Open Peer Review on Qeios

Big Data, Granger Causality Analysis, and the Undecidability Property of Neuroimaging

Patrick Bloniasz[1]

1 Boston University

Funding: The author(s) received no specific funding for this work.

Potential competing interests: The author(s) declared that no potential competing interests exist.

Abstract

Much excitement has surrounded the idea of ‘big data’ and its potential to drive science into a new epistemological era–one of data-intensive exploration. However, there are open interpretive questions regarding how to interpret results derived from such massive and (nearly)-complete data sets. One view of big data, called here the ‘End of Theory’ (EOT) view, advocates that identifying statistical patterns in large data sets is sufficient for generating scientific results. The present paper demonstrates that EOT is untenable in at least one big data environment in neuroscience: Granger causality analysis (GC). The present paper systematically outlines the foundations for GC and its neural correlate Granger-Geweke causality analysis (GGC) by drawing on statistics and information theory. In doing so, the present paper introduces new terminology that clarifies the role of GGC in the era of big data and establishes a standard for result interpretation. Specifically, the “undecidability property of neuroimaging” (UPN) is introduced. The need for UPN is demonstrated by the concept resolving an existing conflict in the literature that occurred in the late 2010s between Barrett *et al.* (2018a; 2018b) and Stokes and Purdon (2017a; 2017b). UPN is then applied to a current research thread in cognitive neuroscience to develop a standard for how to interpret positive and null results from GGC during big data ‘exploratory analyses.’

Patrick F. Bloniasz[1,2,3]

[1] Program in Neuroscience, Bowdoin College, Brunswick, Maine, United States, 04011

[2] Program in Digital and Computational Studies, Bowdoin College, Brunswick, Maine, United States, 04011

[3] Center for Computational Neuroscience and Neural Technology, Boston University, Boston, Massachusetts, United States, 02215

Introduction

Much excitement has surrounded the idea of ‘big data’ and its potential to drive science into a new epistemological era–one of data-intensive exploration. Extensive, (nearly-)complete data sets allow researchers to use powerful algorithms to uncover patterns in data that were not previously apparent. Neuroscience, especially cognitive

neuroscience, has borrowed generously from the impact of big data approaches (e.g., computational cognitive neuroscience). At the forefront of this movement in neuroscientific data analysis is neuroimaging; in other words, since at least the early 2010s, "it is safe to say that human neuroimaging is now, officially, a 'big data' science" (Van Horn & Toga, 2014, p. 324).

While neuroimaging techniques are not new, the big data label typically amounts to the newer approach of using supervised or unsupervised algorithms to sift through immense data sets to uncover statistical relationships that a researcher would previously test by hand. Consider one example of an old technique receiving updated attention: electroencephalography (EEG). Developed in 1929, EEG is able to record extensive data sets quickly with great temporal resolution at a reasonable cost (Tudor et al., 2005). Aided by big data environments, EEG's capability has been extended by using deep learning algorithms to analyze time series for clinical purposes, such as in studying epilepsy (Golmohammadi et al., 2019; Yedurkar & Metkar, 2020) or by automatically analyzing data produced by massive numbers of participants.

While what constitutes a 'big data' approach is often vague, it is helpful to think of these computational approaches as an automatic exploratory analysis. Typically, a researcher using standard hypothesis-based statistical tests will use theory and previous empirical work to develop detailed hypotheses. Then, using data collected within a given experimental context, a hypothesis will be tested for practical and statistical significance. Conversely, big data approaches allow for new hypotheses to be identified by analyzing underlying statistical dependencies outside of the original scope of research.

While promising, there is an open epistemological question of how to characterize the use of big data approaches as exploratory analyses. To clarify what is at stake, I borrow the framework provided by Kitchin (2014) which presents at least two possibilities for how big data can impact neuroimaging. Kitchin (2014) thoroughly described two camps as advocating for either 1) a radically new 'data-driven science' or 2) a form of neo-'empiricism.'

The new data-driven science "seeks to hold to the tenets of the scientific method, but is more open to using a hybrid combination of abductive, inductive and deductive approaches to advance the understanding of a phenomenon" (Kitchin, 2014, p. 5). The novelty of this view comes from using big data to generate hypotheses to further explore possible connections or phenomena that were unlikely, or impossible, to uncover previously. This view does not erase the scientific ideal of deductive, causal reasoning, but rather adds a precursive layer of induction *before* deduction by finding patterns in the data.

The neo-'empiricism' view advocates for the end of theory–in other words, data explain themselves. For example, consider Chris Anderson (2008), former editor of the journals *Nature* and *Science*, writing in an online commentary piece in WIRED, saying:

> *The data deluge makes the scientific method obsolete…There is now a better way. Petabytes allow us to say: 'Correlation is enough.' … We can analyze the data without hypotheses about what it might show. We can throw the numbers into the biggest computing clusters the world has ever seen and let statistical algorithms find patterns where science cannot … Correlation supersedes causation, and science can advance even without coherent models, unified theories, or really any mechanistic explanation at all. There's no reason to cling to our old ways.*

Let this view be called the 'end of theory' (EOT) view, where EOT states that patterns identified in data using big data environments stand on their own as valid findings. While few are as crass as Anderson in their position regarding the potential for big data, there is reason to be careful and explain the implications such a view, held implicitly or explicitly, has on data interpretation in any given context.[1] In neuroimaging research, there is a need to understand the implications of assuming EOT, or some version of it, in analyzing large data sets because discourse in this area is severely lacking. The present write up will ultimately show that, at least in one area of big data science, EOT necessarily results in spurious or ambiguous results due to what I call the "Undecidability Property of Neuroimaging" (UPN) that is intrinsic to measurements generated from neuroimaging.

The present paper discusses one exceedingly valuable hypothesis test, Granger causality analysis (GC) and its neural correlate Granger-Geweke causality (GGC) analysis in the context of extracranial EEG neuroimaging. GC typically refers to a class of statistical techniques (i.e., there are many test derivatives) that are considered to be "big data environment[s]" (Song & Taamouti, 2019) and therefore fall within the aforementioned epistemological debate. GC utilizes characteristics of time series (e.g., time lags of an EEG channel recording) and tests whether those characteristics are useful in predicting another distinct time series, or set of time series, at some later time. The interpretation of there being a statistical relationship between the selected time series is that of 'information' flowing from one process to another.

The analysis offered in this paper demonstrates that when looking at GGC closely through the lens of neuroscience and information theory, both of which are required for giving GGC meaning in EEG research (Dimitrov et al., 2011), it will become clear that the EOT view is incompatible with creating valid biological GGC interpretations due to UPN. In making this argument, the present article will contribute to understanding the uses and misuses of 'big data' approaches or environments in neuroimaging, as well as to offer some guidance on interpreting results using GGC in EEG research. It will demonstrate that GGC can be used in exploratory science to generate new hypotheses to explore, but cannot provide evidence to reinterpret existing uncorroborated hypotheses.

Stokes and Purdon (2017a, 2017b) attempted to raise a concern similar to UPN, which was unnamed in their papers, but they failed to sufficiently communicate the point. This led to an existing debate in the literature between Barrett *et al.* (2018a, 2018b) and Stokes and Purdon (2017a, 2017b) regarding how information flow can be interpreted biologically. UPN resolves this well-known debate–a debate which makes clear what is at stake when the EOT view is applied to Granger causality tests.

Section 1 will offer a brief historical introduction to the original test of Granger causality, which originated in economics (Granger, 1969). The section will then proceed to formally describe how GC was updated for neuroscience as Granger-Geweke Causality (GGC). The section will then, briefly, point to other test derivatives that improve on Granger-Geweke causality, such as renormalized partial directed coherence and the directed transfer function. All of these tests are generally interpreted in neuroscience to be the 'directional flow of information.'

Section 2 will provide the background from information theory required to understand what 'information' is when the tests from section 1 are applied in a biological context (i.e., information is mutual information or entropy transfer); it will also discuss what is required for valid interpretations of information flow from the tests described in section 1.

