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The elusive concept of brain network Comment on "Understanding brain networks and brain organization" by Luiz Pessoa

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As the poet John Donne said of man -"No man is an island entire of itself; every man is a piece of the continent, a part of the main." - so the neuroscience research community now says of brain areas. This is the topic that Luiz Pessoa expands upon in his thorough review of the paradigm shift that has occurred in much of brain research, especially in cognitive neuroscience [1]. His key point is made explicitly in the Abstract: "I argue that a network perspective should supplement the common strategy of understanding the brain in terms of individual regions." In his review, Pessoa covers a large range of topics, including how the network perspective changes the way in which one views the structure-function relationship between brain and behavior, the importance of context is ascertaining how a brain region functions, and the notion of emergent properties as a network feature. Also discussed is graph theory, one of the important mathematical methods used to analyze and describe network structure and function.

The insightful introduction to brain network analysis provided by Pessoa's paper starts with the age-old attempt by scientists at determining structure-function relationships. He argues, as have many others, that rather than thinking that specific brain functions are implemented by specific brain areas, it is better to think that brain networks are the units of behavior. Multiple examples are cited, including, for instance, a frontal-parietal network responsible for rapid adaptive control such as switching between different tasks [2]. This leads into an important discussion of the fact that a given brain region can be a member of several networks, with the context within which the region functions playing a significant role in determining the functional network it operates in – a notion articulated previously by McIntosh [3,4] and others [5]. As sophisticated brain imaging techniques have become more available, so too have the analysis methods used to investigate brain networks. Pessoa discusses several of these techniques, including graph theory [6,7].

Although alluded to in the paper, Pessoa does not spend much time discussing the underlying neural basis of how a brain region can shift from being a constituent of one network to being a member of another, depending on such factors as task instructions or context. A number of neurally based mechanisms, such as the action of modulatory neurotransmitters (e.g., dopamine) on synaptic functioning, can be proposed [8], but a

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significant source of this phenomenon lies with the neural populations comprising the specific brain region. For example, applying a network analysis method called structural equation modeling (SEM) to human functional brain imaging data, McIntosh et al. [9] showed that primary visual cortex was a member of both the visual object processing and the spatial processing cortical networks. This wasn't a particularly surprising result since it was known from nonhuman primate studies that there are multiple types of neuronal populations in primary visual cortex: some respond to color, some to shape, some to motion and so forth [10,11]. These different populations project to different brain regions in higher-order cortex. There is no reason to believe that any other cortical area that would constitute a network node does not contain multiple and diverse neural populations and thus that such an area could be a member of multiple processing networks. Now it may be that one could divide such a node into smaller structures, each functionally distinct (e.g., [12]), but it is likely that even structures as small as a single voxel will contain multiple neuronal populations [13]. Thus, a significant source of changes in functional/effective connectivity between two regions of interest is likely to correspond to which set of neuronal populations in each brain area responds to the combination of stimulus/context/task-instructions that is operative at a given time.

A second topic, related to the first, that I believe needs more emphasis concerns how does one determine what a change or difference in functional or effective connectivity means in terms of the underlying neural interactions. A change in connectivity can result, for example, from a change in the experimental condition. For instance, Pessoa gave an example in which presenting images of faces in an affective context to subjects resulted in an enhanced fMRI functional connectivity between early visual areas [14]. A plausible neurally-based explanation for the change in functional connectivity was that afferents from the amygdala modulated the ventral stream interregional connections. Differences in functional or effective connectivity between patients and healthy individuals are also targets of functional neuroimaging studies. Indeed, alterations in functional connectivity have been proposed as biomarkers for a variety of brain disorders [15,16]. For example, one of the earliest functional connectivity findings using resting state functional neuroimaging was a reduced anterior-posterior functional connectivity in patients with Alzheimer disease (AD) compared to healthy subjects [17], a finding that has been replicated multiple times with fMRI (e.g., [18]). In this case, the functional abnormality has been attributed to a reduction in cortico-cortical structural connectivity resulting from a loss of pyramidal neurons in AD patients [19, 20]. The question is how can such hypothesized interpretations of the functional connectivity be validated, or at least supported? Mostly, the way in which such interpretations have been justified is by means of converging experimental evidence. For example, if a reduced functional connectivity is found in a patient group relative to controls, and if it is also found using diffusion tensor imaging data that there is a reduced white matter tract in the patient group, then one can say that the structural results support the functional findings.

However, because brain networks consist of multiple nodes that can interact along a variety of direct and indirect pathways, the kind of converging evidence argument just discussed may be inadequate to account for the complexity of the large number of interactions simultaneously occurring in the network under study. I [21–23] and others (e.g., [24–27] have proposed that one can use large-scale, biologically realistic neural modeling to help understand the underlying neural mechanisms that manifest themselves in terms of the functional neuroimaging signals (both the regional activations and the interregional functional/effective connectivities). For example, Husain et al. [28] devised a large-scale neural model of the auditory object processing pathway in which simulated neuronal activities in each region were comparable to those measured in nonhuman primate electrophysiological studies, and in which the corresponding simulated fMRI BOLD signal in each region also displayed reasonable agreement with empirical human data. Comparisons to fMRI functional connectivities also were undertaken [23], although the agreement between simulation and experimental data was not as clear as one would have wished. These simulations explicitly demonstrated that the hemodynamic response function, because of its relatively slow temporal response to changes in neural activity, can muddy the interpretation of the fast neural changes in interregional neural connectivity that are taking place. A number of functional/effective connectivity analysis methods have been developed that have tried to overcome this problem (e.g., dynamic causal modeling [29], switching linear dynamic systems [30]). It also should be noted that one can use large-scale neural modeling to test how well such connectivity analysis methods actually work, since in a large-scale neural model, unlike the brain, the “answer” is known, and this allows one to see if the interpretation about the meaning of the changes in connectivity that is being proposed in fact corresponds to the changes that were made in the underlying neural architecture (see, for example, [23,31]).

In conclusion, Luiz Pessoa’s review article [1] is extremely valuable in demonstrating the way in which the network paradigm has become predominant in cognitive neuroscience, and indeed, in much of brain research. However, as I tried to indicate, interpretation of what the changes in network connectivity may mean remains elusive due to the complexity of network interactions. However, as I write, new data are being acquired, and new analysis methods are being developed, and thus, there is hope that progress can be achieved in how we understand brain network interactions.

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