Brain network science needs to become predictive

Comment on “Understanding brain networks and brain organisation” by Luiz Pessoa

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In his thought-provoking review of current concepts in neuroscience, Pessoa [1] addresses the ongoing paradigm shift of the field, in which the perspective has moved from individual nodes to distributed networks in order to account for distributed brain function. Within this perspective, Pessoa describes diverse aspects and topological features of brain networks that are potentially relevant for brain function. As he notes, however, the shift to networks does not solve all problems of linking brain function to structure.

In particular, Pessoa considers one issue to be central, the *correspondence problem* of mapping many functions to many elements, where a single element may contribute to multiple functions, and a particular function may involve many system elements. This problem is not simply resolved by attributing function to network features, such as modules, hubs, rich clubs, etc., instead of nodes. Nonetheless, it seems that the problem can be addressed in a straightforward manner by defining indices for participation, similar to the diversity profiles described by Pessoa, or comparable measures for localization and specialization derived from functional contribution matrices, e.g. [2]. In such approaches, which consider the functional contributions of a set of neural elements to a set of tasks, elements that are contributing highly and significantly to a particular task can be said to be *specialized* for the task, while functions that show particularly high involvement of some elements might be said to be *localized* in these elements. (Naturally, as also pointed out by Pessoa, an important question is how functions of neural elements should be defined in the first place. Any definition that is not matched to the actual biophysical, computational or functional properties of the elements is of little value [3].)

While the correspondence problem may be addressed in a straightforward way, there exist some other, fundamental problems of the network perspective, of which we outline two.

First, the role of statistical procedures in network research needs to be discussed on a much more fundamental level. Current research into brain networks is largely exploratory and focuses on issues such as computing centrality indices or evaluating whether the brain possesses small world features. It is important to note that there is little value *per se* in such explorative findings. The purpose of exploratory research is to help forming intuitions about the object at hand (i.e., the brain), but ultimately this intuition needs to lead to concrete hypotheses about the way the brain is organized and functions. Such hypotheses then need to be tested independently by sound statistical methods. Currently however, findings in network science are frequently interpreted in a circular way. For example, the fact that a network community detection algorithm re-discovers certain well-characterized brain regions is taken as evidence for the 'importance' of these regions, just confirming preconceptions. Instead, what is needed are concrete hypotheses and statistical tests. In the language of statistics, the research in brain networks needs to move from the exploratory mode to the confirmatory mode [4]. Of course, there is a huge problem: brain networks have a large amount of inherent randomness, and it is currently completely unclear how to deal with the induced variation both across measurement methods and across subjects by sound statistical procedures. We believe, however, that it is an urgent task to establish such procedures.

Second, a *causal attribution* of brain function to network elements cannot simply be based on functional correlation with properties of neural elements, whether they are individual nodes or more intricate network components. Pessoa notices this problem and seeks to address it by considering the *network embedding* of nodes. Ultimately, however, the only way to establish a causal relationship is by systematic perturbation of network elements and recording the associated change in performance. If this is done in all possible ways (i.e., by considering all individual lesions, as well as all couples, triplets, etc. in all possible orders), it becomes possible to quantify the causal contribution of each network element to network function in an exact and unique manner, using concepts from game theory [5]. While this approach provides a powerful way of characterizing functional contributions and interactions of *nodes*, an equivalent approach for identifying the causal contribution of *network features* appears harder to implement. After all, in the network perspective, circuits and features of connectivity such as motifs, loops, paths, hubs, modules and their combination are the basis of systems function, rather than individual elements. Such features, however, cannot be simply enumerated. Moreover, many currently considered features of brain networks are confounded [6]. Nonetheless, a systematic manipulation or perturbation of features remains key to address the issue of causal attribution of brain function to network elements.

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References

[1] Pessoa, L (2014) Understanding brain networks and brain organization. *Phys Life Rev*, http://dx.doi.org/10.1016/j.plrev.2014.03.005 [in this issue]
[2] Ruppin, E (2002) Evolutionary autonomous agents: a neuroscience perspective. *Nat Rev Neurosci* 3, 132–141
[3] Young, MP *et al.* (2000) On imputing function to structure from the behavioural effects of brain lesions. *Phil Trans R Soc Lond B* 355, 147–161; Uttal, WR (2004) Hypothetical high-level cognitive functions cannot be localized in the brain: Another argument for a revitalized behaviorism. *The Behavior Analyst* 27, 1
[4] Tukey. JW (1980) We need both exploratory and confirmatory. *The American Statistician* 34, 23-25
[5] Keinan, A *et al.* (2004) Fair attribution of functional contribution in artificial and biological networks. *Neural Comput* 16, 1887–1915; Keinan, A *et al.* (2006) Axiomatic scalable neurocontroller analysis via the Shapley value. *Artificial Life* 12, 333–352
[6] Bounova, G and de Weck, O (2012) Overview of metrics and their correlation patterns for multiple-metric topology analysis on heterogeneous graph ensembles. *Phys Rev E* 85, 016117