Section 3 will return to the EOT view described above and explain how, when applied to GGC, it threatens to produce spurious results due to the undecidability property intrinsic to neuroimaging. Such undecidability property is defined and

explained. The introduction of UPN is justified by fleshing out a literature debate that occurred in the late 2010s by Barrett *et al.* and Stokes and Purdon. It will be shown that the introduction of UPN clarifies and resolves the conflict. Section 3 goes on to offer a practical example of a current research thread in cognitive neuroscience which deals with episodic memory processes in the frontoparietal network. The example will make it clear, using the proposed UPN, what a proper and improper interpretation of a hypothetical negative and positive result would look like in the literature when using Granger causality as a big data, exploratory approach.

The paper closes by doubling down on the value and potential of Granger causality and other tests that use information-theoretic measures in neuroscience, as long as they meet the present paper's proposed standard.

Section 1: Functional connectivity and the rise of Granger causality analysis

Much of contemporary cognitive neuroscience research, especially work driven by neuroimaging, has recently moved to study functional integration (i.e., how distinct brain regions process information as a transient system or network; Friston, 1994). This is opposed to measuring local activation of brain regions. To underline the turn in this research focus, it should be noted that 2010 was the first time the raw count of annual publications about functional integration overtook publications focused on localizing brain function (Friston, 2011). Functional integration is typically conceptualized as two different approaches: functional connectivity analysis and effective connectivity analysis. Functional connectivity is the statistical analysis of the relationships between two or more variables (usually brain 'sources' that produce neuronal signals). However, functional connectivity says nothing about the *physical structure* of the brain or how sources are structurally connected, which is more characteristic of effective connectivity (Lang et al. 2012). Ultimately, both effective and functional research threads are focused on supplementing the study of the 'connectome,' which is the complete description of the structural connectivity of the brain. Functional and effective connectivity are not in competition, but rather make different assumptions and allow for different interpretations about data (Seth et al., 2015). The present paper is concerned with functional connectivity.

One conceptually rigorous statistical framework for approaching functional connectivity analysis is Granger causality analysis (G-causality, GC). GC is based on the intuitive notion that causes precede their effects and that characteristics of causes help to predict characteristics of effects. It was first described in economics by Clive Granger (Granger, 1969). Granger originally used linear vector autoregressive (VAR) models of stochastic time-series data, where some variable value at a given time is modeled as the weighted sum of its own past (Seth et al., 2015). A 'variable' is a stochastic time series that is related to itself, typically, using time lag operators. Lag operators allow different models (e.g., autoregressive, VAR) to access previous elements of the time series of interest.

A lag operator, designated with *L*', can be easily understood through its formal definition. Suppose a set of elements $X = X_1, X_2, \ldots, X_{(n-1)}, X_n$, where each element is a time slice (matrix value) of a stochastic time series. In neuroscience, that element or characteristic is the voltage of neural activity, for example either from a cell or via a dipole. Thus, a time lag can simply be formulated as $LX_t = X_{(t-1)}$ given $\{t \in R \mid t > 0\}$; less formally, the lag operator is the neural activity that precedes some other neural activity in some unit of real time. As such, using lag operators, GC fits VAR models by essentially finding optimal matrix weights that minimize estimation errors between the model and the measured neural

data.

To make this clear, consider the following bivariate, linear autoregressive model example adapted from Granger (1969). Suppose two variables X_1 and X_2:

$$(1)\ X_1(t) = \sum_{j=1}^{p} A_{11,j} X_1(t-j) + \sum_{j=1}^{p} A_{12,j} X_2(t-j) + E_1(t) \quad X_2(t) = \sum_{j=1}^{p} A_{21,j} X_1(t-j) + \sum_{j=1}^{p} A_{22,j} X_2(t-j) + E_2(t)$$

given that p is the model order (i.e., maximum number of lagged observations), A is the model coefficient matrix (the lagged observations as they related to each of the processes X_1 and X_2), and E_1 and E_2 are the prediction errors to be minimized. Given the parameters of the Granger causality hypothesis test, $X_1(t)$ "G-causes" $X_2(t)$ if E_1 is minimized by including the X_2 term in the top equation more than compared to when the term is absent. This can also run the opposite direction, where $X_2(t)$ "G-causes" $X_1(t)$ if E_2 is minimized by including the X_1 term in the top equation compared to when the term is absent. The test can be run in both directions, but G-causality does not hold in both directions necessarily.

The power of this test comes from "G-causality" being interpreted as "information flow" from one variable to another. Information flow in this instance is merely the directed version of Shannon's (1948) mutual information (i.e., transfer entropy). Information flow and transfer entropy will be dealt with systematically in the next section to flesh out the importance of this fact.

However, for now, it is important to generalize Granger causality from merely a bivariate analysis to one that can also accommodate a spectral domain (i.e., analyzing specific frequency bands in neuroscience, such as the Theta band at 4-8 Hz). As Geweke (1982) demonstrated, (1) can be updated using a simple Fourier transform. As Kaminski *et al.* (2001) demonstrated, this would give the following derivation:

$$\begin{pmatrix} A_{11}(f) & A_{12}(f) \\ A_{21}(f) & A_{22}(f) \end{pmatrix} \begin{pmatrix} X_1(f) \\ X_2(f) \end{pmatrix} = \begin{pmatrix} E_1(f) \\ E_2(f) \end{pmatrix} \qquad (2)$$

where

$$A_{lm}(f) = \delta_{lm} - \sum_{j=1}^{p} A_{lm}(j) e^{-i\,2\pi\,f\,j)}$$

$$\delta_{lm} = 0\ (l = m)$$

$$\delta_{lm} = 0 = 1\ (l \neq m)$$

Notice that rewriting (2) to

$$\begin{pmatrix} A_{11}(f) & A_{12}(f) \\ A_{21}(f) & A_{22}(f) \end{pmatrix} \begin{pmatrix} E_1(f) \\ E_2(f) \end{pmatrix} = \begin{pmatrix} X_1(f) \\ X_2(f) \end{pmatrix} \qquad (2, \textit{rewritten})$$

allows the derivation of the following:

$$\begin{pmatrix} H_{11}(f) & H_{12}(f) \\ H_{21}(f) & H_{22}(f) \end{pmatrix} = \begin{pmatrix} A_{11}(f) & A_{12}(f) \\ A_{21}(f) & A_{22}(f) \end{pmatrix}^{-1}$$

where H is the transfer matrix and A is the same as previously defined. As such, the spectral G-causality from j to i is:

$$I_{j \to i}(f) = -\ln\left(1 - \frac{(\Sigma_{jj} - \frac{\Sigma^2_{ij}}{E_{ii}})\, H_{ij}(f)^2}{S_{ii}(f)}\right)$$

where the power spectrum of variable i at frequency f is $S_{ii}(f)$ (Kaminski et al. 2001).

It has been shown that the application of Geweke's spectral G-causality to recordings with more than two time series is problematic, because it can produce negative "G-causality" results, which make no biological sense (Chen et al., 2006). Practically, this is a large issue; consider, for example, that EEG can have many more time series than 2, such as a 128 channel apparatus. Because of this issue, there are many derivations of Granger-Geweke causality analysis, but GGC is still used frequently. Examples of these derivations include, but are not limited to, partial directed coherence (Baccala & Sameshima 2001), renormalized partial directed coherence (Schelter et al., 2009), and the directed transfer function (Kaminski et al. 2001). Each of these rely on the fundamental concepts of GC outlined above,*but should not be conflated improperly with Granger's notion of causality*. The differences in each of them are minor, yet powerful in each of their own respects–allowing for the logic of GC, but for instances where the population of time series are $n > 2$.

Thus, as the present paper proceeds to the next section, keep in mind that the concepts of information flow discussed, and later critiqued, apply specifically to Granger-Geweke causality analysis. This critique could possibly apply to other derivatives of the Granger logical paradigm that rely specifically on transfer entropy[2], because the critique itself is lobbied at the underlying probabilistic description of 'information' rather than the specifics of the test; however, Granger-Geweke causality is highlighted.

