REPLY TO BARNETT ET AL.:

Regarding interpretation of Granger causality analyses

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The main points of our work were (*i*) to characterize statistical properties of the traditional computation of Granger–Geweke (GG) causality and (*ii*) to analyze how the dynamics of the system are represented in the GG-causality measure.

Barnett et al. (1) point out that the issues with bias and variance in the conditional GG causality can be addressed using a state-space approach and a single-model fit. We certainly agree that this is the case and demonstrated this in the doctoral thesis by Stokes (2). We also acknowledge that the MVGC toolbox uses a single-model fit as described in ref. 3 (a correction has been submitted to address this error). Unfortunately, many investigators still use separate model fits. We hope our article in PNAS (4) raises awareness of the problems with doing so, particularly in frequency-domain analyses, which again can be avoided by using appropriate state-space methods under a single-model fit.

Barnett et al. (1) emphasize that Granger causality reflects a "directed information flow." But how does one meaningfully interpret that information flow? In neuroscience studies the objective is typically to characterize the mechanism of some observed effect. However, as we have shown, the dynamics of the effect nodes are absent in GG causality (4). Ignoring these observed dynamics is simply not compatible with the goal of understanding them.

Barnett et al. (1) make a distinction between physiological or "physical causal mechanisms" and "directed information flow." However, we perceive that in practice the need to interpret and ascribe meaning to data analyses would tend to lead investigators to interpret "directed information flow" in mechanistic terms. So, the notions of "information flows" versus mechanisms, though distinct in the abstract, are less distinct in practice.

While GG causality is decipherable in reference to the selected model and its component dynamics, it is not understandable without these details. Unfortunately, many studies employing GG causality do not provide the estimated model, or a breakdown of its component dynamics, and instead treat causality alone as "the result." In doing so, investigators also overlook that GG causality is a statement about the chosen model and the product of the model selection and fitting process. If a different model is chosen, then the causality may obviously change, and if the model is inadequate for the data or question, then any subsequent inference will be worthless.

We focused our analysis on GG causality. However, we also expressed concerns that other causality measures with distinct formulations and properties might have their own interpretational problems, complicated further by the fact that these methods are often referred to interchangeably as "Granger causality." We certainly believe it is possible to quantify directed dynamical influences in ways that correspond appropriately to different scientific questions of interest, but doing so will require closer partnerships between neuroscientists and quantitative scientists. In the meantime, as we suggest in ref. 4, a good starting point would be for analysts to pay more attention to the underlying models, the dynamics they represent, and the overall modeling process, all of which form the foundations for subsequent inferences on directed influences.

1 Barnett L, Barrett AB, Seth AK (2018) Misunderstandings regarding the application of Granger causality in neuroscience. *Proc Natl Acad Sci USA*, 10.1073/pnas.1714497115.

2 Stokes PA (2015) Fundamental problems in Granger causality analysis of neuroscience data. PhD thesis (Massachusetts Institute of Technology, Cambridge, MA).

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The authors declare no conflict of interest.

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3 Barnett L, Seth AK (2014) The MVGC multivariate Granger causality toolbox: A new approach to Granger-causal inference. *J Neurosci Methods* 223:50–68.
4 Stokes PA, Purdon PL (2017) A study of problems encountered in Granger causality analysis from a neuroscience perspective. *Proc Natl Acad Sci USA* 114:E7063–E7072.