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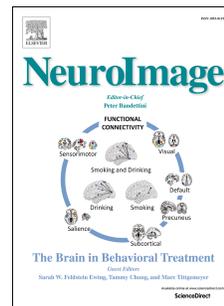
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Journal Pre-proof

# Measuring Directed Functional Connectivity Using Non-Parametric Directionality Analysis: Validation and Comparison with Non-Parametric Granger Causality

Timothy O. West<sup>1,2</sup>, David M. Halliday<sup>3</sup>, Steven L. Bressler<sup>4</sup>, Simon F. Farmer<sup>5,6</sup>, and Vladimir Litvak<sup>2</sup>

<sup>1</sup>*Centre for Mathematics and Physics in the Life Sciences and Experimental Biology, UCL Department of Physics and Astronomy, Gower Street, London, WC1E 6BT, UK.*

<sup>2</sup>*Wellcome Centre for Human Neuroimaging, UCL Queen Square Institute of Neurology, London, WC1N 3AR, UK.*

<sup>3</sup>*Department of Electronic Engineering and York Biomedical Research Institute, University of York, YO10 5DD, UK*

<sup>4</sup>*Centre for Complex Systems and Brain Sciences, Florida Atlantic University, 777 Glades Road, Florida, USA.*

<sup>5</sup>*Department of Neurology, National Hospital for Neurology & Neurosurgery, Queen Square, London WC1N 3BG, UK.*

<sup>6</sup>*Department of Clinical and Movement Neurosciences, Institute of Neurology, UCL, London, WC1N 3BG, UK.*

\*Corresponding Author ([timothy.west.10@ucl.ac.uk](mailto:timothy.west.10@ucl.ac.uk))

## 21 Abstract

22 **Background:** ‘Non-parametric directionality’ (NPD) is a novel method for estimation of directed  
23 functional connectivity (dFC) in neural data. The method has previously been verified in its ability to  
24 recover causal interactions in simulated spiking networks in Halliday et al. (2015).

25 **Methods:** This work presents a validation of NPD in continuous neural recordings (e.g. local field  
26 potentials). Specifically, we use autoregressive models to simulate time delayed correlations between  
27 neural signals. We then test for the accurate recovery of networks in the face of several confounds  
28 typically encountered in empirical data. We examine the effects of NPD under varying: a) signal-to-  
29 noise ratios, b) asymmetries in signal strength, c) instantaneous mixing, d) common drive, e) data  
30 length, and f) parallel/convergent signal routing. We also apply NPD to data from a patient who  
31 underwent simultaneous magnetoencephalography and deep brain recording.

32 **Results:** We demonstrate that NPD can accurately recover directed functional connectivity from  
33 simulations with known patterns of connectivity. The performance of the NPD measure is compared  
34 with non-parametric estimators of Granger causality (NPG), a well-established methodology for  
35 model-free estimation of dFC. A series of simulations investigating synthetically imposed confounds  
36 demonstrate that NPD provides estimates of connectivity that are equivalent to NPG, albeit with an  
37 increased sensitivity to data length. However, we provide evidence that: i) NPD is less sensitive than  
38 NPG to degradation by noise; ii) NPD is more robust to the generation of false positive identification  
39 of connectivity resulting from SNR asymmetries; iii) NPD is more robust to corruption via moderate  
40 amounts of instantaneous signal mixing.

41 **Conclusions:** The results in this paper highlight that to be practically applied to neural data,  
42 connectivity metrics should not only be accurate in their recovery of causal networks but also resistant  
43 to the confounding effects often encountered in experimental recordings of multimodal data. Taken  
44 together, these findings position NPD at the state-of-the-art with respect to the estimation of directed  
45 functional connectivity in neuroimaging.

## 46 Highlights

- 47 • Non-parametric directionality (NPD) is a novel directed connectivity measure.
- 48 • NPD estimates are equivalent to estimates of Granger causality but are more robust to signal  
49 confounds.
- 50 • Multivariate extensions of NPD can correctly identify signal routing.

## 51 Keywords

52 functional connectivity; directionality; EEG; MEG; signal-to-noise; volume conduction; neural  
53 networks; computational neuroscience; multimodal data; local field potentials.

## 54 Abbreviations

55 dFC – Directed functional connectivity

56 EEG – Electroencephalogram

57 LFP – Local field potential

58 MEG – Magnetoencephalogram

59 MVAR – Multivariate autoregressive (model)

60 NPD – Non-parametric directionality

61 (mv) NPG – (multivariate) Non-parametric estimator of Granger causality

62 SMA – Supplementary motor area

63 SNR – Signal-to-noise ratio

64 STN – Subthalamic Nucleus

## 65 1 Introduction

66 Questions regarding the causal relationships between anatomically connected regions of the brain  
67 have become of fundamental importance across many domains of neuroscience (Sporns 2010;  
68 Swanson 2012). A novel method for estimating directed functional connectivity (dFC), termed non-  
69 parametric directionality (NPD), has been recently described in Halliday (2015). This method has  
70 been demonstrated to yield physiological insights into the connectivity of the cortico-basal-ganglia  
71 network when applied to (continuous) field recordings made in rodents (West et al. 2018). In this  
72 work we evaluate NPD's performance at recovering known patterns of connectivity in the face of  
73 several confounding factors and compare it with another popularly used measure – the estimation of  
74 Granger causality.

75 Functional connectivity is based on a description of the statistical dependencies between different  
76 neural signals and is typically estimated through time or frequency domain correlations (Bastos and  
77 Schoffelen 2016; Friston 2011). Magnitude squared coherence, equivalent to a frequency domain  
78 coefficient of correlation, has been widely adopted as the estimator of choice for functional

79 connectivity in the neuroimaging community (Brillinger 1975; Halliday et al. 1995). Undirected  
80 measures of functional connectivity (such as coherence) are symmetrical, giving no indication of the  
81 temporal precedence of correlations, a property understood to be a necessary result of causation in  
82 time evolving systems (Wiener 1956), nor the predictability of one time series from that of the other.  
83 dFC aims to estimate statistical asymmetries in the correlated activity of a set of signals in order to  
84 infer the causal influence (or predictability) of one signal over another. Similar to the role played by  
85 coherence in measuring undirected functional connectivity, Wiener-Granger causality has emerged as  
86 a first-choice estimator of directed connectivity due to its well established theoretical basis (Bressler  
87 and Seth 2011; Ding et al. 2006) and its successful application to questions concerning causal  
88 networks inferred from large-scale neural recordings (e.g. Brovelli et al. 2004; Richter et al. 2018).

89 Estimates of dFC are most frequently computed in the literature using methods estimating Granger  
90 causality (Dhamala et al. 2008a; Geweke 1982; Granger 1969; Kamiński et al. 2001). Granger  
91 causality is expressed in terms of the capacity of the information in the past of one signal,  $X$ , to predict  
92 the future of another signal,  $Y$ . Granger (1969) introduced a straightforward method of estimation  
93 through the comparison of an autoregressive model by which the explained variance of  $Y$  is compared  
94 between that of a ‘full’ model (i.e. accounting for the past of  $X$  and  $Y$ ) with that of a restricted model  
95 (i.e.  $Y$  only). If a prediction of the future of  $Y$  is aided by information from the past of  $X$ , then  $X$  is said  
96 to ‘Granger-cause’  $Y$ . The method requires factoring out the autoregressive component of the signal  
97 (i.e. the ‘restricted’ model) to avoid trivial correlations that occur simply due to the periodicity in the  
98 signals.

99 Efforts to estimate Granger causality without resorting to autoregressive models have resulted in an  
100 extension of the method termed non-parametric Granger causality (NPG), which avoids the estimation  
101 of transfer functions from multivariate autoregressive (MVAR) coefficients (Dhamala et al. 2008a). In  
102 NPG, transfer functions and noise covariances are estimated through the spectral factorization of  
103 (non-parametrically derived) Fourier coefficients rather than MVAR model parameters. Here, we  
104 directly compare NPG with NPD as an estimator of dFC. Both methods share the property of being  
105 non-parametric (model-free) approaches which can be derived from identical spectral transforms  
106 made either via Fourier or wavelet techniques.

107 NPD is founded on the same principles of causality as Granger, namely that temporally lagged  
108 *dependencies* indicate causal direction. NPD works by decomposing the coherence into three  
109 temporally independent components separated by the relative lag of the dependencies between the  
110 signals: 1) forward lagged; 2) reverse lagged; and 3) instantaneously correlated. Rather than using a  
111 naïve cross-correlation estimator that is susceptible to spurious peaks resulting from the individual  
112 signals’ autocorrelations, NPD takes an approach akin to the factoring out of a ‘restricted’ model (i.e.  
113 of  $Y$  only) used in Granger. This is achieved through a process of spectral pre-whitening which acts to

114 bring the individual signal's spectra closer to white-noise but preserves the correlations between them.  
115 In the original paper (Halliday 2015), the method was validated using a simple three node network  
116 with each node's dynamics simulated using a conductance model of a spiking neurone in order to  
117 generate a series of discrete point processes. The authors demonstrated that NPD was successful in  
118 recovering the connectivity from a range of simulated architectures. Furthermore, the method was  
119 applied to spike timings (a point process) recorded from muscle spindle and shown to yield  
120 physiologically plausible estimations of causality. Our recent work has extended the application of  
121 NPD to continuous local field potential (LFP) recordings made from an *in vivo* preparation of the  
122 cortico-basal ganglia system (West et al. 2018).

123 Estimation of empirical dFC in continuous neural recordings such as the LFP or  
124 magneto/electroencephalogram (M/EEG) is complicated by a number of factors. These include: low  
125 and possibly unequal signal-to-noise ratios (SNRs), instantaneous volume conduction, common drive,  
126 signal routing via parallel but disjoint paths, and the presence of cyclic paths within a network. All  
127 pose potential confounds for the metrics described here. The failure of Granger causality estimators in  
128 the presence of large amounts of measurement noise is a well-established shortcoming (Newbold  
129 1978) which becomes particularly acute in noisy electrophysiological recordings (Nalatore et al.  
130 2007). Differences in the recording gain between signals is also known to confound estimation of  
131 Granger causality, with the most commonly used estimator demonstrating bias towards favouring the  
132 strongest signal as the driver (Bastos and Schoffelen 2016; Haufe et al. 2012). This property is likely  
133 to be a nuisance when investigating causation between multimodal signal sets such as in experiments  
134 involving simultaneous measurements of MEG and LFP where significant differences in recording  
135 gain are to be expected (Litvak et al. 2011).

136 Instantaneous mixing of the electromagnetic signals generated by distinct sources in the brain has  
137 long been known to make estimation of functional connectivity based on recordings such as the EEG  
138 difficult (Haufe et al. 2012; Nunez et al. 1997; Srinivasan et al. 2007). Common presynaptic drive  
139 produces correlations in pairs of output spike trains (Farmer et al. 1993), and in pairs of evoked  
140 potentials (Truccolo et al. 2002). This problem can lead to spurious estimates of directed connectivity  
141 if delays in the arrival of the common input induce lagged correlations between unconnected neurons  
142 or neuronal populations. When the common presynaptic input is measured, extensions of functional  
143 connectivity metrics built upon partial regressions (so called *conditioned* or *partialized* estimates) can  
144 be used to remove common input effects and, subsequently, remove the possibility of spurious  
145 inference of directed connectivity between neurones in receipt of lagged common input. Partial  
146 regression can be used with both NPD and NPG to reduce the influence of common drive. In the case  
147 of NPD, the authors introduced a multivariate extension that can be used to reduce the influence of  
148 common drive through partial regression of a third reference signal (Halliday et al. 2016). This  
149 method relies upon the reference signal substantially encapsulating the activity of the common drive.

150 In the case that the recordings are incomplete representations of the propagating neural activity, the  
151 conditioning will only be partially effective. NPD and NPG conditioned on a third signal can also be  
152 used to infer connectivity patterns where two signals are correlated through interaction with an  
153 intermediary signal (West et al. 2018).

154 Statistical aspects of coherence estimation have been widely studied. Carter et al. (1973a) highlight  
155 that a coherence estimate constructed from averaging over  $n$  independent segments has an asymptotic  
156 standard deviation proportional to  $n^{-0.5}$ , suggesting that a large number of segments are required to  
157 obtain reliable estimates. Carter et al. (1973b) suggest a reasonable range for  $n$  is 32 to 64 segments.  
158 The directional decomposition in NPD is based on the use of time lag in a correlation or partial  
159 correlation function. As the number of lags is related to the segment length, using shorter segments  
160 may impact on the reliability of directional estimates as fewer time lags are available to infer  
161 directional information.

162 In this paper we will assess the performance of NPD's ability to recover the connectomes from  
163 several simulated architectures and in the presence of the previously stated confounds. We compare  
164 the accuracy of connectivity estimation with NPD and NPG under these different conditions.  
165 Furthermore, we also test the efficacy of a multivariate extension of NPD, the conditioned NPD, as a  
166 means of testing for the effects of common drive and its ability to discriminate between parallel signal  
167 routing. The amount of data required for accurate estimation of connectivity will also be assessed.  
168 Finally, we bring the presented methods to the analysis of empirically recorded data from patients  
169 with Parkinson's disease. Using an example recording, we examine how artificially imposed changes  
170 in the signals' SNR and linear mixing can change the estimate of dFC made between signals recorded  
171 from the human cortex and basal-ganglia. Our primary goal is to verify the utility of the proposed  
172 measure in application to real-world neuroimaging data.

## 173 2 Methods

### 174 2.1 Approach

175 In this study we utilize spectral coherence for estimates of undirected FC, and NPD/NPG for  
176 estimates of dFC. We set up models of continuous neural signals with known connectivity  
177 architectures parameterized in MVAR coefficients. Confounds such as signal-to-noise and  
178 instantaneous mixing are then introduced following simulation of the MVAR process using an  
179 observation model. The analyses presented here start with the assumption that any exploratory  
180 analyses of the data are complete, including any artefact rejection and/or preprocessing and that one  
181 or more significant coherence estimates have been identified as a prerequisite for directional  
182 decomposition using NPD. Using coherence, we first establish the existence of coherent frequencies

183 within the modelled data sets. Patterns of connectivity in the models are then recovered using the two  
 184 dFC metrics (NPD and NPG). As connectivity in the models is known (by design) we analyse how the  
 185 metrics perform at accurately recovering the known connectivity profiles. Finally, we look at the  
 186 methods' application to empirical data when used to estimate the directed functional connectivity  
 187 between the basal ganglia and motor cortex in recordings made from a patient with Parkinson's  
 188 disease (PD).