For a helpful discussion on the relationship between the bivariate case of GC and most other Granger derivatives, see Gourévitch *et al.* (2006)[3] and Faes *et al.* (2012). For a helpful discussion on the proper applications and misuses of GC in neuroimaging unrelated to big data exploratory analyses, see Smith *et al.* (2011); Ramsey *et al.* (2010), Seth *et*

al. (2015), and Barnett *et al.* (2018).

Section 2: Biological 'Information' Flow and the Necessity of an Information Model

It is often implicitly or explicitly stated that 'information' in cognitive and neurophysiological signal processing is a commonsensical notion. As it is typically described, information is the set of properties of a signal waveform produced by a neurobiological process that can be measured and characterized, for example, by its covariance to other signals (e.g., Cohen & Kohn, 2011). In general, characterization of waveforms can be offered using associative or causal experimental designs, or can be given at different levels of abstraction in the brain (e.g., single cell, local network oscillators, inter-regional neural oscillations). Regardless of the context, the 'information' in the signal is, supposedly, operationally clear: we are studying action potentials, the summative electrical dipoles of extracellular activity, or some sort of ionic behavior that underlies the action potential (e.g., Na^+/K^+).

Some more concerned with the details of information processing in neuroscience might problematize the obviousness of 'information' by pointing out the various ways it might be encoded in the brain. As de-Wit *et al.* (2016) correctly point out, there are at least six ways actual information could be carried. Information might be carried by:

1. The tonic or phasic firing of a single cell (Bowers, 2009);
2. Populations of cells generating distinct patterns of activity (Pouget et al., 2000);
3. The timing onset of a spike train (Thorpe et al., 2001);
4. The phase of continuous activity (e.g., duty cycle;Schyns et al., 2011);
5. Synchronization and desynchronization of neural oscillations (Singer, 1999);
6. Any or all the above.

This is not too daunting as, most plausibly, there is some sort of relevant information across each of these. For example, when looking at the cardiac ganglion of the *Homarus americanus*, we might be interested in any number of features in a neurophysiological waveform from extracellular cell recordings: the duty cycle, spiking frequency, driver potential and/or spike amplitude, and so forth help with understanding both the underlying dynamics of ionic channels and the emergent behavior of the network (e.g., Cooke, 2002). The challenge comes from isolating each and seeing which waveform feature 'says' what within a given research paradigm, or whether a given characteristic appears consistently but is merely noise.

Determining how information is being propagated is difficult, and is not purely a computational problem, as will be discussed. It is important to problematize 'information' even further in neuroimaging-centered neuroscience. Information theory requires a bit more nuance than neuroscience has given it historically (e.g., discussed in de-Wit et al., 2016) and a gap in its application sets up the critique of the EOT view in section 3. As such, it is worth recalling the foundations of information theory, starting with the required mathematical notations to make sense of the underlying information-theoretic measure, and most importantly the notion of 'information' that underlies the models discussed in section 1.

Section 2.1: Time Series, Random Processes, and Stationarity

As with section 1, we are talking about specific types of systems that transfer 'information.' It was implied with focusing on EEG that the system of interest is neuronal-based, but, for the sake of mathematical notation, what

constitutes a system is worth noting explicitly. Due to their intuitive notation and descriptions, the following notation and derivation in section 2.1 and 2.2 is inspired by Wibral *et al.* (2014).

Assume that the physical systems of interest are neuronal clusters that make up brain areas X, Y, Z. Every brain system produces a measurable time series $\{x_1, \ldots, x_{T-1}, x_T\}$, $\{y_1, \ldots, y_{T-1}, y_T\}$ and $\{z_1, \ldots, z_{T-1}, z_T\}$ at discrete times $t \in 1 \ldots T-1, T$. The measurable time series in the context of EEG corresponds to each electrode, while the discrete time scale is essentially the temporal resolution (i.e., what is the basic unit of time passing) in the recording. While not exceedingly realistic, it is assumed that that x_t, y_t, z_t are realizations of random variables X_t, Y_t, Z_t and are ultimately stationary (i.e., the underlying random variables of a set of observations are from the same distribution). As such, if a random process is defined as 'Gaussian' (i.e., the normal distribution), the random process is described by the Gaussian distribution throughout the total time domain, T (Cekic et al., 2018). With these formalisms out of the way, the next section will introduce the basics of information theory.

Section 2.2: Introduction to Information Theory: A Derivation of Shannon's Mutual Information

Claude Shannon founded information theory in his landmark paper "A Mathematical Theory of Communication" (1948). In it, he provided a formal description for how to quantify the amount of information that can be conveyed over a noisy channel. In other words, think of this as the amount of information of a song you can hear in relation to static noise on a bad MP3 recording. The intuitive appeal of this approach is that it assumes the notion that all measurement is indirect and is therefore probabilistic in nature (Kuhn, 1961; de-Wit et al., 2016).[4]

Shannon's account of information has an incredibly intuitive appeal once shifting past the mathematical background required to engage with it. For Shannon, *information is the reduction in uncertainty obtained when a selected outcome of interest, x, from the probability distribution, p(x), is observed* (Shannon, 1948; Wibral et al., 2014). This is called *Shannon information*. This can be understood through the law of total probability and partitions.

Before any selection of an outcome of interest, the total probability of a chain of events (observations in the time series) is 1. However, after the selection of x, or in probabilistic terms x being observed, all events that do not have a total probability of $p(x)$ are ignored. In this way, the total probability space is partitioned from a whole, into $p(x)$ and $1 - p(x)$. Shannon then goes on to describe this probability as a logarithmic function rather than a direct probability due to the function ultimately having more useful properties (Shannon, 1948). As such, the information gained, $h(x)$, during the observation of x with a probability of $p(x)$ is merely:

$$h(x) = log \frac{1}{p(x)} \qquad (4)$$

As such, if an outcome, x, is relatively improbable, more information is transferred given the event is actually observed and observed consistently. This is an intuitive result, because a non-probable event occurring and occurring consistently can be thought of anthropomorphically as some biological system intentionally sending information to some other biological system. Consider a noisy dinner party where everyone is chatting. There are a lot of 'random events' being

observed by different systems in the room (i.e., chatting among friends). However, if person 1 shouts out the name of person 2 in person 2's direction multiple times and person 2 hears this call, this is a relatively low probability event that is being observed multiple times (i.e., it is more meaningful and, thus, more information is being spread to person 2 relative to the background noise in the room). Through this thought experiment, it would be expected that Shannon information is additive, which is indeed the given each event is independent (i.e., the right side of (5) for observation x and y).

$$h(x,y) = log\frac{1}{p(x,y)} = log\frac{1}{p(x)} + log\frac{1}{p(y)} \; iff \; p(x,y) = p(x)p(y) \qquad (5)$$

To generalize this additive notion for some large number of observations from a random variable X, Shannon describes *Shannon entropy*, given in (6).

$$H(X) = \sum_{x \in A_x} p(x) \qquad (6)$$

At this point, it might be wondered how this measure could apply to channels in EEG, since the observations of interest are not independent of each other. Luckily, this scenario can be described merely as (7), which describes the amount of information in observation x, given that observation y already occurred. This is similar to the dinner party example.

$$h(x \mid y) = log\frac{1}{p(x \mid y)} \qquad (7)$$

In generalizing and averaging this notion, (8) is derived, which is the conditional entropy. Intuitively, $H(X \mid Y)$ can be reinterpreted similar to (7): given the observation of random variable Y, $H(X \mid Y)$ is the average amount of information exchanged once observing X.

$$H(X \mid Y) = \sum_{y \in A_Y} p(y) \sum_{x \in A_X} p(x \mid y) log\frac{1}{p(x \mid y)} = p(x,y)\, log\frac{1}{p(x \mid y)} \qquad (8)$$

It is often noted that $H(X \mid Y)$ can be interpreted as "the [amount of] information that is unique to X" (Wibral et al., 2014). Thus, it should be clear to the reader that the amount of information shared between two variables is the total average information in a variable, shown in (6), minus the average amount of information unique to that same variable, shown in (8), which gives Shannon's (1948) *mutual information*, shown in (9):

$$I(X;Y) = H(X) - H(X \mid Y) = H(Y) - H(Y \mid X) \qquad (9)$$

It is this notion that has been generalized further to allow for the concept of unidirectional information flow or more commonly used metrics such as transfer entropy.

