Journal Club

Editor's Note: These short, critical reviews of recent papers in the *Journal*, written exclusively by graduate students or postdoctoral fellows, are intended to summarize the important findings of the paper and provide additional insight and commentary. For more information on the format and purpose of the Journal Club, please see http://www.jneurosci.org/misc/ifa_features.shtml.

Functional Integration of Large-Scale Brain Networks

Matthias Mittner
Cognitive Science Center Amsterdam, University of Amsterdam, 1018 WS Amsterdam, The Netherlands
Review of Braga et al.

Much interest has recently focused on large-scale networks in the brain and investigating their functional significance. These networks, commonly referred to as intrinsic connectivity networks (ICNs), are identified by similarities in the temporal evolution of activity in different brain areas, which are defined as nodes in the network. They are most commonly extracted by functional connectivity (FC) analyses of functional magnetic resonance imaging (fMRI) data using one of two main techniques: seed-based correlation maps or spatial independent component analysis (spatial ICA). The default mode network (DMN) and the dorsal attention network (DAN) are the two most prominent among the commonly observed ICNs. Numerous studies have shown that activity and connectivity within and between these two and other ICNs are related to behavioral performance and hence likely to be functionally relevant (Weissman et al., 2006; Christoff et al., 2009).

Although the functional significance of ICNs is generally accepted, it is unclear how the networks interact to solve complex tasks. Previous research on the integration of different processes has suggested a "global workspace"-like architecture (i.e., distinct subsystems competing for consciousness in the global workspace; Baars, 2002). Although the neural underpinnings of this putative architecture, i.e., which specific structures or networks fulfill integrating functions associated with the global workspace, are less well understood, it has been speculated that the often-reported fronto-parietal network assumes a role in coordinating the activity of other, more specialized networks (Smallwood et al., 2012).

Approaching the problem from an empirical viewpoint, it has recently been asserted that if there were local structures involved in multi-network integration, they would be expected to locally mirror activity from all ICNs that they integrate (Leech et al., 2012). The argument behind this idea is that the mapping of multi-network activity to a locally restricted structure (referred to as an "echo") would be an ideal mechanism to allow integration of the diverse signals from spatially distributed, functional networks. Hence, the identification of echo-nodes is an important step toward identifying the neural implementation of the global workspace.

In an article recently published in *The Journal of Neuroscience*, Braga et al. (2013) used a data-driven approach to identify regions in the cerebral cortex that can represent such echo-structures. Expanding on their previous work that focused on a single brain structure [the posterior cingulate cortex (PCC); Leech et al., 2012], the authors opted for whole-brain coverage using a novel, searchlight-based approach. First, each of the 16 mm diameter searchlights covering the whole brain were decomposed into independent components using spatial ICA yielding maximally dissimilar spatial maps. By implementing a dual-regression approach, they were able to infer functional connectivity for each component in each searchlight. The authors implemented the FC analysis by first inserting the group ICA maps as a set of spatial regressors in a general linear model (GLM) to produce component time courses. This method of identifying the temporal dynamics of the independent components is superior to simple back-projection (Calhoun et al., 2001) because it takes the between-subject variance into account (Beckmann et al., 2009). Final correlation maps for each component in each searchlight were calculated by propagating the component time course as temporal regressors into a second GLM. By calculating spatial correlations of each of these maps and well established ICNs (taken from three independent sources for validation), Braga et al. (2013) were able to quantify the extent to which the decomposed local activity within a given searchlight echoed the activity from multiple ICNs.

The main result of the study was the identification of nine brain regions containing a significant number of converging network signals. These regions have previously been described as being part of the default-mode network (PCC, precuneus) as well as multimodal association cortices (temporo-occipito-parietal junction, middle frontal gyrus, and anterior cingulate cortex). In contrast, inherently unimodal regions such as the primary visual cortex showed no trace of multiple echoes. The fact that the activity of multiple distributed ICNs could be isolated in the multimodal nodes suggests their active involvement in integrating informa-

Received Sept. 24, 2013; revised Oct. 21, 2013; accepted Oct. 24, 2013.
I thank Birte Forstmann, Quincy Rondei, and Wouter Boekel for valuable discussions.
Correspondence should be addressed to Dr. Matthias Mittner, Cognitive Science Center Amsterdam, University of Amsterdam, Nieuwe Achtergracht 129, 1018 WS Amsterdam, The Netherlands. E-mail: mittner@uva.nl.
DOI:10.1523/JNEUROSCI.4084-13.2013
 0270-6474/13/3318710-02$15.00/0

tion from multiple networks. The ICNs to which these nodes connected contained, among others, the DMN, DAN, cognitive control, and salience networks. However, each echo-node had a specific pattern of networks that were and were not mirrored, suggesting higher-order, functional specialization. The authors applied their analysis to two independent datasets, one using resting-state data ($n = 25$) and one implementing a choice reaction time task (CRT, $n = 15$). Beyond a mere replication, the CRT-dataset exhibited theoretically expected modulations of the associated networks (reduced DMN echoes, increased higher-order visual and salience network echoes), which is a further argument for the method's validity.