## 189 2.2 Analysis Software and Data Availability

190 Data was analysed using a set of custom scripts written in MATLAB R2017a (The MathWorks,  
 191 Natick, MA, USA). Non-parametric directionality was implemented using the Neurospec toolbox  
 192 (<http://www.neurospec.org/>). MVAR models were implemented using the BSMART toolbox (Cui et  
 193 al. 2008). NPG calculations and spectral estimates were implemented in FieldTrip (Oostenveld et al.  
 194 2011b). All scripts for the analyses presented here can be found in a GitHub repository  
 195 ([https://github.com/twestWTCN/NPD\\_Validate](https://github.com/twestWTCN/NPD_Validate)). A full list of script dependencies, toolboxes used,  
 196 their authors, and links to their original source code can be found in Appendix I. The example patient  
 197 data used in this paper is anonymised and available upon request.

## 198 2.3 Functional Connectivity

### 199 2.3.1 Spectra and Coherence

200 Spectral estimates were made using periodogram estimates utilizing Hanning tapers. Unless  
 201 otherwise stated (see section 3.6 in which we investigate the role of data availability), data were  
 202 divided into segments  $2^8$  samples in length ( $\sim 1.3$  s at 200 Hz). We computed the magnitude-squared  
 203 coherence via:

$$|R_{YX}(\omega)|^2 = \frac{|f_{YX}(\omega)|^2}{f_{XX}(\omega)f_{YY}(\omega)}$$

204 (1)

205 where  $f_{XX}$ ,  $f_{YY}$ ,  $f_{YX}$  are the  $X$  and  $Y$  autospectra and  $XY$  cross-spectrum respectively.

### 206 2.3.2 Non-Parametric Directionality

207 Non-parametric directionality provides a model-free estimate of directional correlations within a  
 208 system through the decomposition of the coherence into components separated by their lags yielding  
 209 separate instantaneous, forward-lagging, and reverse-lagging spectra (Halliday 2015). This is  
 210 achieved using pre-whitening of the Fourier transforms. This acts to bring the spectral content of a  
 211 signal closer to that of white noise, in this case using optimal pre-whitening with minimum mean  
 212 squared error to compute the whitening filter. This procedure is equivalent to generating two new  
 213 random processes which have spectra equal to 1 at all frequencies:

$$f_{XX}^w(\omega) = 1, f_{YY}^w(\omega) = 1$$

214 (2)

215 The prewhitening step effectively eliminates the autocorrelation structure of the respective signals but  
 216 retains bivariate correlations between them. The pre-whitening brings the denominator of the  
 217 coherence, the product of the autospectra (a normalization factor) equal to 1. Thus, the coherence can  
 218 be reduced to the magnitude squared of the minimum mean square error (MMSE) pre-whitened cross  
 219 spectrum:

$$220 |R_{YX}(\omega)|^2 = f_{YX}^w(\omega). \quad (3)$$

221 The overall scalar measure of dependence between  $X$  and  $Y$ , denoted as  $R_{YX}^2$ , is defined as the integral  
 222 over the coherence in equation (1). In line with the previous literature, the notation here uses as  $R_{YX}^2$   
 223 to indicate a scalar measure of overall dependence and  $|R_{YX}(\omega)|^2$  to indicate coherence, a function of  
 224 frequency. As the coherence loses all terms in the denominator, the equivalent cross-spectrum can  
 225 then be transformed to the time domain to yield the time-domain correlation function:  
 226

$$227 \rho_{YX}(\tau) = \frac{1}{2\pi} \int_{-\pi}^{+\pi} f_{YX}^w(\omega) e^{i\omega\tau} d\omega. \quad (4)$$

228 This measure can be decomposed (in the time domain) via Parseval's theorem for any desired lag. We  
 229 choose to separate into reverse, instantaneous, and forward components:  
 230

$$231 R_{YX}^2 = \underbrace{\int_{\tau < 0}^0 |\rho_{YX}(\tau)|^2 d\tau}_{X \rightarrow Y} + \underbrace{|\rho_{YX}(0)|^2}_{X \leftrightarrow Y} + \underbrace{\int_0^{\tau > 0} |\rho_{YX}(\tau)|^2 d\tau}_{X \leftarrow Y} \quad (5)$$

232 These components may be abbreviated to:

$$233 R_{YX}^2 = R_{YX,-}^2 + R_{YX,0}^2 + R_{YX,+}^2 \quad (6)$$

234 where component  $R_{YX,-}^2$  yields correlations in which  $Y$  lags  $X$ ,  $R_{YX,0}^2$  instantaneous correlations, and  
 235  $R_{YX,+}^2$  correlations in which  $X$  lags  $Y$ . To create a set of frequency domain measures which decompose  
 236 coherence into three directional components, the three terms in equation (6) are each Fourier  
 237 transformed using the lag ranges in equation (5). This creates three frequency domain measures that  
 238 capture reverse, zero-lag and forward directionality, respectively. Coherence is decomposed by  
 239 direction using a ratio of the relative magnitude-squared values at each frequency as:  
 240

$$241 |R_{YX}(\omega)|^2 = |R'_{YX,-}(\omega)|^2 + |R'_{YX,0}(\omega)|^2 + |R'_{YX,+}(\omega)|^2.$$

242 (7)

243 The prime symbol on the RHS of equation (7) is used to indicate that these are not formal coherence  
 244 measures, but represent one of three directional contributions (reverse, instantaneous and forward) to  
 245 the coherence. Thus, from each component we can assess spectrally resolved directional interaction  
 246 whilst accounting for the signals' autocorrelation structure. For a full derivation of the NPD method  
 247 and details of its algorithmic implementation please refer to Halliday et al. (2016).

### 248 2.3.3 A Multivariate Extension – Conditioned Non-Parametric Directionality

249 In addition to bivariate NPD, we used a multivariate extension that allows the directional components  
 250 of coherence to be conditioned upon a third signal (Halliday et al. 2016). The conditionalization of  
 251 NPD is achieved through a partial regression of  $X$  and  $Y$  conditioned on  $Z$ . This analysis decomposes  
 252 the partial coherence into the same three directional components: forward, reverse, and zero-lag. It  
 253 can indicate if information in the bivariate interaction shares variance common to signals in other  
 254 parts of the network. For example, the partial correlation between  $X$  and  $Y$  with  $Z$  as predictor can be  
 255 used to determine if the flow of information from  $X \rightarrow Y$  is independent of area  $Z$ , or whether the flow  
 256 of information is  $X \rightarrow Z \rightarrow Y$ , in which case the partial coherence between  $X$  and  $Y$  with  $Z$  as predictor  
 257 should be zero. The partial coherence can also be used to investigate if the flow of information is  $Z \rightarrow$   
 258  $X$  and  $Z \rightarrow Y$ , or if it is  $X \rightarrow Y \rightarrow Z$  or  $Z \rightarrow X \rightarrow Y$ , or in the case of common input  $Z \rightarrow X$  and  $Y$ , in  
 259 which cases the partial coherence, and any directional components, should be zero.

260 The relationship between the squared coherence function  $|R_{XY}(\omega)|^2$  and the squared correlation  
 261 coefficient was the starting point for the derivation of the non-parametric directionality method in  
 262 Halliday (2015). The correlation coefficient is given by:

$$R_{YX}^2 = \frac{\sigma_Y^2 - \sigma_{Y|X}^2}{\sigma_Y^2}$$

263 (8)

264 where the conditioned variance,  $\sigma_{Y|X}^2$  is the variance of the error process following a linear regression  
 265 of  $Y$  on  $X$ . It then follows that the correlation coefficient may be conditioned to account for any  
 266 common effect that a process  $Z$  may have on both  $X$  and  $Y$  by also estimating the residuals following  
 267 regression with  $Z$ :

$$R_{YX|Z}^2 = \frac{\sigma_{Y|Z}^2 - \sigma_{Y|X,Z}^2}{\sigma_{Y|Z}^2}$$

268 (9)

269 in which the processes  $X$  and  $Y$  are both conditioned (regressed) against the third process  $Z$ . Partial  
 270 regression is often useful in situations in which it is believed that the tertiary signal  $Z$  can account for

271 some or all of the original association between X and Y. Thus, the objective is to distinguish whether  
 272 there is a genuine correlation  $R_{YX}^2$  that is distinct from the apparent one induced by Z:  $R_{YX|Z}^2$ . In the  
 273 same manner by which the correlation coefficient may be conditioned to account for any common  
 274 effect that a process Z may have on both X and Y, we can condition the estimated coherence  
 275  $|R_{YX}(\omega)|^2$  on Z:

$$|R_{YX|Z}(\omega)|^2 = \frac{|f_{YX|Z}(\omega)|^2}{f_{XX|Z}(\omega)f_{YY|Z}(\omega)}$$

276 (10)

277 In this way we can form a so called ‘partial’ coherence to determine the association of the coherence  
 278 between X and Y with predictor Z. By using this form of the coherence as the starting step we can  
 279 continue with the same decomposition as was made before for bivariate NPD, in order to attain an  
 280 estimate of the NPD between X and Y but conditioned on Z. In practice we achieve conditioning of  
 281 the respective autospectra  $f_{XX|Z}(\omega)$  and  $f_{YY|Z}(\omega)$  using the approach set out in Brillinger (1988). This  
 282 method has been used successfully in LFP recordings to recover known anatomical pathways in the  
 283 basal-ganglia (West et al. 2018). For full details of the derivation and implementation of conditioned  
 284 NPD, see Halliday et al. (2016).

285 Increased levels of additive noise can impact on partial coherence estimates but should not distort any  
 286 temporal precedence present in the triplets of signals (Baccalá and Sameshima 2006). Conditioned  
 287 NPD uses decomposition by time lag to infer directionality so should be robust to increased levels of  
 288 additive noise in the predictor. We explore the extent to which this is true in simulations of triadic  
 289 networks in results section 3.8.

#### 290 2.3.4 Non-Parametric Granger Causality and its Relation to NPD

291 Granger causality is based on the premise that if a signal X causes a signal Y, then the past values of X  
 292 can be used to predict the state of Y beyond that of the information contained in the past of Y alone  
 293 (Granger 1969). This has conventionally been tested in the context of multivariate autoregressive  
 294 models fit to the data, and in which the explained variance of Y via a ‘restricted’ model based on Y  
 295 alone is compared to that of a ‘full’ model using information of both the past of X and Y (Geweke  
 296 1982). Frequency domain extensions of Granger have been developed (Geweke 1982; Kamiński et al.  
 297 2001) and applied widely across many domains of neuroscience (e.g. Brovelli et al. 2004).

298 The requirement to fit multiple MVAR models can cause several difficulties in analyses, namely: i)  
 299 the requirement of large model orders to capture complex spectral features; ii) computational cost of  
 300 model inversion; and iii) assumptions as to the correlation structure of the data in order to capture the  
 301 signal as an MVAR process. In order to avoid the requirement for the estimation of MVAR models,  
 302 Dhamala et al. (2008) proposed a non-parametric estimator of Granger Causality. This estimator can

303 be derived from widely used Fourier or wavelet based spectral estimation methods which do not  
 304 suffer from these complications. The method hinges on the derivation of a spectral matrix directly  
 305 from the spectral transforms of the data (i.e. Fourier or wavelet) instead of the full transfer and noise  
 306 covariance matrices specified in an inverted MVAR model. Subsequently, the spectral matrix is  
 307 factorized to derive the transfer function and noise covariance matrices of the set of signals (Sayed  
 308 and Kailath 2001). Via this technique it is possible to decompose the total power spectrum of Y  
 309 between its intrinsic power and the *causal* contribution from X. The first term refers to the *intrinsic*  
 310 power of Y, the second term to a causal contribution to the power of Y from X. For a full derivation  
 311 and details of its implementation please refer to Dhamala et al. (2008).

312 The difference between the way NPG and NPD determine causal or directional components is that  
 313 NPG uses a decomposition of the signal power into intrinsic and extrinsic components, whereas NPD  
 314 decomposes a normalised correlation coefficient according to time lag. Both NPG and NPD use a  
 315 frequency domain approach. The frequency approach in NPG uses the formulation in Geweke (1982)  
 316 in combination with factorization of the spectral matrix (Wilson, 1972), see Dhamala et al. (2008a,  
 317 2008b) for details. NPD is based on the approach of Pierce (1979) to decompose the product moment  
 318 correlation coefficient and coherence summatively into directional components. The starting point is  
 319 the spectral matrix (as in NPG). The decomposition is achieved by generating an MMSE pre-whitened  
 320 spectral matrix,  $F_w$ , as:

$$321 \quad F_w = \begin{pmatrix} 1 & f_{YX}(f_{XX}f_{YY})^{-0.5} \\ f_{XY}(f_{XX}f_{YY})^{-0.5} & 1 \end{pmatrix},$$

322 (11)

323 where  $f_{YY}$  and  $f_{XX}$  are the autospectra, and  $f_{YX}$  and  $f_{XY}$  are the cross spectra, with frequency argument  
 324 omitted. The effect of this pre-whitening allows coherence to be calculated directly from the cross-  
 325 spectra. NPD thus decomposes coherence according to time lag in the normalised correlation whereas  
 326 NPG decomposes the spectrum into intrinsic and extrinsic factors, the presence of non-zero intrinsic  
 327 factors is taken as indicative of a causal effect in NPG.

### 328 2.3.5 Pairwise Versus Multivariate Applications of Metrics

329 Both NPD and NPG can be used in either a bivariate (pairwise) or a full multivariate (i.e. greater than  
 330 two signals) framework. As pairwise analyses of dFC are by far the most common approach used in  
 331 the current literature we primarily make a comparison of bivariate NPD and NPG computed between  
 332 two signals only. However, when investigating issues such as common drive and the influence of  
 333 tertiary signals we utilize the multivariate extension of NPG (mvNPG; Wen et al. 2013) and compare  
 334 it with conditioned NPD. mvNPG extends Geweke's formulation of Granger beyond pairwise  
 335 analyses using spectral matrix factorization. In combination with Dhamala's approach to obtain

336 spectral matrices from Fourier transforms of data this yields a method by which it is possible to create  
 337 a non-parametric estimator of causality in high dimensional data. mvNPG used here is implemented in  
 338 Fieldtrip (Oostenveld et al. 2011a).

339 Conditioned NPD is indicated by the use of brackets to signify the conditioning signal (e.g. NPD(x)  
 340 signifies NPD conditioned on signal X). This approach is used exclusively in section 3.1 (common  
 341 drive) and 3.8 (incomplete signals for conditioning).