Transfer entropy is the splitting of mutual information into a conditional mutual information, which has been formulated in various ways. Essentially, conditional mutual information is the expected value of mutual information for two random variables, given a third variable (Wyner, 1978).[5] However, while transfer entropy and mutual information are different and have different properties, these different information-theoretic measures rely on Shannon's conception of information: the minimization of uncertainty in a signal. The difference in information-theoretic measures can be thought of as different 'rulers' with different units to measure the same 'thing.' However, instead of the rulers measuring distance, it is the average level of 'information' in a signal, as defined above.

Section 2.3: What is the 'communication system' that shares mutual information?

Shannon demonstrates that information is propagated within a general communication system, which is recreated in figure 1. The system has five components: an information source, a transmitter, a channel, a receiver, and a destination. Outside of the system, there is a noise source (Figure 1). The information source is anything that is producing the 'message' of interest to be received. The transmitter transforms the message into a format that can be propagated over a channel. The channel is any medium that can transmit the signal to some destination and receiver. The receiver performs the "inverse operation of that done by the transmitter, reconstructing the message from the signal" (Shannon, 1948, p. 2). Finally, the destination is merely wherever or whatever the signal was intended for in the overall framework.

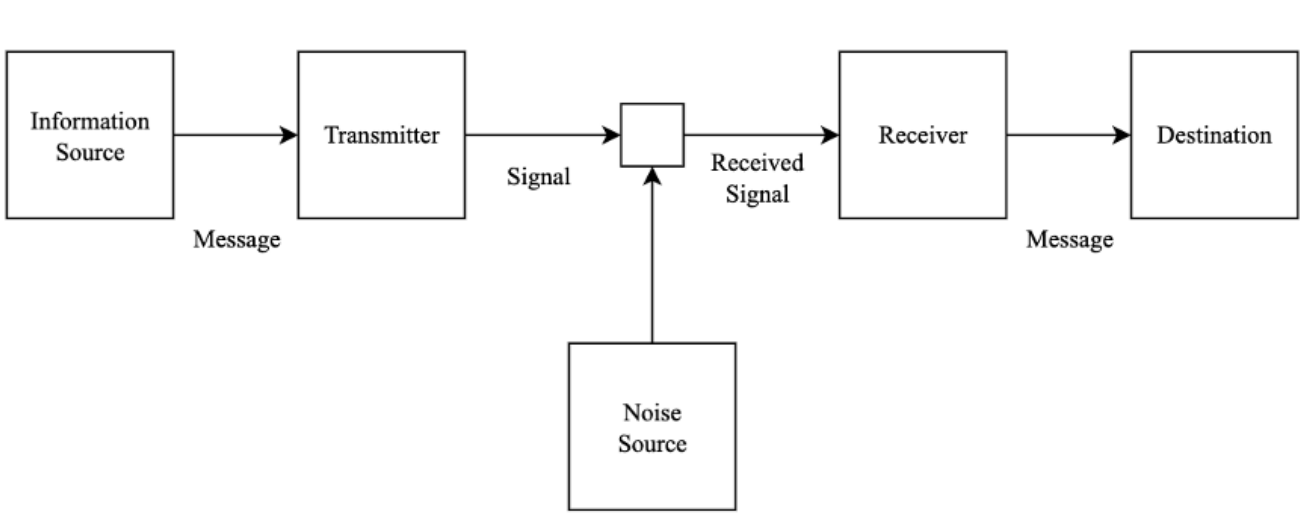

Figure 1. A recreated model of Shannon's (1948) general communication system.

There is a great deal of misinterpretation that occurs when using Shannon's communication system and notion of information, as defined above. It is often missed that when using "Shannon's ideas, for information to truly be information, it has to be a *difference that makes a difference to a receiver*" (de-Wit et al., 2016, p. 1416, original emphasis). As such,

measuring two variables of interest and noting that they are statistically related is not demonstrating information flow in a way that allows for biological interpretations, necessarily. It might be true that there is mutual information flow between *X* and *Y*, or entropy transfer from *X* to *Y* as determined by a Granger causality test, but researchers need to construct a model that explains how the information (i.e., reduction in uncertainty of a given observation in an EEG time series recording) is being used by a receiver. In other words, what difference is that information making to the receiver?

To make a proper interpretation using Granger causality, specifically the Granger-Geweke causality (GGC) established in section 1, the following need to be clear in Shannon's communication framework:

1. The relationship between source of information and receiver of information (namely that a researcher declares a relationship and in GGC the relationship is typically linear).
2. The channel through which the information source and destination are communicating.
3. The code in which the transmitter (coder) sends information across the channel to the receiver (decoder).

In most cases, point 1 and 2 are achieved relatively easily and are done by essentially declaring variables and applying the test. However, point 3 is the difficult requirement. Stokes and Purdon (2017a)[6] seemed to at least approach 3 as being a limitation of Granger causality as it is typically used. However, their critique did not succeed. Because of what can be considered–at least by the present author–a linguistic mistake made by Stokes and Purdon (2017a), their critique of Granger-Geweke causality was brushed off as being an interpretation mistake of *effective connectivity* and *functional connectivity* by Barnett *et al.* (2018a; 2018b). For the sake of completeness, it is worth reconstructing the exchange.

Stokes and Purdon (2017a) raise several issues related to the application of Granger causality in neuroscience, with one of the issues relating to causality interpretation. They ask "[h]ow then do causality values relate to the underlying structure or dynamics of the generative system?" (p. 7067). They go on to do a simulation study to "investigate how GC causality values change as the system's frequency structure varies, to determine whether the changes in the causality values agree with the face value interpretation of causality described above [on pages 7064-7065]" (Stokes & Purdon, 2017a, p. 7067). Their analysis goes on to show that the receiver dynamics are absent from the way GGC functions. They say the following:

> *GG [Granger-Geweke] causality estimates are independent of the receiver dynamics, which can run counter to intuitive notions of causality intended to explain observed effects. Instead, GG causality estimates reflect a combination of the transmitter and channel dynamics, whose relative contributions can be understood only by examining the component dynamics of the estimated model. As a result, causality analyses, even for the simplest of examples, can be difficult to interpret (Stokes & Purdon, 2017a, p. 7069).*

The important takeaway here is that Stokes and Purdon's (2017a) analysis shows that the "transmitter" and "channel" dynamics are independent of the "receiver" dynamics.

Barnett *et al.* (2018a) point out that this independence has been previously identified in an earlier paper of theirs, which indeed is the case (Barrett et al., 2010). They claim in a later paper that the fact there is an independence between the 1) transmitter and channel and 2) the receiver is not a problem. In their second letter, they say, "[b]ut why should this

independence matter" (Barrett et al., 2018b, p. 4). Stokes & Purdon believe this independence matters because "neuroscience investigations seek to determine the mechanisms that produce 'effects' observed at a particular site within a neural system or circuit as a function of inputs or 'causes' observed at other locations" (Stokes & Purdon, 2017a, p. 7070).

