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Comment

Critical perspectives on causality and inference in brain networks: Allusions, illusions, solutions? Comment on: "Foundational perspectives on causality in large-scale brain networks" by M. Mannino and S.L. Bressler

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1. Allusions: What does causality in the brain really refer to?

The human brain is an impossibly difficult cartographic landscape to map out. Within it's convoluted and labyrinthine structure is folded a million years of phylogeny, somehow expressed in the ontogeny of the specific organism; an ontogeny that conceals idiosyncratic effects of countless genes, and then the (perhaps) countably infinite effects of processes of the organism's lifespan subsequently resulting in remarkable heterogeneity [1,2]. The physical brain itself is therefore a nearly un-decodable "time machine" motivating more questions than frameworks for answering those questions: Why has evolution endowed it with the general structure that is possesses [3]; Is there regularity in macroscopic metrics of structure across species [4]; What are the most meaningful structural units in the brain: molecules, neurons, cortical columns or cortical maps [5]? Remarkably, understanding the intricacies of structure is perhaps not even the most difficult aspect of understanding the human brain. In fact, and as recently argued, a central issue lies in resolving the dialectic between structure and function: how does dynamic function arises from static (at least at the time scales at which human brain function is experimentally studied) brain structures [6]? In other words, if the mind is the brain "in action", how does it arise?

Despite the countably finite number of published studies using *in vivo* and other neuroimaging techniques, Mannino and Bressler articulate an uncomfortable ontological truth: Understanding causal interactions between brain structures is a non-trivial problem that cannot merely be surmounted by mountains of data [7]. After all, the brain concedes

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signals quite readily, a technical question that Angelo Mosso remarkably enough began to tackle in the late 19th century [8], and currently is being addressed using multiple imaging modalities. The central question of interest in theoretical neuroscience is the discovery of hidden brain "states" from which these emergent signals emerge [9], a problem that requires us to reverse engineer ourselves towards understanding "neural" interactions [10]. Where within these hidden states might we find causality and what form might such causality assume?

2. "Causal" illusions: A brief history of causality

To highlight the complexity of this question, the authors elegantly outline a comprehensive narrative arc on the relatively recent history of "causality" itself. They first discuss the notion of deterministic causality, enshrined as an emergent property of Newtonian physics, before then ultimately transitioning to current modifications of the notion of causality in the physical world, informed by discoveries in quantum mechanics and quantum entanglements. The journey is brisk, yet illuminating. David Hume's empiricism is considered, an early approach at addressing the ontology of causality through perception and the regularity of events, resulting in the subjective experience of causality. Yet in many ways Hume's considerations were not material to the fundamentals of what the term "causality" really means. The authors then turn to Immanuel Kant's explicitly psychological theory of causality as a category emerging from *a priori* representations that act to process empirical knowledge. As the authors imply, the philosophical Worlds of Hume and Kant emerged from Newton's Universe: Mechanistic order could be modeled by mathematics, an inherently deterministic system. This philosophical world was doomed once the universe on which it was based needed substantive modification. The authors correctly credit Bertrand Russell with insights on the bases of causality that were far ahead of his scientific time, preceding the maturation of quantum mechanics as a fundamental theory of the physical world. In his 1913 classic paper, Russell dealt with causality not in terms of its psychological, but in terms of its ontological basis, suggesting the phrase "functional relations" as a substitute for "causal relationships" between events. In fact, the concept of "functional relations" is almost ideally suited to describing relationships between brain units. When the author's do extend the concept of causality to brain interactions, they invoke the term in a probabilistic (or quantum sense). But before considering causality in large scale brain networks, we must consider what "neural activity" is [11].

Far from being a single and simple unitary construct, "neural activity" does not describe a single process with *specific* functional consequences. Rather the brain is characterized by multiple classes of neural activity within, and across its spatial scales, with these classes of neural activity having distinct or overlapping functional correlates [12], forming complex hierarchies [13]. Mannino and Bressler invoke three concepts crucial in understanding both functional interactions between the brain's constituents, and why deterministic causality is a logical impossibility: First is the notion of mutual causality, a characteristic of brain units (at least at measurable time scales) wherein they exert near contemporaneous effects on each other. The second is the notion of multiple (and therefore causally indeterminate) inputs to single units within the brain, an anatomical lattice that is characteristic of the brain's known architecture. And a third feature is the fact that neurons themselves function as threshold units, such that their outputs (one class of "neural activity" alluded to earlier) may or may not reflect influences from other neuronal populations (leading to indeterminacy in the causal basis of brain signals; more on this below). These three considerations alone highlight the murkiness of thinking of causality between neural units (regardless of spatial scale). The world of the brain is not the world of Newtonian mechanics. Rather it is a world of complex entanglements best explained from the framework of probabilistic rather than deterministic effects.

3. "Solutions": Do formal computational solutions for understanding causality exist?

Implicit in the Mannino and Bressler thesis is the idea that divining causality among constituents in large-scale brain networks is almost impossibly challenging. For while the notion of probabilistic causality is the only viable version of the causality construct, problems abound. For one thing (and not explicitly considered by the authors), the relationship between observed brain signals and the presumed "hidden" states that give rise to them may be close to being indeterminate. The limitations of functional magnetic resonance imaging (fMRI) are highly illuminating in this regard [14]. Despite being the *in vivo* neuroimaging tool of overwhelming choice, current fMRI is blind to aspects of neural activity that we know to be exquisitely detailed, and the technique is thus unable to reliably characterize excitatory–inhibitory circuits within cortical layers, parse apart top-down and bottom-up influences or distinguish