## 342 2.4 Generation of Synthetic Data

### 343 2.4.1 Multivariate Autoregressive Modelling

344 In order to simulate data that models lagged propagation between simple periodic systems we used  
 345 MVAR modelling. MVAR models are an extension to 1-dimensional autoregressive models in which  
 346 a model variable can be expressed as a linear combination of its previous values plus some stochastic  
 347 error term. A  $P^{\text{th}}$  order MVAR model with  $N$  number of states is given by:

$$X_t = c + \sum_{i=1}^P A_i X_{t-i} + \epsilon_t$$

348 (12)

349 where  $X_t$  is a  $[N \times 1]$  vector of values at time  $t$ , and  $X_{t-i}$  are the values at time  $(t - i)$ .  $A_1, \dots, A_P$  are  
 350  $[N \times N]$  matrices of autoregressive coefficients at lag  $i$ ,  $c$  is a vector of constants, and  $\epsilon_t$  is  
 351 innovation noise (Gaussian) with zero mean and covariance  $R$ . An AR model of order  $P$  describes the  
 352  $N$  values at time,  $X_t$ , as a linear combination of  $P$  previous values,  $X_{t-i}$ , a set of constants,  $c$ , and a  
 353 vector of additional noise values,  $\epsilon_t$ . The  $P$  matrices  $A_i$  ( $i = 1, \dots, P$ ) specify the linear dependencies  
 354 in the model at time lag  $i$ . Simple periodic signals may be engineered in the MVAR formulation by  
 355 setting of alternating signed coefficients at different lags. For example, to obtain a lag two periodicity  
 356 of the system variable  $X$  we set  $A_{1,2} = [1 \ -1]$ . The alternating signs of the coefficients set up the  
 357 signal to oscillate with a period equal to the difference in lags. In order to introduce correlations  
 358 between variables we introduced non-zero coefficients off the diagonal. In this way we simulate  
 359 lagged connectivity by setting positive coefficients between nodes at lags greater than 1. For the  
 360 parameters of the simulated MVAR models please see appendix II. Simulations were made using the  
 361 BSMART toolbox. All simulations were run with sample length  $T$ , where  $T = 5 \times 10^4$  data samples  
 362 (except in sets of simulations investigating data availability and benchmarking; see below). In order to  
 363 set a time scale of the simulations we chose an arbitrary sampling frequency of 200 Hz which places  
 364 simulations around the frequencies typically observed in neural data. This yields total simulation time  
 365 of 250s (unless otherwise stated). The model architecture for each set of figures is outlined using a  
 366 ball and stick diagram next to the main results. All MVAR models used were tested for asymptotic

367 stability by determining that the absolute value of the eigenvalues of a model's companion matrix  
 368 were less than 1 (as per Lütkepohl 2005).

### 369 2.4.2 Observation Modelling

370 To introduce the effects of changes in SNR and instantaneous mixing of signals that can arise due to  
 371 the practical aspects of experimental recordings of neural signals, we construct an observation model  
 372 on top of the model of the dynamics that maps from the hidden internal variables  $X$  onto the  
 373 externally observed variables  $Y$ . This function adds observation noise to the MVAR signal and then  
 374 applies an instantaneous linear combination of the internal variables:

$$Y = z(LX) + \lambda\gamma \quad (13)$$

375 where  $Y$  is a vector of observations created using the vector of internal variables,  $X$ , combined with a  
 376 vector of additive observation noise (i.i.d, zero-mean, unit-variance, white noise)  $\gamma$  weighted by  
 377 scalar factor  $\lambda$  which determines the effective SNR of the observed variables. The function  $z(\cdot)$   
 378 indicates z-standardization to zero mean and unit variance. A  $[N \times N]$  mixing matrix  $L$  is used to  
 379 introduce dependencies between the observed signals. There is a constraint on the diagonal of  $L$  such  
 380 that  $L_{i=j} = 1, i = 1, \dots, N$  such that the gain of the signals themselves was unaltered. Thus, we specify  
 381 the mixing between signals by specifying the off-diagonal entries of matrix  $L$ . When applied to z-  
 382 normalized, uncorrelated data, the mixing matrix introduces shared variance equal to the square-root  
 383 of the off-diagonal coefficients of  $L$  (Halliday et al. 2016).

385 We compute the decibel SNR as the log ratio of signal variances i.e. 1:1 SNR is equivalent to 0 dB. In  
 386 some simulations we investigate the role of asymmetric SNR and so report the difference of SNRs  
 387 between signals:  $\Delta SNR_{XY} = SNR_{X(dB)} - SNR_{Y(dB)}$ . Assuming one signal is held constant then a  
 388 difference in SNRs of 10 dB is equivalent to 10 times increase in the noise in the other signal, 20 dB  
 389 equivalent to 100 times increase, etc. SNR calculations are computed from the ratios of the mean  
 390 narrowband power within the range of the peak frequency of activities  $\pm 5$  Hz with that of the  
 391 background noise, providing good coverage over the example signals used here. In empirical  
 392 neuroimaging data where multiple origins of noise exist, this is a much harder quantity to estimate  
 393 (Parkkonen 2010). We however use +12 dB as the level for the weakest signal, equivalent to a good  
 394 quality EEG recording (Goldenholz et al. 2009).

## 395 2.5 Benchmarking the Metrics: Data Length, Number of 396 Connections, and Combined Confounders

397 To determine the quantity of data required to use either NPD or NPG for the accurate estimation of  
 398 dFC, we setup a benchmark test and then examine how the score of this benchmark changes with the

399 amount of available data and number of connections in a given network. We also use this benchmark  
400 to assess how a combination of confounding effects can influence network estimation. First, we  
401 randomly simulate three sets of 24 random directed graphs with a fixed number of vertices ( $n = 3$ ) and  
402 including either one, two, or three edges in total. These graphs are then simulated as MVAR models  
403 (as detailed above) by placing non-zero autoregressive coefficients with a random lag uniformly  
404 distributed in the interval [1 3]. The simulated data is then analysed with NPD and NPG. By using a  
405 non-parametric permutation test to form confidence intervals (see section 2.7.1 below) for each  
406 measure we determine the detection of a directed connection if 10% of the spectra for the given pair  
407 of nodes is over the 99.99% confidence limit to yield a predicted adjacency matrix  $\hat{M}$ . For every  
408 element of  $\hat{M}$  that is equal to that in the actual adjacency matrix  $M$  (i.e. a true positive or negative) the  
409 score is +1; for every non-equal element (i.e. false positive or negative) the score is -1. Thus, the  
410 maximum score in a three-node network is +6 (all correct) and the minimum is -6. We report scores as  
411 percentages of the maximum from -100% to 100%.

412 In the first set of benchmarks we investigate both the role of data availability and the number of  
413 connections in a graph. We perform the benchmark with the 24 random graphs using: i) a fixed  
414 amount of data (500s), but variable trial length ( $2^3$  to  $2^{10}$ ) (such as is the case when deciding how to  
415 epoch data from a ‘steady-state’); and ii) a variable amount of data but a fixed number of trials ( $n =$   
416 100) (such is the case when analysing an event related study with a set number of repetitions).

417 In the second set of benchmarks we investigate how the combination of asymmetric SNR and signal  
418 mixing effects act to confound connectivity estimation. We make a 12 x 12 design, adding noise to the  
419 target node to achieve a range of narrowband (50-60 Hz)  $\Delta SNR_{1,2}$  of -45 dB to 0 dB and then adding  
420 signal mixing to achieve 0% to 100% shared variance. The weakest signal is again clamped to 12 dB.  
421 Note that the adjustment of SNR is done before signal mixing. The benchmark is then applied for data  
422 simulated from the 24 random graphs described above.

## 423 2.6 Experimental Data

### 424 2.6.1 Experimental Protocol

425 In the final experiment of this paper, we investigate how the two dFC metrics (NPD and NPG)  
426 perform when estimating the dFC between the cerebral cortex (supplementary motor area; SMA) and  
427 the subthalamic nucleus (STN). This connection has been reported to be predominantly cortically  
428 leading in patients with Parkinsonism (as estimated with NPG in Litvak et al. 2011, 2012). In this  
429 paper we use an example recording in which NPG reveals a clear directed component from SMA  $\rightarrow$   
430 STN. This recording was taken from a cohort of patients with PD who have undergone surgery for  
431 deep brain stimulation (DBS). The experimental data contains recordings made using whole head  
432 MEG and simultaneous LFP recordings from DBS electrodes implanted into the STN. The recordings

433 were made for approximately 3 minutes with the patient quietly at rest with their eyes open.  
434 Experiments investigated the differences in MEG and LFP activity and connectivity when patients  
435 were withdrawn from their usual dose of L-DOPA (OFF) versus the L-DOPA treated state (ON).  
436 Patients were not undergoing stimulation with DBS at the time of the recording. The two-time series  
437 analysed were 183s in duration with MEG from a right SMA virtual sensor recorded simultaneously  
438 with an LFP from the right STN in a PD patient in the OFF state at rest. All experiments were  
439 conducted in a study approved by the joint ethics committee of the National Hospital of Neurology  
440 and Neurosurgery and the University College London Institute of Neurology. The patient gave their  
441 written informed consent. For full details of the surgery, implantation, recording, and experimental  
442 paradigm please see Litvak et al. 2011.

## 443 2.6.2 Preprocessing

444 The MEG and LFP signals were first down-sampled to 200 Hz. They were then preprocessed using a  
445 high-pass filter (passband at 4 Hz, finite impulse response, two-pass, filter order optimized for data  
446 length). Recordings were truncated 1s at either end to remove border artefacts arising due to  
447 movement and equipment initialization. Finally, data were visually inspected to determine the  
448 presence of large abnormalities and high amplitude transients. In the case of the example data used  
449 here, none were found.

450 We performed estimation of the empirical SNR of the signals as detailed in section 2.4.2. The  
451 empirical data was first standardized to unit variance and then spectral peaks in the 14-31 Hz were  
452 compared with that of a white noise surrogate also with unit variance. The ratio between the peaks is  
453 reported as the estimated empirical SNR, equivalent to the difference of the spectral peak (in beta  
454 band) with that of the noise floor.

455 Changes to the SNR, asymmetric SNR, and linear mixing of the empirically derived signals were  
456 introduced using the same process as listed in section 2.4.2. This treatment ignores the fact that the  
457 data by necessity of empirical recording have already undergone observation with a transform similar  
458 in form to that in equation (13) but with unknown parameters regarding the lead-field (mixing matrix)  
459 and observation noise. Instead we take the empirical recordings as a ground-truth and investigate  
460 subsequent changes following artificially induced confounds.

## 461 2.7 Statistics

### 462 2.7.1 Permutation Confidence Intervals

463 In order to form confidence intervals for the connectivity metrics we make no assumptions as to the  
464 form of their distributions but instead form permutation distributions of the metrics estimated from  
465 surrogate data and computed using a non-parametric rank order significance threshold (Theiler et al.  
466 1992). We adopt a phase randomization approach to generate surrogates (Breakspear and Terry 2002;

467 Lancaster et al. 2018) which acts to preserve the magnitudes of the spectral estimates whilst  
468 scrambling the phase and hence disrupting any interaction between signals. For details and a  
469 discussion of the algorithm please see appendix I as well as Lancaster et al. (2018). For each test we  
470 generated 1000 realizations of the surrogate process. We obtain the  $P = 0.001$  confidence limit by  
471 taking the 99.9<sup>th</sup> percentile of the resulting distribution. Limits are plot in figures as a dashed line with  
472 arrows on the side of the axis to indicate their values.

### 473 2.7.2 Least-Squares Regression

474 In the case of some confounds the response profiles were found to be sigmoidal functions with a  
475 maximum response, midpoint  $x_0$ ; and steepness  $\kappa$ . We used a least-squares regression to fit the  
476 logistic function. All reported fits exceeded  $R^2 > 0.95$  and we report the estimated parameters of the  
477 curves as summary statistics of the connectivity metrics' modulation by a confound.

## 478 3 Results

### 479 3.1 Organization of the Results

480 In the following section the effects of common drive, degradation of SNR, asymmetric SNR,  
481 instantaneous signal mixing, data availability, and simultaneous confounders upon estimation of dFC  
482 using NPD and NPG are investigated. In figures 1-4 examples of the impact of these individual  
483 confounding factors upon the power and connectivity spectra are presented. In order to summarise the  
484 effects of the confounds across a much larger range of scales, in figure 5 the effects of SNR, unequal  
485 SNR, and signal mixing are visualized as a plot of the relevant statistic of the connectivity (i.e.  
486 strength or asymmetry) against a scale of values of the confounding factor. In each of the following  
487 sections (3.2-3.5) we inspect first the example spectra displayed in figures 1-4, and then go on to  
488 establish the total effect over the full range of the confound using the data illustrated in figure 5.  
489 Figures 6 and 7 use a benchmarking approach to quantify the accuracy of recovery given differing  
490 data lengths and mixed confounds. In the final section and figure 9 we look at application of the  
491 metrics to empirically recorded data.

### 492 3.2 Effects of Lagged Dependencies and Common Drive

493 We first demonstrate the efficacy of the metrics at recovering simple hierarchical architectures and  
494 establish how common input can act to confound them. To this end we present results from a simple  
495 3-state, 3<sup>rd</sup> order MVAR model with no signal mixing and zero observation noise. The MVAR model  
496 is imbued with periodic dynamics that are identical at each node and are driven by noise with fixed  
497 covariance structure. Non-zero (off-diagonal) matrix coefficients are all fixed at 0.5 and the full  
498 MVAR parameters can be seen in table 1 of appendix II. We design the MVAR model (figure 1A)  
499 such that all edges originate at node X and correlations are lagged such that an input arriving at node

500 Z lags that at node Y ( $\delta_1 < \delta_2$ ). This introduces a deliberate confound as dFC methods estimating  
501 causality in a way dependent upon temporal lag will assign spurious causality from Y to Z, due to the  
502 difference in arrival times of input from X. An example time series of the process is shown in figure  
503 1B and the resulting analyses of the functional connectivity are shown in figure 1C.