It is here where Barrett*et al.*(2018a, 2018b) believe that Stokes and Purdon are making a categorical mistake. In reference to the aforementioned line that "neuroscience investigations seek…at other locations" (Stokes & Purdon, 2017a, p. 7070), Barrett *et al.* (2018b) write, "[i]n fact, this view resonates more strongly with approaches such as Dynamic Causal Modelling" (DCM) which is a type of effective connectivity (p. 2). They continue on to say "GGC, on the other hand, models dependencies among observed responses and is therefore an example of (directed) 'functional connectivity'" (Barrett et al., 2018b, p. 2). In other words, as was discussed at the start of the present paper, GGC is about making inferences about directed information flow, whereas a test like DCM is focused on finding "the optimal mechanistic (circuit-level) description that explains observed data" (Barrett et al., 2018b, p. 2; for discussion on DCM, see Valdes-Sosa et al., 2011).

Stokes & Purdon deny that they made any mistake. In their words:

> *[as Barrett et al., 2018a] state, one can 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, might not be distinguished 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 GG-causality works do not provide the estimated model, much less a breakdown of its component dynamics. More fundamentally, treating the causality as "the result," overlooks that it is a statement about the chosen model and the product of the preceding modeling process (Stokes & Purdon, 2017b, p. 2).*

As already mentioned, Barrett *et al.* (2018b) in their full length article reply to this dialogue was unimpressed by this claim, doubling down to say that Stokes and Purdon (2017a, 2017b) were making a mistake between *effective* and *functional* connectivity. Who is right?

As the literature stands presently, it appears that Barrett*et al.* (2018a, 2018b) is mostly correct. However, the present paper contends they're actually both correct, in that, 1) Stokes & Purdon merely did not clarify their worry appropriately and 2) Barrett *et al.* are confusing the way Stokes & Purdon are using the word "model." The disconnect is in how each group of researchers is talking about a 'model' in *neuroscience* terms compared to *information theory*.

The misinterpretation is evident in just two lines now that the discussion has been established. In their reply to Barrett *et al.* (2018a), Stokes and Purdon (2017b) say that "...a crucial priority [in Granger causality-esque methods] will be to ensure that the *models and derived quantities correspond appropriately to the scientific questions of interest*" (p. 2, emphasis added). As mentioned, Barrett *et al.* (2018a, 2018b) make it clear in both their replies that GGC is a*model-free* metric, but can be used either parametrically or non-parametrically. Specifically, they believe that "GGC…is data-driven and 'data-agnostic' (it makes few assumptions about the generative process, beyond that it be reasonably parsimoniously

modelled as a linear stochastic system), and as such is well-suited to exploratory analyses" (Barrett et al., 2018b, p. 2).

Stokes and Purdon (2017a; 2017b) seem to be getting at the following valid issue: according to foundational information theory outlined above, Granger causality does not assume that the statistically significant information flow between two nodes, determined by the GGC outlined in section 1, is *actually* information in a biological sense. Recall that, for information to be information, there not only needs to be evidence of significant information flow being propagated, but that information needs to be used, biologically, by the receiver in the destination. This is a philosophical issue with empirical implications that is derived from the transmitter and channel being independent of the receiver. Barrett *et al.* (2018a, 2018b) are making a classic mistake in interpreting Shannon's communication system; realistically, "there is no such thing as objective information, because it is always subject to interpretation by a receiver" (de-Wit et al., 2016, p. 1417), otherwise, the statistics are not mapping on to reality.

This point can be made using an analogy offered by de-Wit *et al.* (2016). Consider the function of encryption algorithms. Target information (i.e., what is encrypted) will appear as noise to any receiver that does not have the correct decryption key. If someone has the correct decryption key, then the information is interpretable–therefore making it information by Shannon's definition and analyzable using tests like GGC. The key, which allows the decoding of an encrypted code, is the most straightforward way for determining whether the 'sent message' is an interpretable signal or noise. Shannon's information might be a message that is clear to the experimenter, but there is no guarantee, or even a high probability guess, that the potential information that is selected by the experimenter is actually a meaningful signal. This is because *anything* that is being transmitted across any given channel is potentially a signal, because it could be a *signal for something*, but it just might not be the signal the experimenter is interested in. In other words, "[w]hat counts as signal and what counts as noise very much depends on the correct model of the interaction between the sender, the channel and the receiver" (de-Wit et al., 2016, p. 1417). Whether Stokes and Purdon meant to discuss this type of model or not, both groups of researchers should be concerned about its specification.

How could there be an interpretive issue if there is a statistically significant flow of information and the test is statistically sound? The reason is because, in neuroscience at large, it is not clear what the *code* is that is being propagated between neurons or brain regions. It could be any of the codes outlined at the beginning of section 2 (e.g., the time of continuous activity, the synchrony across neuronal populations). Barrett *et al.* might not have detected this issue because, most of the time, researchers using GGC know very well that the brain regions they are looking at are communicating and are, in fact, communicating in a particular code. But de-Wit *et al.* (2016) point out extensively that not even single-cell intracellular recordings directly measure information, in an information theory sense, let alone fMRI or EEG that 'zoom out' several levels of abstractions from the individual neuron. As such, outside of neuroimaging, a lot of work needs to be done.

de-Wit *et al.* (2016) argue that "the purpose of neuroscience is to find the 'correct model of interaction'" for a given experiment (p. 1417). This is the model that Stokes and Purdon seem concerned with, given they are certain they are not making the *effective* vs *functional* connectivity mistake, which they make clear that they are not. As they point out, "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, might not be distinguished in practice" (Stokes & Purdon, 2017b, p. 1). This model of interaction

does not require a physical description in the sense of a circuit diagram that is involved with DCM. Barrett *et al.* are correct in demonstrating that GGC does not need any sort of circuit diagram, because it is "data-agnostic" (Barrett et al., 2018b, p. 2). It does, however, need to be demonstrated, physically, that whatever information is significantly flowing is *used* by the receiver.

This is a known limitation of decoding algorithms and information theory elsewhere in neuroscience. Decoding–even when applied to spike train analysis, which is clearer than EEG and fMRI–"does not consider all the potential ways to transmit information…decoding algorithms may fail to decode stimuli owning to a high-dimensional response space or the use of incorrect assumptions about the recorded data (Quiroga & Panzeri, 2009, p.178). Thus, "[i]n such circumstance it may therefore be dangerous to rule out a candidate neuronal code only because it gives a near-chance performance with a given decoding algorithm (Quiroga & Panzeri, 2009, p.178). Quiroga and Panzeri (2009) also, correctly, point out at least one additional problem with information-theoretic measures: there might be statistically significant information flow, but high information values from a given neuronal code could not be biologically relevant if that specific neuronal system cannot "exploit" all that information. In other words, it is not enough to say that there is information flow, but that information needs to be 1) usable in general by the receiving node, and 2) usable by the receiving node *during the given neuronal function being studied.* However, Barrett *et al.* remain correct that it does not matter how the two nodes are physically being connected and do not need a circuit diagram.

The model that needs to be established is the information processing model (referred to as information model), such as the one in Figure 1. In this way, it is only partially correct to say that "[GGC is] well-suited to exploratory analyses" (Barrett et al., 2018b, p. 2). The next section will outline in what instances GGC can be used for exploratory analyses and in what instances it cannot be used. Because of the extensive amount of miscommunication that occurs in such an interdisciplinary field, new terminology will be introduced to clarify this need for information models in neuroimaging as to avoid future misunderstandings in the literature.

Section 3: The Undecidability of Neuroimaging

This section is tasked with briefly outlining what the present author is calling the *undecidability property of neuroimaging* (referred to in abbreviated form as 'UPN'). The need for this terminology is clear by the miscommunication between Barrett *et al.* and Stokes and Purdon. By introducing this terminology, it outlines a standard that should be included in GGC (and other tests that use the information-theoretic measures of transfer entropy or mutual information) analyses by calling on researchers to explicitly outline 1) the information source, 2) the receiver, 3) the code through which the source and receiver are communicating, and 4) outline the literature or evidence that the receiver can *de-code the code represented within the information flow*.

