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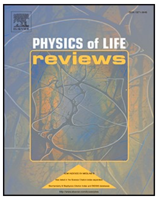

Reply to Comment

Beyond task-based connectivity in fMRI: Reply to comments on “Connectivity analyses for task-based fMRI” by Shenyang Huang, Felipe De Brigard, Roberto Cabeza, Simon W. Davis

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In Huang et al. [1] we offered an introductory review of some of the most widely used task-based connectivity analyses for fMRI data. The generous comments we received on our work revolve around five issues: 1) the lack of discussion on dynamic causal modeling (DCM); 2) the fact that graph-theoretical approaches may be ideal to interpret task-based connectivity in fMRI; 3) evidence that moment-by-moment fluctuations, which are often overlooked in some connectivity analyses, may actually provide key information; 4) the concern that the multiplicity in task-based connectivity approaches risks having results that are essentially incommensurable across research groups, and 5) the issue that lack of physiological and psychological rigor in connectivity and multi-voxel pattern analysis potentially complicate the advancement of task-based fMRI research. We discuss these points in turn.

The first comment, voiced by **Di, Zhang, Zhang and Biswal**, concerns the fact that our review did not include DCM, a somewhat popular analytic framework in fMRI used to model how different brain regions causally influence each other [2]. In general, DCM employes bilinear differential equations to characterize neural and hemodynamic changes, task-based modulations, and intrinsic or task-free connectivity among regions. Model inversion is then implemented using variational Bayes to estimate best fit, given set parameters in the model (e.g., priors), in order to test causal hypotheses in the system [3,4]. Since its inception, as Di and colleagues mention, DCM has been widely and successfully employed to interrogate task-based connectivity data in fMRI, yielding interesting and valuable results [5]. Yet our decision to exclude DCM from our review was deliberate but had nothing to do with the merits of this analytic approach. The main reason, as the authors themselves may suspect, is that our review focuses on functional as opposed to effective connectivity approaches currently employed in task-based fMRI. We reasoned that if we were to include effective connectivity approaches as well, we would have had to discuss not only DCM, but also other related methods, such as Granger Causality [6], structural equation modeling (SEM; [7]), Direct Transfer Function [8], and Partial Directed Coherence [9], to name a few. Moreover, DCM requires a number of modeling assumptions that have been extensively questioned and debated (e.g., [10,11]). The same is true of other effective connectivity methods, such as Granger Causality [12] and SEM [13–15]. As a result, a thorough and even-keeled discussion of both functional and effective connectivity approaches would have turned our review into a much longer paper and, likely, a less focused one.

A second comment, by **Khodaei, McIntyre, Kirse and Laurienti**, serves as an invitation to understand the import of task-based

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fMRI connectivity findings within a graph-theoretical approach. Although we briefly considered graph theoretical approaches in our review, we expand here on our discussion. The idea of seeing the brain as a reticular biological network is not new [16], but the use of the mathematical formalisms of topology and graph theory to try to understand its intricate connectivity is somewhat recent. From this perspective, a network can be thought of as a collection of differentiable elements, or *nodes*, and the pairwise relationships between them, or *edges*. In the case of large-scale brain networks, nodes typically represent brain regions, while edges typically represent anatomical, functional, or effective connections [17,18]. In the case of functional connections, edges are defined as temporal correlations and/or statistical dependencies in the activity of two brain regions or nodes. Graph theory formalizes these arrays of bivariate connections as a topological analysis of matrices and offers an ever-growing list of metrics to describe [19] them [17,20]. At the most basic level of description, metrics like *degree* simply sum the number of edges connected to a node, from which average connectedness can be inferred. The *characteristic path length* measures the average number of edges along the shortest paths between all pairs of nodes, which allows to infer how efficiently information travels through the network. More complex metrics, such as *controllability*, assess how influential a node may be on global network states or state changes—an inference based on this metric's quantification of the entropy associated with moving between low or high eigenmodes of the matrix [21]. Advanced algorithms can also identify modules—clusters of nodes that are more densely connected to each other than to the rest of the network [22,23]. For instance, the modularity algorithm by Blondel et al. [24] can detect non-overlapping modules within functional brain networks. The extent of this modular organization is quantified using the Q statistic:

$$Q = \sum_{i=1}^{k} \left[\frac{e_{ij}}{M} - \left(\frac{a_i}{M} \right)^2 \right]$$

where e_{ij} is a measure of within-module connections for module i, a_i is the total number of connections in module i, and M is the total number of connections in the entire network. Modularity algorithms are designed to maximize the value of Q [24], thus giving the optimal solution for a functional modular structure [25,26]. This algorithm is currently the dominant means by which research labs classify cortical regions into canonical networks (e.g., default mode network).

As neuroscience develops, new graph-theoretic metrics emerge. Yet, in addition to the persistent algorithmic novelty of graph analysis of the brain, inferential and interpretive challenges remain about what these graph properties actually reveal about the brain, and how they can inform task-based connectivity (see Section 4 in our Review). Three controversies are suggested here. First, take for example the concept of modularity, which in its most popular form establishes each node's allegiance to a single module. Three-quarters of the authors of this review are old enough to remember neuroscientists claiming that "the ACC does everything", so discretizing individual nodes to non-overlapping networks belies the flexibility of cortical regions in performing overlapping cognitive processes. Work from Laurienti's group has pioneered algorithms characterizing this flexibility [27,28], affording for modularity schemes that generate overlapping nodes that are more representative of typical task-related fMRI patterns. Second, an honest account of the development of graph techniques towards functional imaging must acknowledge that many of the assumptions and intuitions about multivariate cortical organization rely on resting-state fMRI [29]. Easy to collect and agnostic to pesky psychometric design decisions, resting state matrices have become a convenient currency for the development of graph analysis of functional brain data. It is now common practice to relate resting connectivity metrics to cognitive scores tested outside the scanner, but such approaches do not afford a rigorous means of linking connectivity directly to cognitive theory. Lastly, reducing the brain's biological complexity to nodes and pairwise connections inevitably overlooks a vast amount of meaningful detail. In practice, network models are highly abstract representations. While this abstraction allows for powerful forms of analysis, it also introduces ambiguity, making it difficult to interpret how the formal structures of the models relate to the actual biological systems they aim to represent. Indeed, some have argued that given the abstract nature of network models in neuroscience, they are *not* representations of actual mechanisms, thus reducing their causal and explanatory power [30]—notwithstanding their potential as predictive tools [31]. Recent proposals have even suggested that networks identified by graph-theoretical approaches should be considered as the functional units of the brain, likely requiring a complete overhaul of the more localizationist program that fueled the creation of cognitive neuroscience [32,33]. While it is difficult to argue against cortical interaction as a fundamental property of cognition, such a paradigm shift is quite a tall order. Generalizing the function of multimodal, interactive systems to threatens our understanding of how the subcomponents of such a system might work under different task conditions [34,35]. Further research is certainly needed to fully merge cognitive and network neuroscience as a unified research program.

In the third comment, **Coutanche** reminds us that most representational connectivity methods collapse across time series, typically to maximize signal. However, in so doing, these methods remove information about temporal fluctuations in the signal through the task that are likely informative about the neural and cognitive processes of interest. By bringing together functional connectivity and multi-voxel pattern analysis (MVPA), informational connectivity allows to identify functionally connected brain regions whose patterns of activation through the time series are both synchronized and discriminable [36,37]. As such, a case can be made to the effect that informational connectivity is preferable to representational connectivity methods that collapse across time series, mainly because it can give you not only what the latter offers but also additional temporal information. We offer two thoughts in response to this observation. First, while it is likely that Coutanche is correct in thinking of informational connectivity as superior to other representational connectivity approaches (some of which have other issues of their own, [38]), in our paper we tried our best to offer an unbiased review of extant approaches to identify functional connectivity in task-based fMRI. As a result, we leave to the reader to judge the potential advantages and disadvantages of each method. Second, and relatedly, the analytic method a researcher decides to employ is highly contingent on their particular research question, the structure of the experimental design, and even the features of the scanner and the imaging sequence. As a result, it is unadvisable to proclaim that one method ought to always be preferred over another, since there may be specific instances for which such generalization simply will not apply.