504 This model generates rhythmic activity at ~55 Hz as indicated by the peaked autospectrum for each  
505 node. Functional connectivity as measured using standard coherence shows significant connectivity ( $>$   
506 0.5) between all nodes, albeit reduced for the connection between Y and Z. We next estimate directed  
507 connectivity using NPD. NPD shows that all connections are in the forward direction for  $X \rightarrow Y$  and  
508  $X \rightarrow Z$ . As the full coherence is equal to the sum of the directional components, the overlap of the  
509 forward NPD (spectra in the top-right panel of the figure) with the coherence shows that they are  
510 equivalent in this case. The shorter lag in transmission from node  $X \rightarrow Y$  compared to  $X \rightarrow Z$ , results  
511 in a spurious estimate of coupling from  $Y \rightarrow Z$  when estimated with NPD. However, when we  
512 condition the NPD upon the signal that both node X and Z receive common input from (NPD  
513 conditioned on node X; NPD(X)), we see that the  $Y \rightarrow Z$  correlation is abolished.

514 When pairwise Granger (NPG) was applied to the simulated data, the connectivity from X to Z and Y  
515 was very similar in form to the unconditioned NPD (data not shown). However, as the multivariate  
516 estimator of Granger (mvNPG) considers the full covariance across all nodes, its application acted to  
517 remove the spurious  $Y \rightarrow Z$  correlation that arose due to the common drive. This limitation of pairwise  
518 NPD is readily overcome using the multivariate extension that allows for the conditioning of the  
519 common input. In this way the results between mvNPG and NPD conditioned upon the common input  
520 (NPD(X)) are comparable. Both NPD(X) and mvNPG give estimates of  $Y \rightarrow Z$  that are below the  $P =$   
521 0.001 confidence interval indicating the absence of any significant directed connectivity between X  
522 and Y.

### 523 3.3 Effects of Low Signal-to-Noise Ratios

524 Recordings of field activity in the brain are made in the presence of both endogenous neural  
525 background activity as well as observer noise originating from recording equipment and other sources  
526 outside the brain. In figure 2 we simulate the effects of signal-to-noise ratio (SNR) upon estimates of  
527 functional connectivity. The variance of the MVAR process was standardized and so was equal in all  
528 simulations. We used additive Gaussian noise in the observation model to simulate an SNR of 1:0 (+  
529  $\infty$  dB), 4:3 (+ 5.3 dB), and 1:3 (- 1.0 dB). All functional connectivity metrics were resistant up to  
530 moderate amount of additive noise (SNR<sub>dB</sub> = + 5.3 dB), but all estimates were heavily attenuated for  
531 the greatest noise tested in figure 2 i.e. SNR = -1.0 dB. When looking across a wider range of SNRs  
532 (figure 5A), both NPD and NPG approached 0 when the data became almost entirely noise i.e. SNR  
533 approached 0:1 (-  $\infty$  dB). Responses were sigmoidal for all three metrics measured with half  
534 maximum suppression around 50% signal loss. Non-linear least-squares fitting yielded parameter

535 estimates of the logistic rise for each FC estimator (midpoint  $x_0$  and steepness  $\kappa$ ): coherence  $x_0^{coh} =$   
 536 1.12 dB,  $\kappa^{coh} = 0.12$ ; NPD  $x_0^{NPD} = 1.47$  dB,  $\kappa^{NPD} = 0.11$ ; and NPG  $x_0^{NPG} = +7.1$  dB,  $\kappa^{NPG} = 0.07$ .  
 537 From these estimates and the curves shown in figure 5A, it is clear that coherence and NPD  
 538 effectively share the same response profile to SNR. NPG is more sensitive to noise with estimates  
 539 becoming degraded at higher SNRs ( $x_0^{NPG} > x_0^{NPD}$ ). Overall the two metrics have a difference in the  
 540 midpoints of the calibration curves of  $\sim 8$  dB, with NPG being more sensitive to noise by almost an  
 541 order of magnitude greater than NPD. However, the differences between the NPG estimator and NPD  
 542 result in different SNR thresholds required to detect statistically significant connectivity (i.e. greater  
 543 than the  $P = 0.001$  confidence threshold) and so the measures reach significance at different SNR  
 544 levels: for NPG at -7 dB (SNR = 1:5), and for NPD at -11.5 dB (SNR = 1:14).

### 545 3.4 Effects of Differences in Signal-to-Noise Ratios between Signals

546 Asymmetries in the SNR of different signals are known to distort the estimation of dFC when using  
 547 methods based upon Granger causality (Bastos and Schoffelen 2016; Nolte et al. 2008). We next  
 548 tested whether this was true for NPD. We simplified the model to contain just 2 nodes that were  
 549 reciprocally connected with the same lag. Again, the output of the MVAR model was standardized to  
 550 have unit variance. We then modified the SNR of the first node (X) via the same process as for the  
 551 previous set of simulations but fixing the variance of the noise of the second (Y) node to yield an SNR  
 552 of +13 dB. Signals were constructed with a difference of SNRs between X and Y ( $\Delta SNR_{XY}$ ) equal to  
 553 -17 dB, -7 dB, and 0 dB and calculated with respect to the SNR of Y which was held constant. The  
 554 results of the simulations are shown in figures 3 and 5B. In figure 3 we plot the difference in the  
 555 estimates of the directed connection (i.e.  $X \rightarrow Y$  minus  $Y \rightarrow X$ ;  $\Delta FC_{XY}$ ) to explore any deviation  
 556 away from the symmetry in functional connectivity expected from the MVAR model ( $\Delta FC_{XY} \approx 0$ ).

557 Our simulations confirm that NPG is biased by differences in SNR between signals, showing that  
 558 even at moderate asymmetries ( $\Delta SNR_{XY} = -7$  dB) the weaker signal is estimated to be driven by the  
 559 stronger i.e.  $Y \rightarrow X$ . NPD suffers far less from this confound and maintains estimation of the  
 560 difference in coupling as close to zero for all conditions tested. Analysis with NPD shows far less  
 561 deviation from the ground truth of symmetrical coupling when the SNRs are unequal. When looking  
 562 across a range of SNR asymmetries the response of each measure is apparent (figure 5B). NPG  
 563 spuriously identifies directed coupling, with the bias for Y leading when  $\Delta SNR_{XY}$  is in the range -10  
 564 dB to -50 dB and peaking around -35 dB (zone II of figure 5B). In contrast, the bias for X leading is  
 565 when X has a stronger SNR and  $\Delta SNR_{XY}$  is in range of +10dB to +50 dB, and peaking around  
 566  $\Delta SNR_{XY} = +35$  dB (zone IV). At very large (positive) or very small (negative)  $\Delta SNR_{XY}$  the bias in  
 567 coupling is diminished and there is a return to symmetrical estimate of connectivity as both NPD and  
 568 NPG approach 0 for both directions (zones I and V). However, whilst NPD exhibits a much weaker  
 569 bias than NPG it does still demonstrate an above significant difference in connectivity. However,

570 deviations in estimation of symmetrical coupling arising due to unequal SNR are roughly an order of  
571 magnitude smaller than NPG with a maximum  $\Delta NPD_{XY}$  of -0.045 versus  $\Delta NPG_{XY}$  of -0.42. In terms  
572 of deviation from the difference in measures when  $\Delta SNR_{XY} = 0$  dB, NPD shows a maximum of 1.5  
573 times inflation in asymmetry. For NPG this bias is a maximum of 20 times larger indicating its  
574 increased susceptibility to unbalanced SNRs.

### 575 3.5 Effects of Instantaneous Signal Mixing

576 Neurophysiologically recorded signals such as MEG, EEG, and LFPs are subject to instantaneous  
577 mixing of the underlying dipole currents as a result of field spread effects. We next simulate these  
578 effects by multiplication of the simulated MVAR process with a linear mixing matrix and investigate  
579 the influence of mixing coefficients upon estimates of dFC. We use an identical model to that in  
580 section 3.2 (3 state, 3<sup>rd</sup> order MVAR) but with the addition of the observer model to model signal  
581 mixing at a range of values of  $\lambda$  to yield simulations with 0%, 20%, and 60% shared variance. There  
582 is no observation noise added. The results of the analysis are shown in figure 4.

583 The confounding effect of instantaneous mixing was established by first estimating the degree to  
584 which it may influence the symmetrical zero-lag component of the NPD. As expected, it was found  
585 that the zero-lag NPD is increased by mixing (data not shown), particularly at frequencies outside of  
586 the periodic component of the signal. This occurs as in the case of the unmixed signals, correlation  
587 between processes is dictated by off diagonal MVAR coefficients at lags greater than zero. When  
588 mixing is introduced, common noise from outside the main frequency band of interaction more  
589 readily overcomes the intrinsic noise at each node (which is weaker in power than activity at the  
590 interaction frequency) and so results in the largest zero-lag correlations outside of the main periodic  
591 component of the signals.

592 When using NPD to estimate dFC we found that it accurately reconstructs the designed connectivity  
593 up to a moderate degree of signal mixing (45% shared variance), albeit with a reduction of the  
594 estimated magnitude of connectivity (e.g. 0.6 to 0.4 for  $X \rightarrow Y$ ). At the highest degree of mixing  
595 (90% shared variance) the spurious connectivity between nodes Y and Z (introduced by the lagged  
596 common drive from node X) becomes increasingly symmetrical with an increase in the connectivity  
597 in the reverse direction (i.e.  $Y \rightarrow X$ ) despite the absence of these connections in the model arising  
598 either by design or by lagged common input. Overall, with increased signal mixing, the estimate of  
599 NPD is weakened equally across all connections. Analysis with NPG however shows that mixing has  
600 the effect of introducing spurious connectivity between Y and Z, exhibiting a small but significant  
601 reversal connectivity at  $Z \rightarrow Y$  at even moderate mixing (45% shared variance). At the greatest  
602 degree of mixing, NPG determines statistically significant connections (above  $P = 0.001$  permutation  
603 confidence interval) for  $Y \rightarrow X$  and  $Z \rightarrow X$ , neither of which are in the underlying model. Unlike  
604 NPD, which shows a uniform reduction in magnitude with increased mixing, the magnitude of NPG

605 estimates depends upon the initial SNR of the nodes. In this instance the  $X \rightarrow Z$  connection is  
606 weakened whilst the  $X \rightarrow Y$  is strengthened. This effect is due to the process explored in section 3.4,  
607 by which unequal SNR biases the NPG estimator.

608 When testing across a wider range of degrees of signal mixing (figure 5C) the difference in the  
609 response of NPD and NPG is apparent. When using NPG to estimate dFC the magnitude of the  
610 estimate of  $X \rightarrow Y$  increases to a maximum at around 50% shared variance and then quickly collapses  
611 at very high mixing as instantaneous correlations begin to predominate. This result is related to the  
612 findings of the section 3.4 in which it was shown that signal leakage acts to modify the effective SNR  
613 of the signals such that leakage from one signal can act to bias causality estimates towards another  
614 signal at even moderate amounts of instantaneous mixing. This effect is apparent when looking at the  
615 trace of the standard (symmetrical) coherence (in blue) which drops to a minimum at ~30% shared  
616 variance but then increases as zero-lag correlations take over. As the NPD explicitly ignores the zero-  
617 lag component, it displays simpler behaviour, and reduces in amplitude with increased mixing. This  
618 occurs because zero-lag coherence predominates, and the lagged components become increasingly  
619 small.

## 620 3.6 Effects of Data Availability upon Benchmarks of the Metrics'

### 621 Accuracy

622 Application of functional connectivity metrics to real world data are often limited by the amount of  
623 data that is available to estimate them. In the next series of analyses, we quantify the dependency of  
624 accurate estimation upon the sufficiency of the given data. We use the benchmarking approach laid  
625 out in the methods and examine the role of data availability in two ways: 1) data which is continuous  
626 but of fixed total length (500s) data which is variable in length but with a fixed trial length. The  
627 results of this are shown in figure 6. In figure 6 A and B we compare NPD with mvNPG in the  
628 accurate recovery of known patterns of connectivity using a benchmark score of accuracy (see method  
629 section 2.5) when using a fixed amount of data. We observe a common trend that the overall accuracy  
630 of recovery increases with trial length, reaching a maximum at the highest trial length tested at  $2^{10}$   
631 samples (equivalent to 39 trials each ~5s in duration assuming a 200 Hz sampling rate). The recovery  
632 of denser models required longer trial lengths and overall were estimated less accurately. This effect  
633 occurs due to the introduction of common drive effects inducing false-positive detection of  
634 connections. Sparser networks including just one single connection reached maximum accuracy with  
635 trial lengths as short as  $2^5$  samples (equivalent to 1250 trials each ~0.16s in duration). With a fixed  
636 data length, it was found that NPD required shorter trials than mvNPG to reach similar degrees of  
637 accuracy (figure 6A versus 6B). Accuracy of recovery falls off with longer duration trials as the  
638 reduced number of repetitions hinders accurate estimation.

639 In figures 6 C and D, the total data availability (i.e. 100 trials of variable duration) upon estimator  
640 accuracy was investigated. Again, both metrics displayed improved accuracy with increasing trials  
641 lengths. However, with longer trial lengths, mvNPG was able to accurately recover connectivity of  
642 models with denser connectivity than for NPD: in the case of networks with three random  
643 connections, and with a long trial length of  $2^{10}$ , mvNPG reached ~85% benchmark score versus 65%  
644 for NPD. Sparser models with just one or two connections showed an optimal trial length around  $2^5$   
645 (0.16s at 200 Hz) for mvNPG versus  $2^6$  (0.32s at 200 Hz) for NPD.

### 646 3.7 Effects of Combined Confounds: Instantaneous Mixing and 647 Asymmetric Signal-to-Noise Ratios

648 Empirically recorded signals are subject to several simultaneous confounding effects. In figure 7 we  
649 present results from a benchmarking analysis in which we confound simulated signals by introducing  
650 both asymmetric signal to noise, as well as instantaneous mixing of sources to a range of combined  
651 degrees. In figure 7A and 7B we compare the performance of mvNPG and NPD in the estimation of  
652 connectivity in MVAR models with one random connection. We vary instantaneous mixing from 0 to  
653 100% shared variance; and asymmetric SNR at -45 dB to 0 dB. These simulations show that when  
654 estimating connectivity using NPD in sparse networks with just a single connection there is a highly  
655 accurate recovery (>95% benchmark scores) unaffected by asymmetric SNR, and only with high  
656 shared variance (> 50%) is there any significant drop in accuracy. A combination of strong  
657 asymmetry (-30 dB) and high mixing can however reduce benchmark scores to 30%. In comparison,  
658 mvNPG demonstrates poor accuracy across a much wider area of the conditions tested - with the  
659 benchmark reduced from 100% to 20% in the presence of negative asymmetric SNR greater than -20  
660 dB (i.e. source node is weakest) and at all degrees of mixing above 20%. Benchmark scores are  
661 weakened further by the coincidence of strong instantaneous mixing of the signals.