UPN claims the following: given a neurobiological message that is described by stochastic time process $X(t)$, and is produced from an information source, I, in closed neurological system, S, if the message from I in S is completely measured in a channel, then it is necessarily true that the following decision problem is undecidable. In S, is the received signal, Ω, which is decoded from $X(t)$–given the signal is known to flow to some receiver, ϕ, in destination, D–the exclusive information sent from I to drive some function, F? In a less formal sense, UPN merely claims that neuroimaging,

intrinsically, cannot exhaust all criteria required to determine the information flow from one brain region to another–more empirical work, *consistent with theory to determine the code*, needs to be done outside of the neuroimaging approach. The reason is because, as mentioned, neuroimaging does not *directly* measure information (de-Wit et al., 2016).

It is beyond the scope of this paper to look at each type of neuroimaging and point out 1) why data from a specific type of neuroimaging cannot sufficiently determine information flow and 2) how can that information be disseminated empirically. Methodological experts for each technique ought to hash out this discussion. However, for the purposes of making it clear why this needs to be addressed, consider EEG as an example.

EEG methodologies interested in information flow typically assume the neural assembly hypothesis. It states that the fundamental unit of information processing in the brain is found in the synchronized firing of cells (Nicolelis et al., 1997; for full discussion, see Deolindo et al., 2017). In this case, this hypothesis outlines the *neural code*. If that is the case, it is known that cells can become synchronized due to anatomical connections and that such synchronization allows for transient interaction between networks of neurons (Fries, 2005). As such, EEG is able to measure this synchronization.

However, as it has been discussed elsewhere, EEG recordings could be epiphenomenal (e.g., Collura, 2013). An epiphenomenal process is a feature that always accompanies another process and is caused by the additional process; however, the epiphenomenal process does not, in itself, cause anything. An example of this might be that smoke is always caused by a campfire, but the smoke does not cause the burning of wood or the heat itself. As such, if the study of interest is looking at theta oscillations in source episodic memory retrieval, it needs to be demonstrated that the theta oscillations are what are explaining the memory process *or that there is at least a model through which such an explanation is possible*. Otherwise, they could be connected, but this connection could say nothing about the process of interest. A practical application of providing a model might be seen in the proposal that transient oscillations, specifically theta oscillations, can occur during complex cognitive tasks between distinct brain regions such as episodic memory (Nyhus & Curran, 2010). This would count as a 'model' that explains the interaction.

Raising the worry that EEG recordings could be measuring an epiphenomenal process does not mean that *all* recordings are epiphenomenal, but rather the task of interest is to determine which are epiphenomenal and which are not. Another theoretical approach that would acceptably avoid this concern can be seen in the development of criteria for a specific condition or brain state that sorts between 1) what level of recording 'uncertainty' is acceptable as meaningful brain activity and 2) what level of uncertainty in brain activity is too great to distinguish from epiphenomenal activity (e.g., Trinka & Leitinger, 2015). This can be sorted through biologically, as well; for example, conducting studies *in vitro* would be sufficient. One recent study demonstrates that cortical and hippocampal neurons can be influenced by endogenous electromagnetic fields produced around them (e.g., Fröhlich & McCormick, 2010), validating a potential role for oscillations to 'be used' by a receiver in some types of cells. It is this level of work that is required to characterize whether or not a given cell type can be influenced by, and can de-code, information received.

Section 3.1: Implications for the 'End of Theory' view

While the full details of the present paper should make clear what is wrong with the 'End of Theory' (EOT) view, it is worth explicitly stating for the sake of completeness. Recall that the EOT view essentially claims that, in the age of big data techniques, data can explain themselves in the absence of theoretical justifications. However, when either

aforementioned epistemological view (i.e., EOT or the new “data-driven science”) is applied to Granger-Geweke causality analysis, GGC becomes an ‘exploratory technique’ that can uncover patterns and relationships in the data. Barrett *et al.* noted as much by saying “[GGC is] well-suited to exploratory analyses” (Barrett et al., 2018b, p. 2). They are correct in the sense that some types of exploratory analyses are warranted, but others are not, which parses apart the value, or lack thereof, in each epistemological view.

Any use of GGC is warranted to determine the information flow between two brain regions if and only if it is theoretically or empirically shown that the information source is sending information that the receiver can, in fact, de-code to complete the specific brain task. To demonstrate the logical consequent, a (non-physical) model needs to be proposed or previously established. Otherwise, whether or not a brain region has information flow to another brain region, strictly speaking, is undecidable. Therefore, EOT, without qualification, is untenable. The new “data-driven science” epistemology discussed by Kitchin (2014) is better supported.

It might be helpful to the reader to demonstrate a brief, real research thread being worked on presently. Consider that a study is concerned with understanding the functional connectivity in the brain during source episodic memory retrieval. Previous research has shown the important role of theta oscillations (4-8 Hz) in this process. It is expected that the oscillations would modulate the interactions between the frontal cortex, parietal cortex, and hippocampus (Nyhus & Curran, 2010), which is an established brain network in a variety of brain functions. Due to an extensive literature review (not shown), it might be expected that there is significant information flow from the inferior parietal cortex (IPC) to the prefrontal cortex (PFC). To study this, data could be generated from a cognitive source memory task that is able to discriminate this construct effectively and is recorded by an EEG apparatus (e.g., Nyhus, 2010).

Suppose a case where the hypothesis is corroborated by the data. After running a test that uses information-theoretic measures based on Shannon information and an information model is specified, if there is significant information flow in-line with the hypothesis, the researcher is fully justified to say ‘X’ brain region ‘G-causes’ or is temporally related to ‘Y’ at theta frequency during source episodic memory retrieval processes. An example of a proper exploratory analysis with GGC would be one that looks at the information flow at *other* bands of activity during the same research paradigm. For example, there is information flow at theta frequency, but perhaps there is also significant information flow at beta frequency (12-30Hz). In such an instance, this is a valid exploration of the data to uncover *new* hypotheses to the test. What the researcher would then need to do is understand whether or not the brain regions can successfully communicate at an information code of beta frequency. It might be possible that the same literature which established the first information model could also support the surprise finding. If not, it is important to establish that it is possible; otherwise, it may just be an epiphenomenal process.

Suppose a case where the hypothesis is failed to be corroborated by the data. After running a test that uses information-theoretic measures of transfer entropy or mutual information (e.g., GGC) with an information model specified, if there is significant information flow between ‘X’ and ‘Z’ (instead of ‘Y’), it would *not* be reasonable to say that ‘X’ brain region ‘G-causes’ or is temporally related to ‘Z’ at theta frequency during source episodic memory retrieval processes. To make this clear, suppose that ‘Z’ is the supplementary motor area (SMA) which is in the medial frontal lobe–right next to the PFC. It would not make sense to say, ‘this research establishes the possible role of SMA in source episodic memory retrieval.’ Rather, until an information model for how this could work is established during the brain construct of interest,

this is a negative result and does not establish that the 'information flow' is really information being used by the receiving brain region. In other words, this could be activity for a completely different cognitive process.

Section 4: Future Research and Contributions

Regardless of the interpretive issues that UPN outlines and the untenability of EOT in Granger causal frameworks, it should be noted that GGC, derivatives of GGC, and general information-theoretic measures have a promising future in driving computational neuroscience forward. To borrow a reflection from Barrett *et al.* (2018b), "GGC represents a conceptually satisfying and statistically powerful method for (directed) functional connectivity analysis in neuroscience and neuroimaging" (p. 3). For information-theoretic measures to continue developing in their neuroscientific use, at least two research threads ought to be developed.

The first, which is not discussed here, relates to known computational issues. These include stationarity, linearity, and exogenous influence in the data that drastically affect the statistical assumptions and computational outcomes of GGC and related tests (Stokes & Purdon, 2017a). Continuing with computational issues, when GGC is applied to EEG, there is a novel question of how to deal with a type of pre-processing pipeline 'pluralism' that was recently introduced formally for the first time (Robbins et al., 2020), but has been known informally for quite some time.

