understanding how alterations in neural networks contribute to the development of brain pathology and associated impairments in cognitive function. Graph theory is a branch of mathematics that provides algorithms for determining metrics that characterize networks at both global and local levels of function. One major advantage of graph theory is its flexibility; algorithms can be applied to functional connectivity data, structural connectivity data, as well as to data obtained using MEG, EEG, or fMRI, allowing for a convergence of findings across differing modalities.

Furthermore, network science allows for the characterization of dynamic processes through single metrics, arguably providing more powerful and parsimonious descriptions of heterogeneous data than the previously discussed approaches. Although much work is needed to further validate the use of graph theory for interpreting brain connectivity data, network science represents an exciting new field of research that is increasingly showing associations between network metrics and behavior, as well as abnormalities in networks metrics in individuals with psychiatric and neurological disorders.

Yeo and colleagues use the power of a graph theory approach to show that the structural brain networks of individuals with schizophrenia are characterized by longer characteristic path lengths (suggesting a longer transit time for information) and reduced overall connectivity. These graph theory metrics predicted overall cognitive ability in healthy individuals as well as in individuals with schizophrenia, and the overall connectivity reduction mediated the relationship between diagnosis and overall cognitive ability.

Furthermore, Yeo et al. found that a genetic measure reflecting mutation load predicted both longer characteristic path length and global cognitive ability. Sedeno and colleagues also took a graph theory approach to understanding the mechanisms that might contribute to cognitive and social impairments in fronto-temporal dementia. Used resting state functional connectivity, they showed decreased network centrality, a measure of the importance of a node or brain region's role in a network, in the fronto-temporal–insular network. Furthermore, this network centrality was associated with social cognition and executive function in individuals with fronto-temporal dementia and healthy individuals. Finally, Han and colleagues examined networks associated with goal-directed behavior in individuals with chronic TBI. They observed markedly disrupted long-range interhemispheric and between-network connectivity between the default mode network, the dorsal attention network, and the frontoparietal control network, with as result reduced global and local efficiency.

In summary, we believe that the articles presented in this special issue provide an important entryway into the burgeoning literature on the role of neural networks in cognition and the nature of alterations in circuit level structural and functional connectivity associated with brain pathology. As noted in many of the articles, this field continues to evolve as both the acquisition and analyses methods develop and expand, but the existing evidence points to the functional relevance of these networks to understanding variations in normal development and the critical importance of their structural and functional brain disruption as a means of understanding pathophysiology and potential pathways for intervention or even prevention.

REFERENCES

Betzel, R.F., Byrge, L., He, Y., Goni, J., Zuo, X.N., & Sporns, O. (2014). Changes in structural and functional connectivity among resting-state networks across the human lifespan. *Neuroimage*, *102*(Pt 2), 345–357. doi:10.1016/j.neuroimage.2014.07.067

Biswal, B., Yetkin, F.Z., Haughton, V.M., & Hyde, J.S. (1995). Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. *Magnetic Resonance Imaging*, *34*(4), 537–541. Retrieved from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=8524021

Buckner, R.L., Krienen, F.M., Castellanos, A., Diaz, J.C., & Yeo, B.T. (2011). The organization of the human cerebellum estimated by intrinsic functional connectivity. *Journal of Neurophysiology*, *106*(5), 2322–2345. doi:10.1152/jn.00339.2011

Canavier, C.C. (2015). Phase-resetting as a tool of information transmission. *Current Opinion in Neurobiology*, *31*, 206–213. doi:10.1016/j.conb.2014.12.003

Choi, E.Y., Yeo, B.T., & Buckner, R.L. (2012). The organization of the human striatum estimated by intrinsic functional connectivity. *Journal of Neurophysiology*, *108*(8), 2242–2263. doi:10.1152/jn.00270.2012

Craddock, R.C., James, G.A., Holtzheimer, P.E. III, Hu, X. P., & Mayberg, H.S. (2012). A whole brain fMRI atlas generated via spatially constrained spectral clustering. *Human Brain Mapping*, *33*(8), 1914–1928. doi:10.1002/hbm.21333

Fox, M.D., & Raichle, M.E. (2007). Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. *Nature Reviews. Neuroscience*, *8*(9), 700–711. doi:10.1038/nrn2201

Fox, M.D., Snyder, A.Z., Vincent, J.L., Corbetta, M., Van Essen, D.C., & Raichle, M.E. (2005). The human brain is intrinsically organized into dynamic, anticorrelated functional networks. *Proceedings of the National Academy of Sciences of the United States of America*, *102*(27), 9673–9678. Retrieved from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15976020

Fox, M.D., Snyder, A.Z., Zacks, J.M., & Raichle, M.E. (2006). Coherent spontaneous activity accounts for trial-to-trial variability in human evoked brain responses. *Nature Neuroscience*, *9*(1), 23–25. Retrieved from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16341210

Gerstein, G.L., & Perkel, D.H. (1969). Simultaneously recorded trains of action potentials: Analysis and functional interpretation. *Science*, *164*(3881), 828–830. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/5767782

Gerstein, G.L., Perkel, D.H., & Subramanian, K.N. (1978). Identification of functionally related neural assemblies. *Brain Research*, *140*(1), 43–62. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/203363