662 In figures 7 C and D we vary instantaneous mixing from 0 to 100% shared variance; and asymmetric  
663 SNR at -45 dB to 0 dB. These tests show that mvNPG is more readily corrupted by both confounds  
664 with scores ranging from 80% to 50% along the asymmetric SNR axis, and from 80% to -10% along  
665 the axis in which instantaneous mixing is varied. Furthermore, the estimation of denser connectivity  
666 with NPD is hindered by asymmetric SNR but is less susceptible to combined signal mixing. Whereas  
667 the negative benchmark scores for mvNPG indicate common detection of false positives, scores for  
668 NPD do not drop below 40% for any of the combined confounds tested.

### 669 3.8 Confounds for Conditioned Directed Connectivity Arising from 670 Incomplete Measurement of Signals.

671 We next investigate the properties of the multivariate extension to NPD which we term *conditioned*  
672 NPD. Conditioned dFC provides a more powerful method with which to explore network functional

673 connectivity; however, in empirical cases, conditioning with a tertiary signal  $Z$  may not produce  
674 complete attenuation of the spuriously inferred directed connection between  $X$  and  $Y$  arising from the  
675 common input  $Z$ . This may arise as a result of: i) incomplete capture of the activity occurring at  $Z$ ;  
676 and/or ii) difference in the routing of signals; and/or iii) because there are other sources of the  
677 spuriously inferred connection than  $Z$  alone. In cases where structural connectivity is well understood,  
678 and the conditioned signal  $Z$  is not expected to interconnect the path between nodes  $X$  and  $Y$ , any  
679 attenuation when conditioning can be assumed to arise in information propagated forward in the  
680 network (feedforward). On the other hand, if anatomical connectivity is unclear the effect of  
681 conditioning upon directed connectivity may also be explained by conventional serial routing (i.e.  $X$   
682  $\rightarrow Z \rightarrow Y$ ) but with incompleteness of observed signals at  $Z$  resulting in only partial attenuation of the  
683  $X \rightarrow Y$  estimate. In the next set of tests, we ask whether there are any differences in how the  
684 measures of dFC behave in the face of incomplete signal observation.

685 For this set of simulations, we use a three state, 3<sup>rd</sup> order MVAR model, with all nodes generating  
686 identical autonomous dynamics and identical cross-node coefficients at equal model lags. We test  
687 three model connectivities to compare three types of signal propagation: a) serial (i.e.  $X \rightarrow Z \rightarrow Y$ ); b)  
688 feedforward (i.e.  $X \rightarrow Y \rightarrow Z$ ); or c) recurrent (i.e.  $X \rightarrow Y \rightarrow Z \rightarrow X$ ). We simulate incomplete  
689 observation of  $Z$  by modifying the SNR as was done in section 3.2. The model architectures and  
690 results of simulations are shown in figure 8. We demonstrate that in the simplest case of a serial path,  
691 the NPD conditioned on signal  $Z$  (NPD( $Z$ )) behaves as expected: the estimate of connectivity  $X \rightarrow Y$   
692 is attenuated as all information between them is routed via  $Z$ . With decreasing SNR of the observation  
693 of  $Z$  we show that conditioning has less and less effect and converges to the estimate yielded by the  
694 unconditioned NPD. Pairwise NPD remains constant at all SNRs tested as it does not account for any  
695 of the activity at  $Z$ . In these simulations, multivariate NPG (mvNPG) was also applied as a way to  
696 estimate directed connectivity that accounts for all signals in the model. We find that mvNPG shows a  
697 small decrease ( $\sim 0.025$ ) in the estimate of  $X \rightarrow Y$  with increased SNR of  $Z$ . This weak attenuation  
698 demonstrates that mvNPG can detect serial routing, yet it is not as suited for discriminating direct  
699 connectivity (i.e.  $X \rightarrow Y$ ) from when there is relay via a secondary node ( $X \rightarrow Z \rightarrow Y$ ).

700 We next looked at a feedforward network, where  $X$  propagates directly to  $Y$ , but is then relayed on to  
701  $Z$ . Because some of the information passed  $X \rightarrow Y$  is contained in  $Z$ , we expect conditioning to  
702 attenuate the directed connection. Again, we find that NPD( $Z$ ) behaves as expected, although the  
703 attenuation is weaker than in (A) when  $Z$  mediated the routing entirely. In this way the difference in  
704 values between the NPD and NPD( $Z$ ) yields a measure of how much information of  $X$  is fed forward  
705 from  $Y \rightarrow Z$ . Thus, decreasing SNR of the observation of  $Z$  decreases the attenuating effect of the  
706 conditioned NPD. mvNPG remains at a constant magnitude for all SNRs tested. This demonstrates  
707 that the multivariate estimator of Granger causality is not sensitive to feedforward configurations

708 whereby the estimation of connectivity between X and Y is not influenced by activity at the terminal  
709 (receiving) node.

710 For the third test, we investigated the combination of recurrent loops in the network and incomplete  
711 signal observation- two features likely to occur in real recordings from neural systems. We find that  
712 with complete signal observation (i.e.  $\text{SNR} \rightarrow \infty$ ) the metrics behave similarly to the feedforward  
713 model. A notable difference is the increased NPD of  $X \rightarrow Y$  compared to the feedforward case, as  
714 correlations are reinforced by signals resonating across the loop. NPD(Z) behaves in a similar way as  
715 before, showing attenuation of the conditioned estimate at low noise levels, but converging back to  
716 the unconditioned NPD as the reference signal is obscured by noise and estimation of its confounding  
717 influence is lost. The mvNPG estimate of the connection  $X \rightarrow Y$  decreases by 0.1 as the observation  
718 noise of Z is reduced. This finding indicates that in the case of recurrent connectivity, mvNPG is  
719 sensitive to the quality of the signal recorded at the routing node. In the case of recurrent  
720 configurations, this finding shows that mvNPG can readily discriminate between direct  $X \rightarrow Y$   
721 connectivity and cyclical routing via a secondary signal recorded at Z.

### 722 3.9 Example of Estimation of Directed Functional Connectivity in 723 Confounded Empirical Data: Cortico-Subthalamic Connectivity

724 Using the example dataset described in section 2.6 we examine how changes in the overall SNR,  
725 differences in SNR between signals, and instantaneous signal mixing may act to confound the  
726 estimation of dFC in empirical data recorded from simultaneous MEG and LFP in patients with  
727 Parkinson's disease. We first analyse the original empirical data and then subsequently introduce  
728 synthetic confounding effects as described in the methods section that outlined observation modelling.  
729 The results of this analysis are presented in figure 9.

730 We demonstrate in the original data that there is a clear asymmetry in coupling with both NPD and  
731 NPG indicating a clear dFC from  $\text{SMA} \rightarrow \text{STN}$ . The zero-lag component (top row figure 9) of the  
732 NPD is negligible in the original data. In contrast, the instantaneous component of NPG shows above  
733 significance level connectivity at 20-30 Hz. The empirical SNR of the data was estimated using the  
734 method described in section 2.6.2. We use activity in the beta band (14-30 Hz) to define the signal and  
735 then compare with the noise floor. SNR estimates of the MEG virtual electrode and LFP were + 1.9  
736 dB ( $\text{SNR}_{\text{SMA}} \approx 3:2$ ) and + 4.0 dB ( $\text{SNR}_{\text{STN}} \approx 5:2$ ) respectively. This yields an empirical  $\Delta\text{SNR}$  of -2.1  
737 dB with the LFP measured at the STN having the largest SNR.

738 In the first set of experiments we reduced the SNR of both signals equally (figure 9 A-C). We added  
739 noise to the original signals to yield a range of SNRs: +  $\infty$  dB, + 4.1 dB, and -1.9 dB. These analyses  
740 show that both NPG and NPD estimates of connectivity respond to a uniform reduction in SNR in a

741 simple and predictable way by reducing their overall magnitude approaching zero as the signals  
742 become mostly noise.

743 Subsequently, the effect of changing the SNR of only one of the signals upon dFC estimates was also  
744 investigated (figure 9 D-F). Signals were constructed to have a range of  $\Delta SNR$ : - 3 dB; +16 dB; and +  
745 26 dB. We reduced the SNR of the strongest signal only (STN;  $SNR_{dB}^{STN}$ ), in an attempt to bias the  
746 directionality estimates in the reverse direction (i.e. increase the strength of STN  $\rightarrow$  SMA). However,  
747 it was found for both NPD and NPG that this had a similar effect to reducing the SNR symmetrically  
748 (i.e. when SMA  $\rightarrow$  STN is weakened). This result suggests that for this dataset, it may not be possible  
749 to induce a strong bias in the inferred dFC by making one signal weaker than the other (i.e.  
750  $SNR_{dB}^{SMA} \gg SNR_{dB}^{STN}$ ) as there is no anatomical STN $\rightarrow$ SMA feedback (a situation in contrast with  
751 simulations investigating asymmetric SNR in section 3.4.).

752 In the final column of figure 9 (panels G-I) the effect of signal mixing was measured. We simulated  
753 several degrees of signal mixing:  $\lambda = 0$  (0% shared variance);  $\lambda = 0.075$  (7.5% shared variance); and  $\lambda$   
754 = 0.15 (15% shared variance). Again, it was found that the instantaneous component of the NPD  
755 behaves as expected, increasing in magnitude with increased signal mixing. This is most apparent in  
756 the frequencies outside the main oscillatory bands of activity. When using the instantaneous part of  
757 NPG, we found that there was generally an increase, yet the frequencies around the main component  
758 (of the peak in the lagged connectivity) were negative and uninterpretable. Furthermore, we show that  
759 even moderate increases in the signal mixing (7.5%) corrupt the dFC estimation when using NPG.  
760 This is especially apparent at high mixing levels (15%), where a wide band reverse component  
761 (STN $\rightarrow$ SMA) arises, as well as large second peak in the SMA $\rightarrow$ STN at around 4-12 Hz. NPD  
762 estimates are much more stable in comparison and only show a reduction in the original peak with  
763 increased mixing, but no spurious peaks emerge outside of this range at any of mixing degrees tested.

## 764 4 Discussion

765 The results presented in this paper further support the NPD methodology as an accurate and robust  
766 method for the estimation of dFC in continuous neural data. We first provided a face validation of  
767 NPD for estimation of the directed interactions between MVAR processes. Secondly, we assessed the  
768 performance of the NPD measure in the presence of several confounding factors that are likely to  
769 arise in experimental recordings of neurophysiological networks, namely: volume conduction,  
770 common drive, low SNR, unequal SNRs between signals, and recurrent connectivity. Thirdly, we  
771 provided a direct comparison of NPD with a well-established estimate of dFC based on Granger  
772 causality – NPG. Finally, our results show that the additional information gained from using a  
773 conditioned, multivariate extension of the NPD method allows for some of the confounding  
774 influences of common drive, or non-trivial signal routing, to be mitigated. The degree to which this is

775 achieved is dependent upon the extent to which the signal captures the neural activity at the recording  
776 site.

## 777 4.1 A Summary of Effects of Signal Confounds

### 778 4.1.1 Effects of Common Drive

779 Common input to two parallel neural populations has long been known to be a confounding factor  
780 when estimating functional connectivity (Aertsen et al. 1989; Farmer et al. 1993; Horwitz 2003). The  
781 limitations of finite sampling over the brain means that no FC measure is immune to this problem as  
782 there always remains the potential for an unmeasured common input to the recorded populations from  
783 which an FC estimate is made. Our simulations demonstrate this effect where both pairwise NPD and  
784 NPG estimates indicate spurious causality in the case of lagged common input. However, when using  
785 multivariate extensions of the two methods, in which the common drive signal is factored out, it is  
786 possible to avoid spurious estimation of connectivity between nodes sharing a common drive. This is  
787 shown to be true when using the multivariate NPG which accounts for the total covariance across the  
788 network. On the other hand, NPD in its simplest form is measured in a pairwise manner and cannot  
789 account for the action of a tertiary signal on the naïve estimate. However, we demonstrate that this  
790 issue can be remedied using the multivariate extension of NPD in which the influence of a common  
791 drive may be regressed out in order to eliminate spurious connectivity between the driven nodes.  
792 Whilst this is a solution when the common drive is observed, there still remains the potential  
793 confound of an unobserved common signal, to which NPD and NPG are equally susceptible. These  
794 issues can be addressed by model based estimators of effective connectivity such as dynamic causal  
795 modelling which allow for the inference of unobserved states in a causal network (Friston et al. 2013).

### 796 4.1.2 Effects of Asymmetric Signal-to-Noise Ratios

797 Functional connectivity estimates are subject to the limits of inference implied by the SNR of the  
798 available recordings. We demonstrate (figure 5A) that coherence, NPD, and NPG are degraded by  
799 poor SNR with similar logistic decays. However, NPG exhibits a greater susceptibility to degradation  
800 by noise than NPD. NPG magnitude are reduced at SNRs an order of magnitude higher than those that  
801 would elicit an equal reduction in NPD. Despite this, both measures show a remarkable resistance to  
802 even high levels of noise, with the range of SNRs at which both NPG and NPD provide statistically  
803 significant estimates of connectivity (i.e. having a magnitude exceeding the  $P = 0.001$  confidence  
804 interval) reaching as low as  $\text{SNR} = 1:30$  (equivalent to  $-15$  dB). This would suggest that both are  
805 robust to the occurrence of false-negative errors as a result of poor SNR in neural recordings. These  
806 findings can also explain the common empirical finding of significant functional connectivity in the  
807 absence of obvious peaks in the power spectra.

808 A number of authors have noted that estimation of Granger causality is biased by the existence of  
809 unequal SNRs (Bastos and Schoffelen 2016; Haufe et al. 2013; Nolte et al. 2008). Our simulations  
810 reiterate this fact and demonstrate that NPG is biased to estimate the driving node as the strongest  
811 signal (section 3.4; figure 5B). This is an important problem as all neurophysiological signals  
812 comprise some unknown mixture of the signal of interest and background noise on a source by source  
813 basis. As a result, it can rarely be assumed that the SNRs of two signals are balanced. We find that  
814 when investigating the simultaneous effects of unequal SNR and instantaneous mixing, that NPG is  
815 most easily corrupted by the asymmetry in the signals, whereas NPD is most sensitive to mixing.