Opposite of open computational questions is the problem of defining the neural code that underlies a neurological signal of interest. de-Wit *et al.* (2016) extensively demonstrated, across several fields of neuroscience that use neuroimaging, the problem is pervasive throughout. As such, understanding what the 'information' (i.e., the signal uncertainty that is being minimized) is in a given context. On this view, the computational work in neuroscience's use of information theory is further ahead than the biological understanding of those computational tools.

It is hoped that the introduction of UPN gives researchers the linguistic tools to clearly outline their research frameworks to properly make use of the powerful tools afforded from information theory. While this present paper focused primarily on GGC, there are countless derivative tests and a great deal of work to make their computational underpinnings more accessible to a non-computationally focused audience. Similarly, there is a great need, regardless of specific tests in question, to flesh out measurement theory in neuroscience. This will enable researchers to understand the philosophical implications of these tools and will improve existing knowledge of neurological systems and, ultimately, the human brain.

Footnotes

[1] For critical discussion of both neo-"data-driven science" and neo-"empiricism", see Kitchin (2014).

[2] Transfer entropy is the most common information-theoretic measure used in neuroscience and underlies Granger causality when data are Gaussian (Wibral et al., 2014; Barnett et al., 2009).

[3] Note that rPDC is not discussed in Gourévitch et al. (2006), because it entered the literature in 2009. However, because it is just a different version of renormalizing the original version of PDC, the description is still relevant.

[4] It should be briefly noted that, outside of the practical use of information theory in engineering, little work has been done to understand the implications of using information-theoretic accounts of measurement in terms of theory of measurement for naturally occurring events. Two exceptions can be found in Finkelstein (1975) and Mari (1999). While the present paper is not the place for approaching this analysis, there is a great need in

neuroscience to address this gap, as the implications of failing to grapple with underlying measurement theory are drastic. For example, in psychometrics, there is no shortage of recent critical literature on the topic (Michell, 2000; Michell, 2008; Trendler, 2009; Speelman & McGann, 2013, 2020; Michell, 2021; Bloniasz, 2021).

[5] For one formal description of transfer entropy, see Schreiber (2000) and for an intuitive description of the logic transfer entropy see Wibral et al. (2014).

[6] Note that the dates in the citations of Barrett *et al.* (2018a, 2018b) and Stokes and Purdon (2017a, 2017b) seem to be entirely after or before one another, respectively. However, the years are different merely because of how slowly different journal letters were published. The correct order of papers are Stokes and Purdon (2017a), Barrett *et al.* (2018a), Stokes and Purdon (2017b), and Barrett *et al.* (2018b).

References

- Anderson, C. (2008), "The End of Theory: The Data Deluge Makes the Scientific Method Obsolete",*Wired*, 23 June, available at: https://www.wired.com/2008/06/pb-theory/ (accessed 30 December 2021).
- Baccalá, L.A. and Sameshima, K. (2001), "Partial directed coherence: a new concept in neural structure determination", *Biological Cybernetics*, Vol. 84 No. 6, pp. 463–474.
- Barnett, L., Barrett, A.B. and Seth, A.K. (2009), "Granger causality and transfer entropy are equivalent for Gaussian variables", *Physical Review Letters*, Vol. 103 No. 23, p. 238701.
- Barnett, L., Barrett, A.B. and Seth, A.K. (2018a), "Misunderstandings regarding the application of Granger causality in neuroscience", *Proceedings of the National Academy of Sciences of the United States of America*, 17 July.
- Barnett, L., Barrett, A.B. and Seth, A.K. (2018b), "Solved problems for Granger causality in neuroscience: A response to Stokes and Purdon", *NeuroImage*, September.
- Barrett, A.B., Barnett, L. and Seth, A.K. (2010), "Multivariate Granger causality and generalized variance", *Physical Review. E, Statistical, Nonlinear, and Soft Matter Physics*, Vol. 81 No. 4 Pt 1, p. 041907.
- Bloniasz, P.F. (2021), "On Educational Assessment Theory: A High-Level Discussion of Adolphe Quetelet, Platonism, and Ergodicity", *Philosophies*, Multidisciplinary Digital Publishing Institute, Vol. 6 No. 2, p. 46.
- Bowers, J.S. (2009), "On the biological plausibility of grandmother cells: implications for neural network theories in psychology and neuroscience", *Psychological Review*, Vol. 116 No. 1, pp. 220–251.
- Cekic, S., Grandjean, D. and Renaud, O. (2018), "Time, frequency, and time-varying Granger-causality measures in neuroscience", *Statistics in Medicine*, Vol. 37 No. 11, pp. 1910–1931.
- Chen, Y., Bressler, S.L. and Ding, M. (2006), "Frequency decomposition of conditional Granger causality and application to multivariate neural field potential data", *Journal of Neuroscience Methods*, Vol. 150 No. 2, pp. 228–237.
- Cohen, M.R. and Kohn, A. (2011), "Measuring and interpreting neuronal correlations", *Nature Neuroscience*, Vol. 14 No. 7, pp. 811–819.
- Collura, T.F. (2013), *Technical Foundations of Neurofeedback*, Routledge.
- Cooke, I.M. (2002), "Reliable, responsive pacemaking and pattern generation with minimal cell numbers: the crustacean cardiac ganglion", *The Biological Bulletin*, Vol. 202 No. 2, pp. 108–136.
- Deolindo, C.S., Kunicki, A.C.B., da Silva, M.I., Lima Brasil, F. and Moioli, R.C. (2017), "Neuronal Assemblies Evidence

Distributed Interactions within a Tactile Discrimination Task in Rats", *Frontiers in Neural Circuits*, Vol. 11, p. 114.

- Dimitrov, A.G., Lazar, A.A. and Victor, J.D. (2011), "Information theory in neuroscience", *Journal of Computational Neuroscience*, Vol. 30 No. 1, pp. 1–5.
- Faes, L., Erla, S. and Nollo, G. (2012), "Measuring connectivity in linear multivariate processes: definitions, interpretation, and practical analysis", *Computational and Mathematical Methods in Medicine*, Vol. 2012, p. 140513.
- Finkelstein, L. (1975), "Representation by Symbol Systems as an Extension of the Concept of Measurement", *Kybernetes. The International Journal of Cybernetics, Systems and Management Sciences*, MCB UP Ltd, Vol. 4 No. 4, pp. 215–223.
- Fries, P. (2005), "A mechanism for cognitive dynamics: neuronal communication through neuronal coherence", *Trends in Cognitive Sciences*, Vol. 9 No. 10, pp. 474–480.
- Friston, K.J. (1994), "Functional and effective connectivity in neuroimaging: A synthesis", *Human Brain Mapping*, Wiley, Vol. 2 No. 1-2, pp. 56–78.
- Friston, K.J. (2011), "Functional and effective connectivity: a review", *Brain Connectivity*, Vol. 1 No. 1, pp. 13–36.
- Fröhlich, F. and McCormick, D.A. (2010), "Endogenous electric fields may guide neocortical network activity", *Neuron*, Vol. 67 No. 1, pp. 129–143.
- Geweke, J. (1982), "Measurement of Linear Dependence and Feedback between Multiple Time Series", *Journal of the American Statistical Association*, Taylor & Francis, Vol. 77 No. 378, pp. 304–313.
- Golmohammadi, M., Harati Nejad Torbati, A.H., Lopez de Diego, S., Obeid, I. and Picone, J. (2019), "Automatic Analysis of EEGs Using Big Data and Hybrid Deep Learning Architectures", *Frontiers in Human Neuroscience*, Vol. 13, p. 76.
- Gourévitch, B., Bouquin-Jeannès, R.L. and Faucon, G. (2006), "Linear and nonlinear causality between signals: methods, examples and neurophysiological applications", *Biological Cybernetics*, Vol. 95 No. 4, pp. 349–369.
- Granger, C.W.J. (1969), "Investigating Causal Relations by Econometric Models and Cross-spectral Methods", *Econometrica: Journal of the Econometric Society*, [Wiley, Econometric Society], Vol. 37 No. 3, pp. 424–438.
- Kamiński, M., Ding, M., Truccolo, W.A. and Bressler, S.L. (2001), "Evaluating causal relations in neural systems: granger causality, directed transfer function and statistical assessment of significance", *Biological Cybernetics*, Vol. 85 No. 2, pp. 145–157.
- Kitchin, R. (2013), "Big data and human geography: Opportunities, challenges and risks", *Dialogues in Human Geography*, SAGE Publications, Vol. 3 No. 3, pp. 262–267.
- Kitchin, R. (2014), "Big Data, new epistemologies and paradigm shifts", *Big Data & Society*, SAGE Publications Ltd, Vol. 1 No. 1, p. 2053951714528481.
- Kuhn, T.S. (1961), "The Function of Measurement in Modern Physical Science", *Isis; an International Review Devoted to the History of Science and Its Cultural Influences*, The University of Chicago Press, Vol. 52 No. 2, pp. 161–193.
- Lang, E.W., Tomé, A.M., Keck, I.R., Górriz-Sáez, J.M. and Puntonet, C.G. (2012), "Brain connectivity analysis: a short survey", *Computational Intelligence and Neuroscience*, Vol. 2012, p. 412512.
- Mari, L. (1999), "Notes towards a qualitative analysis of information in measurement results", *Measurement*, Vol. 25 No. 3, pp. 183–192.