Interestingly, this last point dovetails with the fourth comment on our paper, in which **Uddin** raises a valid and urgent concern revealed by our review, namely “that there is a tremendous amount of variability in the literature [on task based functional connectivity in fMRI] that is due to research degrees of freedom, or flexibility in researcher’s analytic choices” (p. 20). The field of resting-state connectivity has faced a similar challenge, in response to which the Organization for Human Brain Mapping (OHBM) commissioned a group of neuroscientists to come up with a set of “best practices” to collect, analyze, and report resting-state functional connectivity fMRI data [39]. The possibility of standardizing not only the nomenclature and vocabulary in resting state connectivity, but also to more objectively and quantitively compare resting-state connectivity results from different labs, is a step in the right direction to increase the validity and generalizability of these findings [40]. We certainly agree and believe that the field would benefit if similar efforts were taken to guarantee the commensurability of task-based connectivity measures across different research groups.

Such a path forward is suggested by the final comment on our Review by **Ladyka-Wojcik and Ritchey**, who suggest that a rigorous science of task-related connectivity will draw from conceptual precision and methodological rigor. Like Uddin, they raise significant concerns about noise from physiological artifacts that “might impact estimates from multi-voxel activity patterns and their derived connectivity measures” (p. 102), and also highlight that noise reduction constitutes a major challenge for task-based connectivity analyses [41]. Thankfully, a number of approaches to improve signal quality in fMRI are now available, including methods based on independent component analysis (e.g., ICA-FIX and ICA-AROMA, [42,43]) as well as component-based noise correction (e.g., CompCor; [44]). As discussed above, the appreciation of these factors has received much attention in the analysis of resting state fMRI data, and task-based functional connectivity owes much to the fastidiousness of resting state researchers in establishing reliable preprocessing protocols to minimize these physiological artifacts [45]. But as Ladyka-Wojcik & Ritchey suggest, the expansion of methodologies for task-related connectivity beyond bivariate connectomes will require additional consistency. Researchers interested in task-based functional connectivity in fMRI may seek to maximize signal-to-noise ratio in the BOLD signal by reducing noise due to physiological artifacts. But beyond physiology, consistency in both psychological design and the network-level target of study will be necessary for task-based connectivity to improve scientific rigor. In this respect, the notion of process-specific alliances (or PSAs) offers some effective framework for thinking about how small teams of brain regions might rapidly assemble to mediate a cognitive process [46]. The same PSA (e.g., PFC + primary visual cortex), might assemble to mediate attentional modulation of visual processing across a range of tasks, but in contrast to resting networks, PSAs afford the possibility of thinking of the brain as a dynamic, overlapping regions that offer a component-based explanation of neurocognitive processes, and which can be directly (and not implicitly) linked to cognitive theory.

All told, we find points of confluence: appreciation for the diversity of techniques, and acknowledgement that fMRI data is noisy and collective efforts to reliably account for motion and other physiological artifacts are critical for the future of connectivity analysis. And we find points of contention: identifying the appropriate technique, and the proper conceptualization of terms like “network” and “connectivity”. It is our shared understanding of these complimentary and competing views, and our willingness to incorporate those views into reviews such as this, which we believe will ultimately lead towards better science of cognitive connectivity. As such, we thank the authors for their essential viewpoints on the proper review of task-based connectivity and celebrate their contributions to our shared endeavor.

Declaration of competing interest

The authors declare no conflicts of interest.

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