816 This is particularly important when looking at directed connectivity between signals recorded from  
817 two different modalities (e.g. MEG and LFP) where the estimate will be biased in favour of the higher  
818 gain recording (to lead). For instance, in our data we show a difference in empirical SNRs of 4.5 dB  
819 between the LFP and virtual channel signals. This has led some authors to suggest the usage of time-  
820 reversed data as surrogate comparison for dFC methods (Haufe et al. 2013) because if a true causal  
821 effect is present then time reversal should flip the sign of the directionality. Future validations should  
822 explore whether this approach can reduce the susceptibility of the NPD method to so called “weak”  
823 data asymmetries. However, the simulations here demonstrate that estimates made using NPD are far  
824 less subject to this confound than NPG. NPD is still affected by decreased SNR (both asymmetric and  
825 symmetric) but shows no bias, as directional estimates decrease uniformly as the SNR goes down.  
826 This finding leads us to suggest that in future studies of dFC in multimodal data or in other cases  
827 where the signals are likely to be of differing SNR, the NPD method provides a more robust and  
828 readily interpretable result over Granger based approaches.

### 829 4.1.3 Effects of Simulated Volume Conduction through Signal Mixing

830 The extent to which signals recorded from the brain are subject to the influence of volume conduction  
831 is generally more severe with decreasing distance between the recording electrodes. Experiments have  
832 demonstrated that LFPs measured from electrodes separated by a distance of 5 cm will typically show  
833  $R^2$  values indicating approximately 50% shared variance (Nunez et al. 1997) and so analyses of  
834 directed functional connectivity are likely to be significantly affected by instantaneous mixing at  
835 distances much closer than this (e.g. recordings made from neighbouring contacts of the same  
836 intracranial electrodes). Instead, some authors have shown that functional connectivity analyses are  
837 better suited to source localized signals due to the reduced extent of signal leakage (Schoffelen and  
838 Gross 2009). This is likely to hold true for the application of NPD analysis to whole brain recordings.  
839 It is difficult to find a limit for when zero-lag effects will corrupt a method such as NPG as this  
840 ultimately depends on the nature of the lagged connectivity present in the data. In our simulations, we  
841 show that the bias on NPG induced by mixing is dependent upon the original SNR of the signals as a  
842 result of confounding by the mechanism of SNR asymmetry discussed in the previous section.

843 In addition to the benefit of being less susceptible to corruption by volume conduction, NPD provides  
844 explicit frequency resolved estimation of the zero-lag component of coherence, making it possible to  
845 estimate the extent to which coupling is influenced by instantaneous effects. This characteristic  
846 affords NPD an advantage over corrected methods of FC such as imaginary coherence or the phase  
847 locking index (Nolte et al. 2004; Vinck et al. 2011) which are set up to ignore zero-phase coherence.  
848 In this respect it is important to note that zero-phase coherence can reflect synchronous physiological  
849 coupling (Roelfsema et al. 1997). We also note that volume conduction is manifest not only through  
850 the mixing of known sources of interest, but also hidden sources (Bastos and Schoffelen 2016). This  
851 introduces a confound like that of limited signal observation (see below) in which the influence of a  
852 node can only be estimated if it is directly observable.

#### 853 4.1.4 Effects of Data Length on Estimation Accuracy

854 Estimation of connectivity in empirical data is limited by the availability of recorded data due either  
855 to experimental design or practical limitations of storage and acquisition. In figure 6 we presented a  
856 set of tests to determine the sensitivity of the two methods to data length. Overall, we find that NPG is  
857 the most robust of the two and can make accurate recovery at trial lengths two orders (to the power of  
858 2) shorter than NPD. As expected, this exact effect is dependent upon the complexity of the model to  
859 be evaluated. In the case where more dense networks are to be estimated, the required amount of data  
860 is larger than for simpler models with one or two connections. These limitations are likely due to the  
861 variance of the spectral estimators from which the two metrics are decomposed, with coherence  
862 known to be sensitive to having a larger number of samples to restrict estimates.

863 It is well known that insufficient sampling will hinder parametric estimators of Granger causality  
864 (Seth et al. 2015). Simulations here suggest that with a good number of trial repetitions ( $> 35$ ) at a  
865 sampling rate of 200 Hz, trial lengths from 0.5 to 1 second are required for accurate estimation with  
866 NPD. For NPG, this requirement is reduced to a minimum of 0.2 seconds, although these guidelines  
867 are likely to depend upon the SNR, as well as frequency band of the interaction of interest in the  
868 analysed data.

#### 869 4.1.5 Effects of Limited Signal Observation

870 The argument that conditioned metrics of dFC such as conditioned NPD provide an increased ability  
871 to infer the causal structure of real-world neural networks hinges upon the assumption that a recorded  
872 signal truly captures the complete dynamics of the underlying population through which the signal is  
873 routed. In section 3.8 we provide an analysis of how the incomplete observation of signals acts to  
874 confound the estimates of dFC under several hypotheses of signal propagation: A) serial; B)  
875 feedforward; and C) recurrent connectivity (figure 8). In the case of the simplest architecture - serial  
876 propagation, the metrics behave as expected – the more poorly the signal used to perform the  
877 conditioning captures the underlying dynamics, the less the conditioning can inform accurate

878 estimation of directed connectivity. In the case of complete signal capture, the conditioning procedure  
879 (NPD(Z)) completely attenuates the directed connection ( $X \rightarrow Y$ ), as there is no possibility that any of  
880 the information contained in  $Y$  concerning node  $X$  is exclusive of  $Z$ . Therefore, if the signal recorded  
881 at  $Z$  completely captures the dynamics of  $Y$  then there is the potential to attenuate the  $X \rightarrow Y$   
882 connection entirely using a conditioning on  $Z$ . In the case of feedforward propagation, conditioning  
883 will also act to attenuate the estimate, but unlike serial processing (where the reference node  $Z$   
884 provides an intermediate node in the chain of propagation between  $X$  and  $Y$ ) the attenuation can never  
885 be complete as the variance introduced at  $Z$  is not shared with  $X$  or  $Y$ . In case C we show that the re-  
886 entrant connection acts to increase the overall coherence due to cyclical passage of information in the  
887 circuit. Furthermore, conditioning acts to bring the NPD estimate closer to that of the feedforward  
888 model (where the re-entrant connection is missing). In the case of recurrent connectivity, the  
889 multivariate NPG also acts to discount the reconnection via  $Z$ . When  $Z$  is completely captured (SNR  
890 is high) then the NPG gives an estimated connectivity equivalent again to the feedforward model.

891 These observations make it clear that if conditioning removes the inferred connectivity in its entirety  
892 then the conditioned node must be in a relay like position (i.e.  $X \rightarrow Z \rightarrow Y$ ). For instance, this was  
893 found to be the case in West et al. (2018) where conditioning of NPD between the striatum and  
894 subthalamic nucleus upon the external segment of the globus pallidus removed connectivity almost  
895 entirely, leading to the conclusion that information propagated serially in the network, a finding in-  
896 line with known anatomical details of the indirect pathway of the basal-ganglia. However, the  
897 findings described in the present paper regarding the combination of circuit organization and SNR of  
898 conditioned signals introduce ambiguity when interpreting the results of conditioned or multivariate  
899 estimates of directed connectivity in empirical data. For instance, incomplete attenuation of  
900 conditioning may arise either from poor SNR of the reference signal in a serial network or may  
901 indicate that the conditioned signal is placed in either a feedforward or recurrent configuration. In this  
902 case it is necessary to combine evidence from multiple conditioning steps (e.g. also conditioning  $X \rightarrow$   
903  $Z$  on  $Y$ ) in order to determine the exact signal routing. Previous work has argued that additive noise  
904 only impairs estimation rather than distorts temporal structure of the signals (Baccalá and Sameshima  
905 2006), here we show that this disruption is dependent upon the exact routing of the signals.  
906 Specifically, in networks containing a high degree of reciprocity, partialized estimated of coherence  
907 (both directed and undirected) are likely to be confounded. This finding could be used in principle to  
908 further specify the role of a conditioned node by determining its effect upon directed connectivity in  
909 response to additive noise.

## 910 4.2 Extensions and Final Conclusions

911 We have presented a validation of NPD, a novel tool for the assessment of dFC, in continuous neural  
912 recordings such as that measured in methods commonly used for human neuroimaging. We argue that

913 in the face of common practical issues arising from the physical limitations of many experimental  
914 recording methods, as well as from the complex biology of the systems that they aim to explore, NPD  
915 and its conditioned extension provide a useful method that builds upon the founding principles of the  
916 more established Granger causality. The NPD measure (conditioned and unconditioned) has been  
917 recently demonstrated to provide insights into the patterns of propagating neural activity in animal  
918 electrophysiology in the basal-ganglia (West et al. 2018) and hippocampus (Halliday et al. 2016); as  
919 well as in human motor networks (Halliday 2015; Spedden et al. 2019). and is likely to have wide  
920 application across other domains of clinical and experimental neuroscience. The finding that NPD is  
921 robust to the confounding effects of SNR asymmetry means that it may be readily applied to multi-  
922 modal neural recordings without some of the concerns that may arise with Granger-based methods.

923 The validation provided here is not extensive: there is a wide range of other existing dFC metrics to  
924 which we have not made comparison, and so it is possible that other metrics may perform better than  
925 NPG (for an extensive comparison of many metrics, not including NPD, see Wang et al. 2014).  
926 Granger causality-based methods have become a staple of the dFC toolbox and form the statistical  
927 foundation for several methods developed since including the directed transfer function (Kaminski  
928 and Blinowska 1991) and partial directed coherence (Baccalá and Sameshima 2001). An adaptation of  
929 the directed transfer function aimed at improving estimation of directed connectivity (i.e.  $X \rightarrow Y$ )  
930 introduced by Korzeniewska et al. 2003 may perform better at recovering known patterns of  
931 connectivity in the face of common drive than the metrics presented here. Furthermore, the role of  
932 time reversal procedures (Haufe et al. 2013) in alleviating some of these shortcomings in the metrics  
933 should be the subject of future study. This is likely to be important when investigating more complex  
934 networks or high dimensional data such as that measured with magneto- or electroencephalographic  
935 recordings. However, NPD shows broadly equivalent results to the Granger based measure but  
936 exhibits more robust performance in the recovery of complex network topologies in highly  
937 confounded data. The full extent to which this is true either in networks of a greater size or density  
938 will need to be tested.

939 We conclude that the NPD measure of directed functional connectivity is inexpensive to compute,  
940 makes limited assumptions of the properties of the data, is flexible to the form of the original spectral  
941 estimate and is conceptually simple to formulate. It eschews the computationally expensive estimation  
942 of model parameters required for parametric estimates of Granger causality or directed transfer  
943 function and doesn't require iterative binning procedures such as that use in information-based  
944 metrics like transfer entropy. Overall, NPD provides a simple and compact statistical description of  
945 directed dependencies between signals and is readily interpretable, providing the basis for testable  
946 hypotheses of causation in real neural systems.

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## 957 7 Competing Interests

958 The authors have no competing interests to declare.

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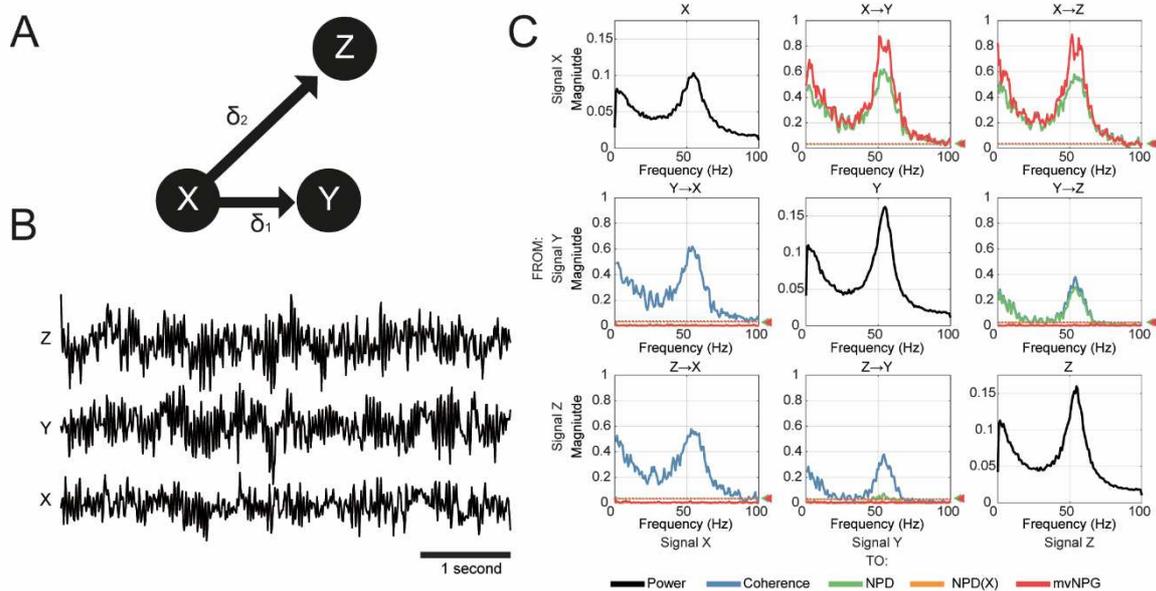
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## 1096 9 Figures