Braga et al.'s (2013) results have strong theoretical implications for the understanding of the default-mode network. Some of the nodes identified by their method (in particular the PCC and precuneus) are commonly seen to be part of the core hubs of the DMN. Correspondingly, Braga et al. (2013) propose that the observation of a coherent DMN is actually an artifact of the summation over the activity of many ICNs converging on the central DMN nodes where they are echoed in distinct subparts. The task-related deactivation of these nodes could then simply be explained by a lower number of specialized ICNs involved in solving simple experimental tasks. This interpretation fits remarkably well with previous research on the functional specialization of different DMN nodes. Andrews-Hanna et al. (2010) found that, rather than being a functional entity, the DMN is fractionated into functionally and neuroanatomically distinct components that are connected by two hub nodes (the anterior medial prefrontal cortex and the PCC/precuneus). One of the subnetworks mainly involves the medial-temporal lobe, and one contains the dorsal medial prefrontal cortex. The data presented by Braga et al. (2013) strengthens and enhances this interpretation by providing evidence for multi-network integration in the PCC/precuneus even beyond these two subnetworks.

Furthermore, Braga et al.'s (2013) findings open a new perspective for the interpretation of research investigating functional connectivity, e.g., in the DMN, using classical seed-region-based approaches. Conventionally, to extract the DMN from resting state fMRI data, a relatively small region of interest in the PCC (e.g., a $3 \times 3 \times 3$ cube surrounding previously reported MNI coordinates) is used as seed region (Smith et al., 2012). Given the results from Braga et al.'s (2013) study that the PCC and precuneus are actually composed of spatially distinct subregions that connect to distinct functional networks, the exact location of the seed voxels can be crucial for the interpretability of the results: correlation maps based on slightly shifted seeds (e.g., resulting from different references and thus different seed coordinates being used) could result in qualitatively different results. For the PCC/precuneus, this effect has been shown in Margulies et al.'s (2009) study, in which distinct connectivity patterns emerged when a seed region within the precuneus and PCC was slightly shifted. Their finding indicates that rather than being a functional entity, the PCC/precuneus do indeed consist of spatially and functionally separate substructures that are differentially correlated with distinct networks. Critically, the results from Braga and colleagues (2013) now also pinpoint other structures in the brain that show a similar parcellation in terms of connectivity to distinct functional networks.

Finally, Braga et al.'s (2013) study is complementary to the work by Smith et al. (2012). Rather than using a spatial ICA, Smith et al. (2012) revealed spatiotemporal brain states [referred to as temporal functional modes (TFMs)] using temporal independent component analysis. These authors showed that some brain regions interact with different functional networks over time. This implies that these areas are temporally shared nodes of multiple networks in the sense that they communicate with different networks at different points in time. In contrast, Braga et al.'s (2013) study identified multi-network nodes based on the local node structure, i.e., they showed that some nodes are shared spatially between networks. Together, these two findings offer the exciting possibility that the dynamic pattern of network integration can potentially be revealed by a combination of the methodologies of the two studies: the application of Braga et al.'s (2013) searchlight-based method using temporal rather than spatial ICA. In such a design, the overlap with, e.g., the TFMs identified by Smith et al. (2012), would allow investigation of transient patterns of network integration in the identified echo-structures. Even though a searchlight-based approach using temporal ICA is inherently challenging due to the relatively unstable nature of temporal ICA (and, correspondingly, a large number of required samples), recent advances in the temporal resolution of fMRI acquisition will empower future work to pursue such a line of research.

References

Andrews-Hanna JR, Reidler JS, Sepulcre J, Poulin R, Buckner RL (2010) Functional-anatomic fractionation of the brain's default network. Neuron 65:550–562. CrossRef Medline

Baars BJ (2002) The conscious access hypothesis: origins and recent evidence. Trends Cogn Sci 6:47–52. CrossRef Medline

Beckmann C, Mackay C, Filippini N, Smith S (2009) Group comparison of resting-state FMRI data using multi-subject ICA and dual regression. Neuroimage 47[Suppl 1]:S148. CrossRef

Braga RM, Sharp DJ, Leeson C, Wise RJ, Leech R (2013) Echoes of the brain within default mode, association, and heteromodal cortices. J Neurosci 33:14031–14039. CrossRef Medline

Calhoun VD, Adali T, Pearlson GD, Pekar JJ (2001) A method for making group inferences from functional MRI data using independent component analysis. Hum Brain Mapp 14:140–151. CrossRef Medline

Christoff K, Gordon AM, Smallwood J, Smith R, Schooler JW (2009) Experience sampling during fMRI reveals default network and executive system contributions to mind wandering. Proc Natl Acad Sci U S A 106:8719–8724. CrossRef Medline

Leech R, Braga R, Sharp DJ (2012) Echoes of the brain within the posterior cingulate cortex. J Neurosci 32:215–222. CrossRef Medline

Margulies DS, Vincent JL, Kelly C, Lohmann G, Uddin LQ, Biswal BB, Villringer A, Castellanos FX, Milham MP, Petrides M (2009) Precuneus shares intrinsic functional architecture in humans and monkeys. Proc Natl Acad Sci U S A 106:20069–20074. CrossRef Medline

Smallwood J, Brown K, Baird B, Schooler JW (2012) Cooperation between the default mode network and the frontal-parietal network in the production of an internal train of thought. Brain Res 1428:60–70. CrossRef Medline

Smith SM, Miller KL, Moeller S, Xu J, Auerbach EJ, Woolrich MW, Beckmann CF, Jenkinson M, Andersson J, Glasser MF, Van Essen DC, Feinberg DA, Yacoub ES, Ugurbil K (2012) Temporally-independent functional modes of spontaneous brain activity. Proc Natl Acad Sci U S A 109:3131–3136. CrossRef Medline

Weissman DH, Roberts KC, Visscher KM, Woldorff MG (2006) The neural bases of momentary lapses in attention. Nat Neurosci 9:971–978. CrossRef Medline