- Michell, J. (2000), "Normal Science, Pathological Science and Psychometrics", *Theory & Psychology*, SAGE Publications Ltd, Vol. 10 No. 5, pp. 639–667.
- Michell, J. (2008), "Is Psychometrics Pathological Science?", *Measurement: Interdisciplinary Research and Perspectives*, Routledge, Vol. 6 No. 1-2, pp. 7–24.
- Michell, J. (2021), "Representational Measurement Theory: Is Its Number Up?", *Theory & Psychology*, SAGE Publications Ltd, Vol. 31 No. 1, pp. 3–23.
- Nicolelis, M.A., Fanselow, E.E. and Ghazanfar, A.A. (1997), "Hebb's dream: the resurgence of cell assemblies", *Neuron*, Vol. 19 No. 2, pp. 219–221.
- Nyhus, E. and Curran, T. (2010), "Functional role of gamma and theta oscillations in episodic memory", *Neuroscience and Biobehavioral Reviews*, Vol. 34 No. 7, pp. 1023–1035.
- Pouget, A., Dayan, P. and Zemel, R. (2000), "Information processing with population codes", *Nature Reviews. Neuroscience*, Vol. 1 No. 2, pp. 125–132.
- Quian Quiroga, R. and Panzeri, S. (2009), "Extracting information from neuronal populations: information theory and decoding approaches", *Nature Reviews. Neuroscience*, Vol. 10 No. 3, pp. 173–185.
- Ramsey, J.D., Hanson, S.J., Hanson, C., Halchenko, Y.O., Poldrack, R.A. and Glymour, C. (2010), "Six problems for causal inference from fMRI", *NeuroImage*, Vol. 49 No. 2, pp. 1545–1558.
- Robbins, K.A., Touryan, J., Mullen, T., Kothe, C. and Bigdely-Shamlo, N. (2020), "How Sensitive Are EEG Results to Preprocessing Methods: A Benchmarking Study", *IEEE Transactions on Neural Systems and Rehabilitation Engineering: A Publication of the IEEE Engineering in Medicine and Biology Society*, Vol. 28 No. 5, pp. 1081–1090.
- Schelter, B., Timmer, J. and Eichler, M. (2009), "Assessing the strength of directed influences among neural signals using renormalized partial directed coherence", *Journal of Neuroscience Methods*, Vol. 179 No. 1, pp. 121–130.
- Schreiber, T. (2000), "Measuring information transfer", *Physical Review Letters*, Vol. 85 No. 2, pp. 461–464.
- Schyns, P.G., Thut, G. and Gross, J. (2011), "Cracking the code of oscillatory activity", *PLoS Biology*, Vol. 9 No. 5, p. e1001064.
- Seth, A.K., Barrett, A.B. and Barnett, L. (2015), "Granger causality analysis in neuroscience and neuroimaging", *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, Vol. 35 No. 8, pp. 3293–3297.
- Shannon, K.M., Gage, G.J., Jankovic, A., Wilson, W.J. and Marzullo, T.C. (2014), "Portable conduction velocity experiments using earthworms for the college and high school neuroscience teaching laboratory", *Advances in Physiology Education*, Vol. 38 No. 1, pp. 62–70.
- Singer, W. (1999), "Neuronal synchrony: a versatile code for the definition of relations?", *Neuron*, Vol. 24 No. 1, pp. 49–65, 111–25.
- Smith, S.M., Miller, K.L., Salimi-Khorshidi, G., Webster, M., Beckmann, C.F., Nichols, T.E., Ramsey, J.D.,*et al.* (2011), "Network modelling methods for FMRI", *NeuroImage*, Vol. 54 No. 2, pp. 875–891.
- Song, X. and Taamouti, A. (2019), "A better understanding of Granger causality analysis: A big data environment", *Oxford Bulletin of Economics and Statistics*, Wiley, Vol. 81 No. 4, pp. 911–936.
- Speelman, C.P. and McGann, M. (2013), "How Mean is the Mean?", *Frontiers in Psychology*, Vol. 4, p. 451.
- Speelman, C.P. and McGann, M. (2020), "Statements About the Pervasiveness of Behavior Require Data About the

Pervasiveness of Behavior", *Frontiers in Psychology*, Vol. 11, p. 594675.

- Stokes, P.A. and Purdon, P.L. (2017a), "In reply to Faes et al. and Barnett et al. regarding 'A study of problems encountered in Granger causality analysis from a neuroscience perspective'", *arXiv [stat.ME]*, 29 September, available at: https://arxiv.org/abs/1709.10248.
- Stokes, P.A. and Purdon, P.L. (2017b), "A study of problems encountered in Granger causality analysis from a neuroscience perspective", *Proceedings of the National Academy of Sciences of the United States of America*, Vol. 114 No. 34, pp. E7063–E7072.
- Thorpe, S., Delorme, A. and Van Rullen, R. (2001), "Spike-based strategies for rapid processing", *Neural Networks: The Official Journal of the International Neural Network Society*, Vol. 14 No. 6-7, pp. 715–725.
- Trendler, G. (2009), "Measurement Theory, Psychology and the Revolution That Cannot Happen", *Theory & Psychology*, SAGE Publications Ltd, Vol. 19 No. 5, pp. 579–599.
- Trinka, E. and Leitinger, M. (2015), "Which EEG patterns in coma are nonconvulsive status epilepticus?", *Epilepsy & Behavior: E&B*, Vol. 49, pp. 203–222.
- Van Horn, J.D. and Toga, A.W. (2014), "Human neuroimaging as a 'Big Data' science", *Brain Imaging and Behavior*, Vol. 8 No. 2, pp. 323–331.
- Wibral, M., Vicente, R. and Lindner, M. (2014), "Transfer Entropy in Neuroscience", in Wibral, M., Vicente, R. and Lizier, J.T. (Eds.), *Directed Information Measures in Neuroscience*, Springer Berlin Heidelberg, Berlin, Heidelberg, pp. 3–36.
- de-Wit, L., Alexander, D., Ekroll, V. and Wagemans, J. (2016), "Is neuroimaging measuring information in the brain?", *Psychonomic Bulletin & Review*, Vol. 23 No. 5, pp. 1415–1428.
- Wyner, A.D. (1978), "A definition of conditional mutual information for arbitrary ensembles", *Information and Control*, Vol. 38 No. 1, pp. 51–59.
- Yedurkar, D.P. and Metkar, S.P. (2020), "Big Data in Electroencephalography Analysis", in Kulkarni, A.J., Siarry, P., Singh, P.K., Abraham, A., Zhang, M., Zomaya, A. and Baki, F. (Eds.), *Big Data Analytics in Healthcare*, Springer International Publishing, Cham, pp. 143–153.