## 1097 9.1 Figure 1(COLOR)

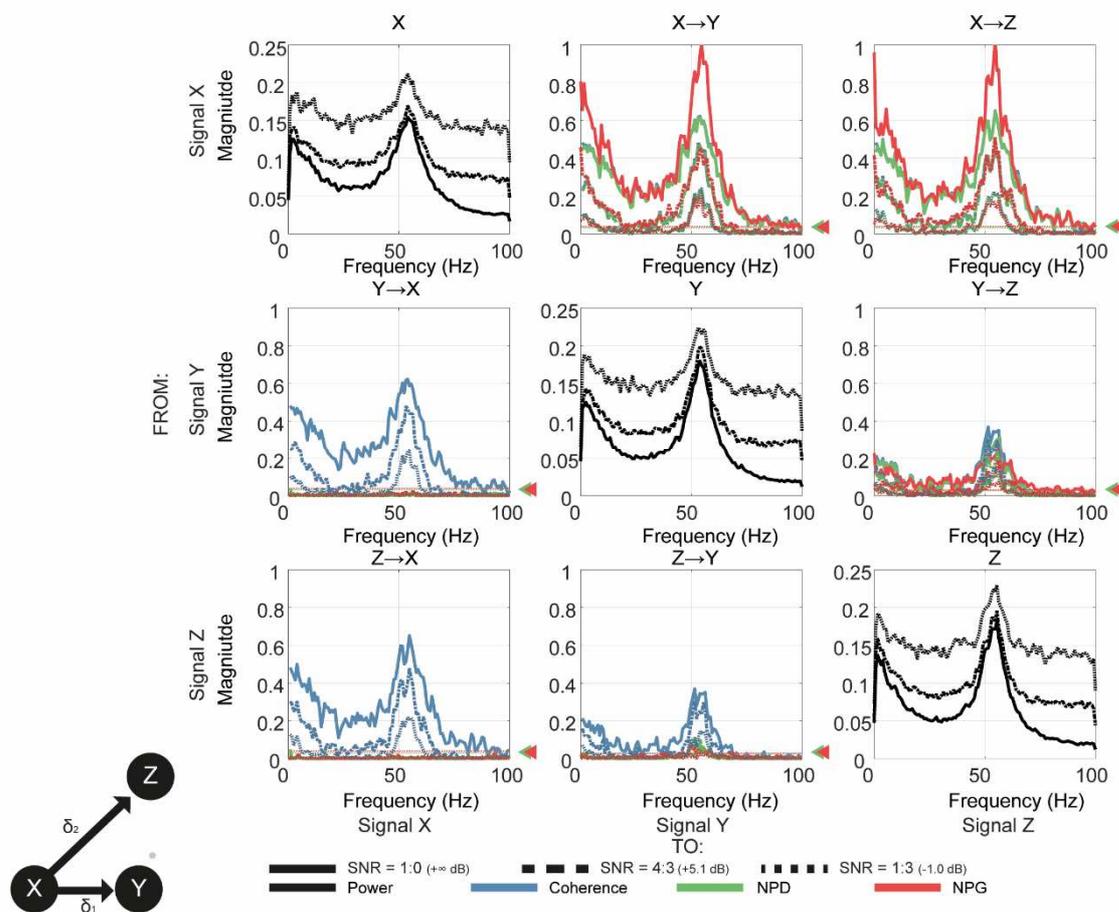


1098

1099 **Figure 1 – Three -node simulation of MVAR model to compare functional connectivity**  
 1100 **measures.** (A) A simple three state, 3<sup>rd</sup> order MVAR model was used to simulate coupling of  
 1101 autonomous periodic signals. Connectivity was simulated using non-zero coefficients at lag 2 for node  
 1102  $X \rightarrow Y$ , and lag 3 for  $X \rightarrow Z$ . Correlations are lagged such that the time delays are unequal (i.e.  $\delta_1 <$   
 1103  $\delta_2$ ). (B) Example 5-second realization of the simulated MVAR processes. (C) Connectivity matrix of  
 1104 the coupled signals. Autospectra are shown on the diagonal (black). Undirected functional  
 1105 connectivity (coherence) is shown in blue. Estimates of directed connectivity are shown for  
 1106 multivariate non-parametric Granger causality (mvNPG; red); Non-parametric Directionality (NPD;  
 1107 green); and NPD conditioned on signal X (NPD(X); orange). NPD identifies spurious directional  
 1108 connectivity between Y and Z due to the lagged correlations of  $X \rightarrow Y$  relative to  $X \rightarrow Z$ . Spurious  
 1109 connectivity is removed partializing the NPD estimate upon the signal at the common source at node  
 1110 X (NPD(X)) which acts to remove all spurious connectivity. Permutation confidence intervals ( $P =$   
 1111 0.001) are shown for NPD and mvNPG by the green and red dashed lines and arrows respectively.

1112

## 1113 9.2 Figure 2 (COLOR)

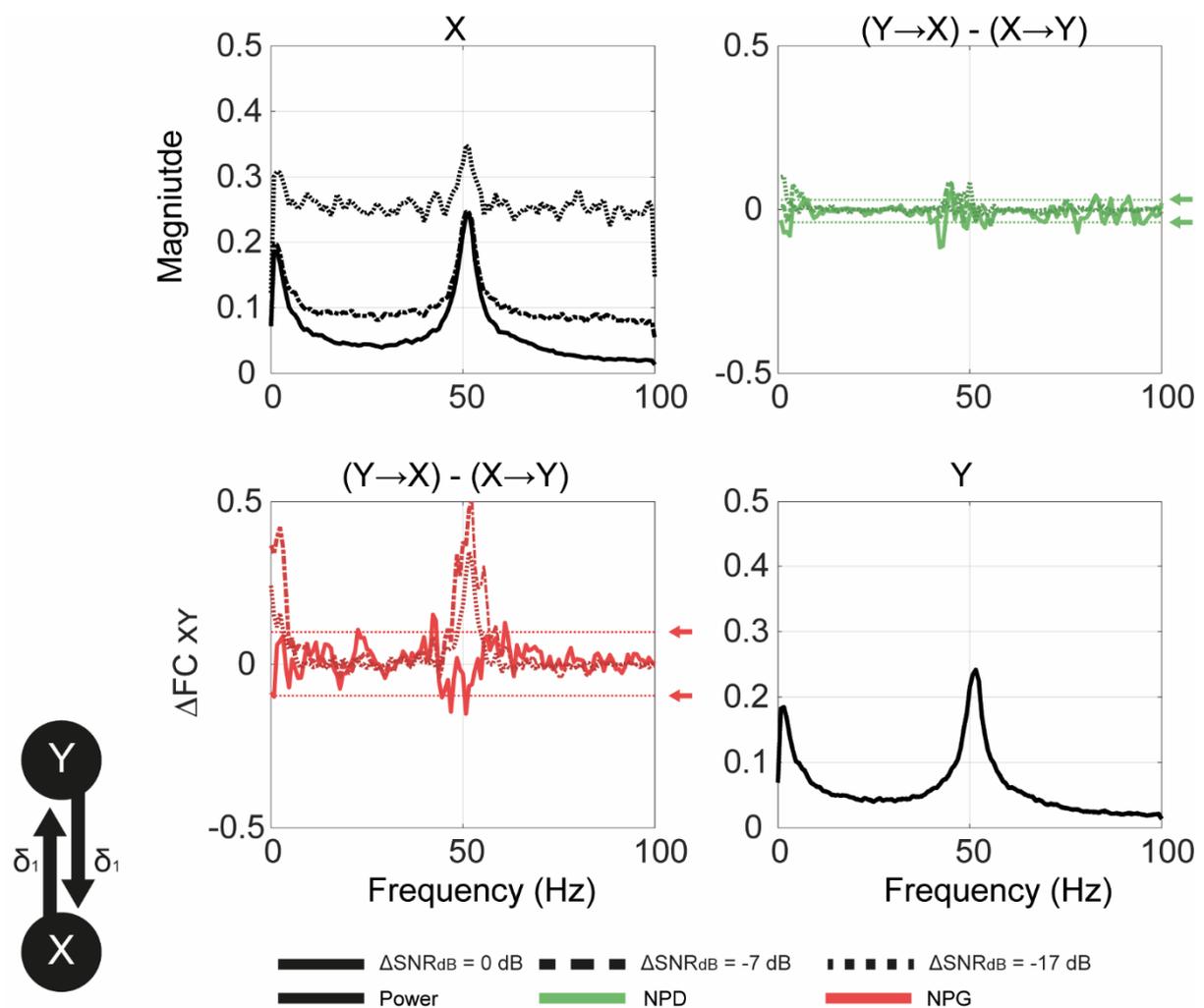


1114

1115 **Figure 2 – Analysis of the effects of signal-to-noise ratio (SNR) upon estimators of directed**  
 1116 **functional connectivity.** The confounding effects of poor SNR were simulated by adding Gaussian  
 1117 noise to the MVAR processes and standardizing the overall variance equal to 1. The MVAR model is  
 1118 identical in form to that used in figure 1 and its structure is given by the ball and stick diagram in the  
 1119 inset. Simulated narrowband (45-55 Hz) SNRs at: 1:0 (+∞ dB; bold), 4:3 (+5.3 dB; ---), and 1:3 (-  
 1120 1.0 dB; ···). The effects upon coherence (blue), NPD (green), and non-parametric Granger causality  
 1121 (NPG) were investigated. All estimators were reduced by increased levels of noise. Permutation  
 1122 confidence intervals ( $P = 0.001$ ) are shown for NPD and NPG by the green and red dashed lines and  
 1123 arrows respectively.

1124

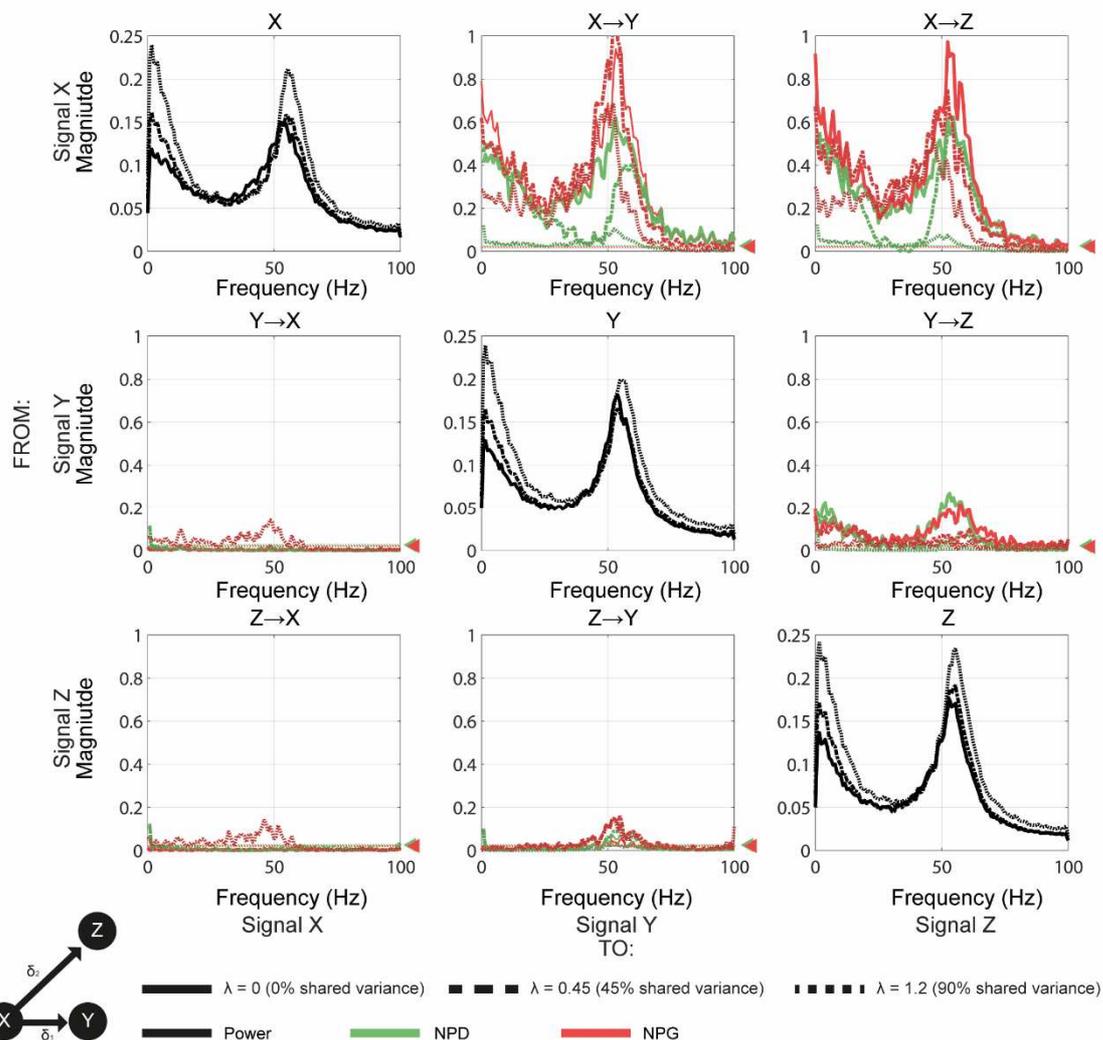
## 1125 9.3 Figure 3 (COLOR)



1126

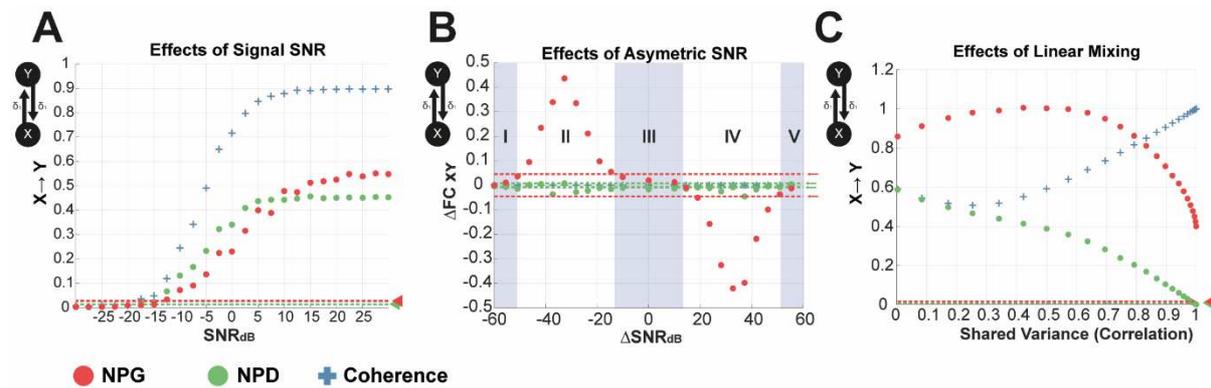
1127 **Figure 3 – Analysis of the effects of unequal signal-to-noise ratios, measured as a difference of**  
 1128 **the SNRs between X and Y ( $\Delta SNR_{XY}$ ) upon symmetrical directed functional connectivity (dFC).**  
 1129 The confounding effect of connected signals having different SNRs was simulated by the addition of  
 1130 Gaussian noise to signal X but fixing the noise of node Y to yield +13 dB. A range of differences in  
 1131 SNR between X and Y ( $\Delta SNR_{XY}$ ) were simulated at 0 dB (bold), -7 dB (---), and -17 dB (···).  
 1132 Connectivity was held fixed to be symmetrical. We assessed dFC by plotting the difference in  
 1133 magnitudes of the connectivity for each direction ( $\Delta FC_{XY}$ ) with  $\Delta FC_{XY} \approx 0$  as the ground truth.  
 1134 Results from both non-parametric directionality (NPD; green) and non-parametric Granger causality  
 1135 (NPG; red) are shown. In the face of medium amounts of SNR asymmetry, NPG spuriously identifies  
 1136 the strongest signal as the driving node. NPD suffers less from this issue and yields approximately  
 1137 symmetrical estimates for all conditions tested.