Geschwind, N. (1965a). Disconnexion syndromes in animals and man. I. *Brain*, *88*(2), 237–294. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/5318481; http://brain.oxfordjournals.org/content/brain/88/2/237.full.pdf

Geschwind, N. (1965b). Disconnexion syndromes in animals and man. II. *Brain*, *88*(3), 585–644. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/5318824; http://brain.oxfordjournals.org/content/brain/88/3/585.full.pdf

Gordon, E.M., Laumann, T.O., Adeyemo, B., Huckins, J.F., Kelley, W.M., & Petersen, S.E. (2016). Generation and evaluation of a cortical area parcellation from resting-state correlations. *Cerebral Cortex*, *26*, 288–303. doi:10.1093/cercor/bhu239

Hermundstad, A.M., Bassett, D.S., Brown, K.S., Aminoff, E.M., Clewett, D., Freeman, S., … Carlson, J.M. (2013). Structural foundations of resting-state and task-based functional connectivity in the human brain. *Proceedings of the National Academy of Sciences of the United States of America*, *110*(15), 6169–6174. doi:10.1073/pnas.1219562110

Horn, A., & Blankenburg, F. (2015). Toward a standardized structural-functional group connectome in MNI space. *Neuroimage*, *124*(Pt A), 310–322. doi:10.1016/j.neuroimage.2015.08.048

Horn, A., Ostwald, D., Reisert, M., & Blankenburg, F. (2014). The structural-functional connectome and the default mode network of the human brain. *Neuroimage*, *102*(Pt 1), 142–151. doi:10.1016/j.neuroimage.2013.09.069

Ketz, N.A., Jensen, O., & O'Reilly, R.C. (2015). Thalamic pathways underlying prefrontal cortex-medial temporal lobe oscillatory interactions. *Trends in Neurosciences*, *38*(1), 3–12. doi:10.1016/j.tins.2014.09.007

Laird, A.R., Fox, P.M., Eickhoff, S.B., Turner, J.A., Ray, K.L., McKay, D.R., … Fox, P.T. (2011). Behavioral interpretations of intrinsic connectivity networks. *Journal of Cognitive Neuroscience*, *23*(12), 4022–4037. doi:10.1162/jocn_a_00077

Messe, A., Rudrauf, D., Giron, A., & Marrelec, G. (2015). Predicting functional connectivity from structural connectivity via computational models using MRI: An extensive comparison study. *Neuroimage*, *111*, 65–75. doi:10.1016/j.neuroimage.2015.02.001

Miranda-Dominguez, O., Mills, B.D., Grayson, D., Woodall, A., Grant, K.A., Kroenke, C.D., & Fair, D.A. (2014). Bridging the gap between the human and macaque connectome: A quantitative comparison of global interspecies structure-function relationships and network topology. *The Journal of Neuroscience*, *34*(16), 5552–5563. doi:10.1523/JNEUROSCI.4229-13.2014

Perkel, D.H., Gerstein, G.L., & Moore, G.P. (1967). Neuronal spike trains and stochastic point processes. II. Simultaneous spike trains. *Biophysical Journal*, *7*(4), 419–440. doi:10.1016/S0006-3495(67)86597-4

Pittman-Polletta, B.R., Kocsis, B., Vijayan, S., Whittington, M.A., & Kopell, N.J. (2015). Brain rhythms connect impaired inhibition to altered cognition in schizophrenia. *Biological Psychiatry*, *77*(12), 1020–1030. doi:10.1016/j.biopsych.2015.02.005

Power, J.D., Cohen, A.L., Nelson, S.M., Wig, G.S., Barnes, K.A., Church, J.A., … Petersen, S.E. (2011). Functional network organization of the human brain. *Neuron*, *72*(4), 665–678. doi:10.1016/j.neuron.2011.09.006

Smith, S.M., Miller, K.L., Moeller, S., Xu, J., Auerbach, E.J., Woolrich, M.W., … Ugurbil, K. (2012). Temporally-independent functional modes of spontaneous brain activity. *Proceedings of the National Academy of Sciences of the United States of America*, *109*(8), 3131–3136. doi:10.1073/pnas.1121329109

Uhlhaas, P.J., & Singer, W. (2015). Oscillations and neuronal dynamics in schizophrenia: The search for basic symptoms and translational opportunities. *Biological Psychiatry*, *77*(12), 1001–1009. doi:10.1016/j.biopsych.2014.11.019

Wig, G.S., Laumann, T.O., Cohen, A.L., Power, J.D., Nelson, S.M., Glasser, M.F., … Petersen, S.E. (2014). Parcellating an individual subject's cortical and subcortical brain structures using snowball sampling of resting-state correlations. *Cerebral Cortex*, *24*, 2036–2054. doi:10.1093/cercor/bht056

Yeo, B.T., Krienen, F.M., Sepulcre, J., Sabuncu, M.R., Lashkari, D., Hollinshead, M., … Buckner, R.L. (2011). The organization of the human cerebral cortex estimated by intrinsic functional connectivity. *Journal of Neurophysiology*, *106*(3), 1125–1165. doi:10.1152/jn.00338.2011