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Reply to comment

Reply to comments on "Foundational perspectives on causality in large-scale brain networks"

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We thank all the commentators on our paper, whose expertise and insight have proved to be invaluable for refining our thoughts, and for future considerations of the concepts discussed in our paper. Overall, the comments represent a variety of viewpoints, each coming from an individual niche of knowledge and presented in a constructive manner. Moreover, we thank the editor of this journal for allowing us the chance to respond publicly to (public) comments on our ideas.

Our source paper attempts to provide a foundational framework for causality in the brain, considered as a complex system. The term causality (or causation) is widely used in cognitive and computational neuroscience, and such a deeply-rooted philosophical term requires a full, rigorous, conceptual analysis. As Griffiths [4] correctly states, "The appropriate characterization of causality in neural systems, therefore, is a question at the very heart of systems neuroscience." Moreover, in terms of large-scale neurocognitive networks, given that nodes or regions may influence one another in a variety of ways, we find it appropriate to ask, what does "causal influence" mean in the context? Thus, our paper tries to define the epistemic limitations and ontological suppositions about causality in the brain. Finally, in our paper, we wrestle with an important question: is the human brain a deterministic or nondeterministic system?

First, Pessoa and Najafi [1] take an interesting, broad-minded approach to causality in the brain, considered as a complex system. We have no argument with their preferred term "complex system causality" to replace our "probabilistic causality (PC)", as long as it is clear that complex systems causality is, in fact, probabilistic. Although they confirm our overall claim that classical conceptions of causality fail when considering the brain's structural and functional networks, Pessoa and Najafi are largely concerned with disentangling the contributions of different systems,

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such as those for cognition and emotion. We agree that the issue of decomposability is essential for understanding brain function. In many complex systems, a large number of parts interact in ways that do not allow for any one part to be analyzed in isolation, as in their coupled billiard ball example. As they state, "... simple ways of reasoning about causation are inadequate when unraveling the workings of a complex system such as the brain." They go on to suggest that removing the focus on causation as explanation in neuroscience is the appropriate tactic in this case. In the context of dynamic brain networks, their suggestion is to offer a mathematical formalism that describes the multivariate covariance structure of brain data, of which one particular example is the Bayesian Dynamic Covariance Model. This model considers the covariance between pairs of brain regions, and includes a previously missing component, a time-varying matrix, which allows for a temporal regression. We agree that this model may give considerable insight into brain networks. However, it does not explicitly address the critical issue of causal influence in the brain. We question the reliance on the covariance (or correlation) structure of neural data, and propose that the causal influence structure of the data is more informative and neurobiologically realistic.

Tang [2] underscores our point that Wiener–Granger Causality (WGC), and similar methods, work by quantifying PC, which offers a theoretical framework for explaining why these methods are successful at measuring functional connectivity. Furthermore, along the lines of Barnett and Seth [3], Tang suggests that state space modeling may be a useful addition to WGC for characterizing PC in hidden states. This is an interesting suggestion that nicely extends the notion of PC to hidden states.

Griffiths [4] makes some astute (and well-received) observations that justify our project, as well as a challenge to our thesis. First, Griffiths points out that our proposal "resonates well" with the probabilistic notion of causality, especially with what he calls *phenomenological* approaches, which rely on directly observed variables. He stresses, however, that these approaches are inherently different from others, such as DCM, which he labels *physiological*. Physiological approaches are not causality-centric in that they do not *infer* causal relations, but rather *assume* them. Griffiths rightly proposes that the PC formalism be expanded to include the "mechanistic" causal relations implicit in the physiological approach. We agree that such an expansion would be an interesting development, and could be theoretically possible. In fact, we consider the field of causal modeling, particularly the work of Judea Pearl [5,6], as providing this kind of development. Briefly, we follow Hitchcock [7] in suggesting that Pearl's Bayesian approach to causal modeling can be used to infer underlying causal structure by "using information about probabilistic correlations." Although we cannot provide an in-depth analysis of the causal modeling approach in this short Reply, we note that Pearl's a structural causal model consists of a set of structural equations, where each equation represents a mechanism or "law" working in the world. Formally, it consists of an ordered triple set $\langle U, V, R\rangle$, where U is a set of exogenous variables, V is set of endogenous variables, and R is the set of structural equations which govern the relationships of these variables. Causal graphs or diagrams, including directed acyclic graphs and casual loop diagrams, usually accompany the model to visually represent these relationships. We believe that, in the future, Pearl's approach may offer the appropriate expansion that Griffiths rightly asks for. Already, White et al., [8] have linked Pearl's work to WGC.

Kozma and Hu [9] take a different approach in their commentary. They state that they strongly support our claims, and offer two additional examples which give further support to our notion of causality in the brain. First, they acknowledge our claim that PC is better able to handle issues of spurious causality when analyzing neurobiological data, and they extend our introduction of PC by introducing what they refer to as New Causality (NC) [10]. First, they claim that this new concept of causality is "less susceptible to spurious causal effects" and has already been applied to human EEG data. We agree that NC may indeed be a practical extension of PC. Second, Kozma and Hu consider the mathematical theory of neuropercolation to support PC, because it describes the brain in terms of self-organizing criticality, in which neural networks follow phase transitions from coherent to non-coherent phases. Although neurons are overwhelmingly local entities, they can also exert non-local effects due to axonal projection. Interestingly, and partly because of these phase transitions, neuropercolation "incorporates Freeman's principles of neurodynamics". We agree that, in the context of complex systems, Freeman's neurodynamical theory fits well with our notion of PC, and phase transitions are important for understanding brain network function. We speculate that neural phase transitions represent a change from one coordination state to another (Bressler & Kelso, 2015), and that probabilistic causal relations are exerted as brain areas interact within a coordination state. Finally, Kozma and Hu suggest that the concept of *circular causality* is more suitable than *linear causality* in large-scale brain networks. We agree that a substitute for linear causality is called for in complex systems. However, we prefer the term *mutual*