## 1138 9.4 Figure 4 (COLOR)



**Figure 4 – Analysis of the effects of instantaneous mixing upon estimates of directed functional connectivity (dFC).** The confounding effects of volume conduction were simulated by multiplication of signals with a mixing matrix with off-diagonal coefficients  $\lambda$ . The unmixed signals were first generated with a three state, 3<sup>rd</sup> order MVAR model (identical to that used in figures 1 and 2). We simulate three mixing conditions:  $\lambda = 0$  (zero mixing; bold line),  $\lambda = 0.45$  (45% shared variance; ---), and  $\lambda = 1.2$  (90% shared variance; ...). dFC is estimated using the lagged components of the NPD (green) or non-parametric Granger (NPG) (red). Permutation confidence intervals ( $P = 0.001$ ) are shown for NPD and NPG by the green and red dashed lines and arrows respectively.

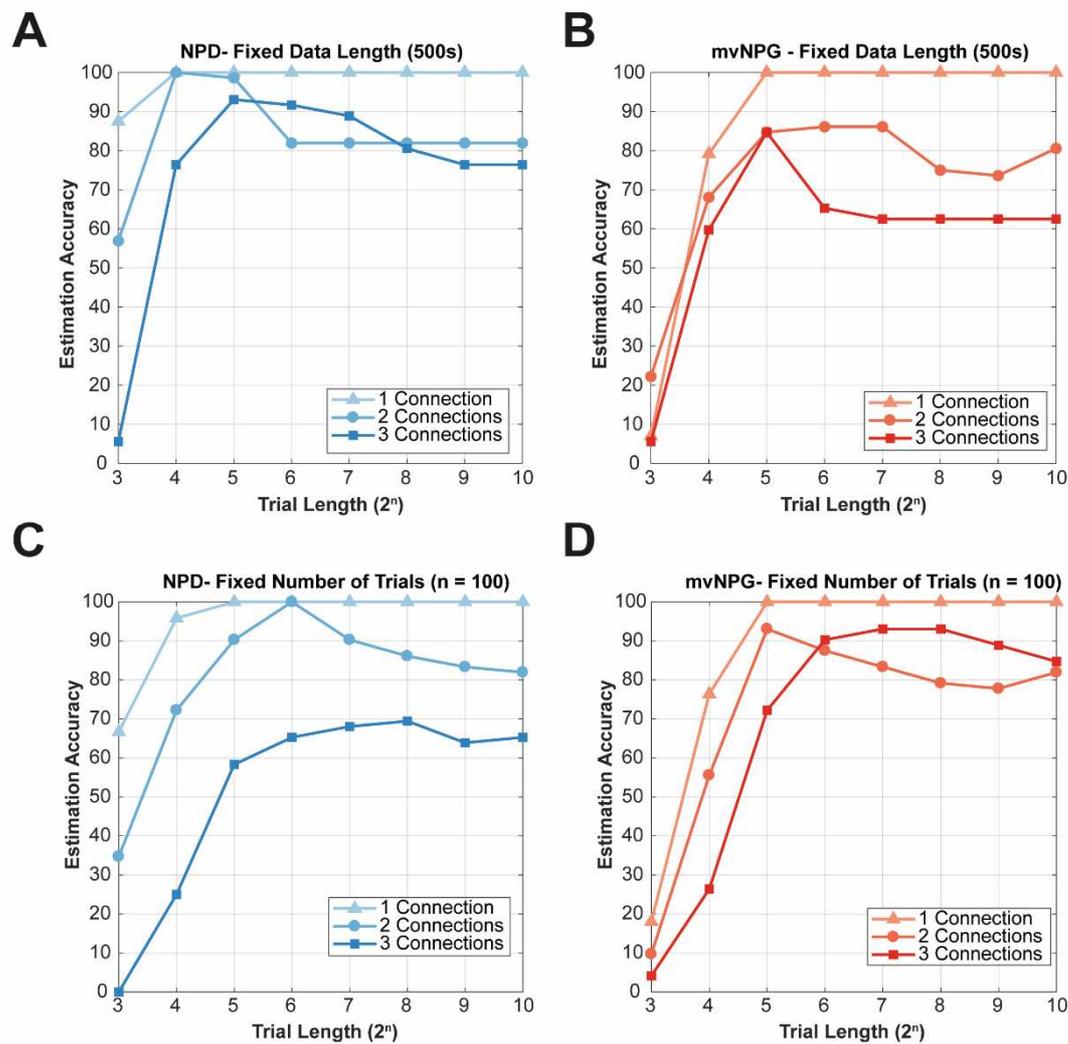
## 1149 9.5 Figure 5 (COLOR)



1150

1151 **Figure 5 – Investigating the effects of signal-to-noise ratios (SNR), SNR asymmetries, and**  
 1152 **instantaneous linear mixing upon functional connectivity measures: coherence (blue), non-**  
 1153 **parametric directionality (NPD; green), and non-parametric Granger causality (NPG; red).** All  
 1154 measures are reported as the peak value for each individual estimate. Permutation confidence intervals  
 1155 ( $P = 0.001$ ) are shown for NPD and NPG by the green and red dashed lines and arrows respectively.  
 1156 **(A)** The effect of SNR was tested in the range from -30 dB to +30 dB. All estimators were found to  
 1157 have a sigmoidal response, with half-maximal suppression around  $SNR = 0$  dB. **(B)** The effect of  
 1158 unequal SNR between nodes X and Y ( $\Delta SNR_{XY}$ ) was varied by addition of observation noise to node  
 1159 X or Y separately to yield a range of narrowband  $\Delta SNR_{XY}$  from -60 dB to +60 dB whilst coupling  
 1160 strengths were held fixed. NPG incorrectly identifies asymmetrical coupling for a wide range of  
 1161  $\Delta SNR_{XY}$  (within zone II from -50 dB to -10 dB as well as zone IV from +10 dB to 50 dB). NPD  
 1162 estimates a weak bias towards one signal leading but with differences in directionality remaining  
 1163 close to zero across the range examined. **(C)** The effect of instantaneous signal mixing was examined  
 1164 across a range of mixing coefficients ( $\lambda$ ) to yield a range of 0% to 100% shared variance. Coherence  
 1165 is shown to increase as zero-lag correlations predominate with increasing valued  $\lambda$ . The lagged NPD  
 1166 shrinks to zero as instantaneous component of coherence dominates. NPG increases to a maximum at  
 1167 around 65% signal mixing and then sharply falls to zero. Permutation confidence intervals ( $P = 0.001$ )  
 1168 are shown for NPD and NPG by the green and red dashed lines and arrows respectively.

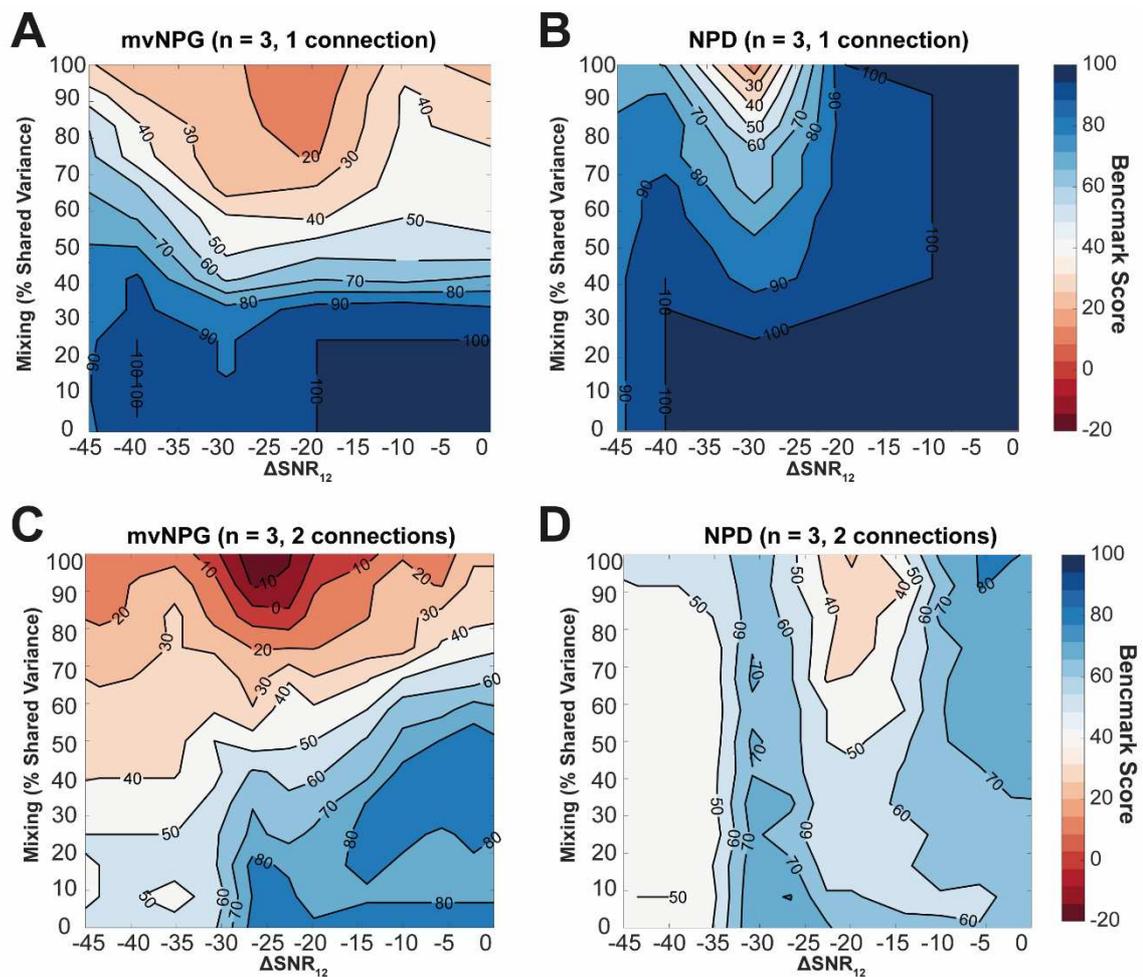
## 1169 9.6 Figure 6 (COLOR)



1170

1171 **Figure 6 – Investigating the role of data availability upon the accuracy of connectivity recovery**  
 1172 **when using non-parametric directionality (NPD; blue), and non-parametric Granger causality**  
 1173 **(NPG; red).** The two estimators were benchmarked against three sets of 24 MVAR models with  
 1174 random connectivity comprising either one, two, or three connections respectively. Different amounts  
 1175 of data were simulated for each model and the accuracy of the recovery was scored using the criteria  
 1176 set out in the methods. Simulated data is sampled at 200 Hz. **(A and B)** Benchmarks recorded from  
 1177 analyses of simulated data in which there was a fixed amount of data (500s) but allowing for variable  
 1178 trial lengths (in samples). **(C and D)** Benchmarks recorded from analyses of simulated data in which  
 1179 there were a fixed number of trials ( $n = 100$ ) but variable total data length.

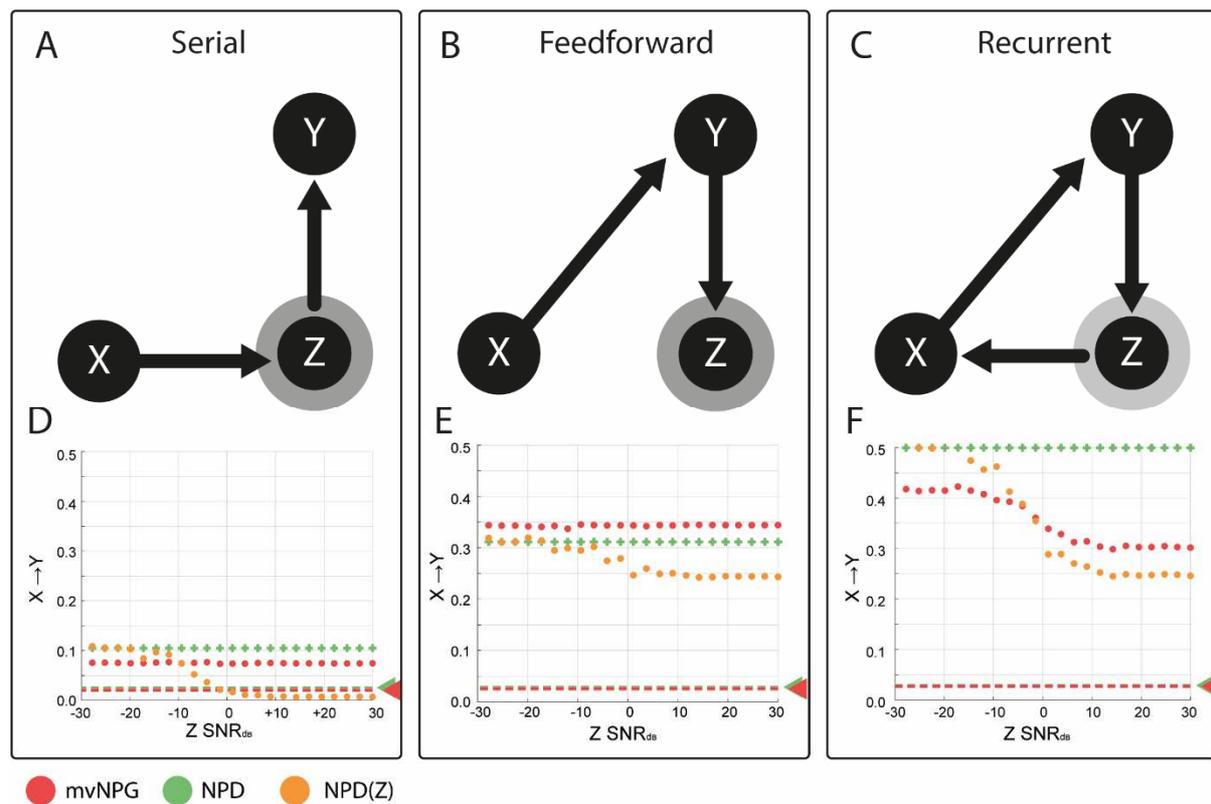
## 1180 9.7 Figure 7 (COLOR)



1181

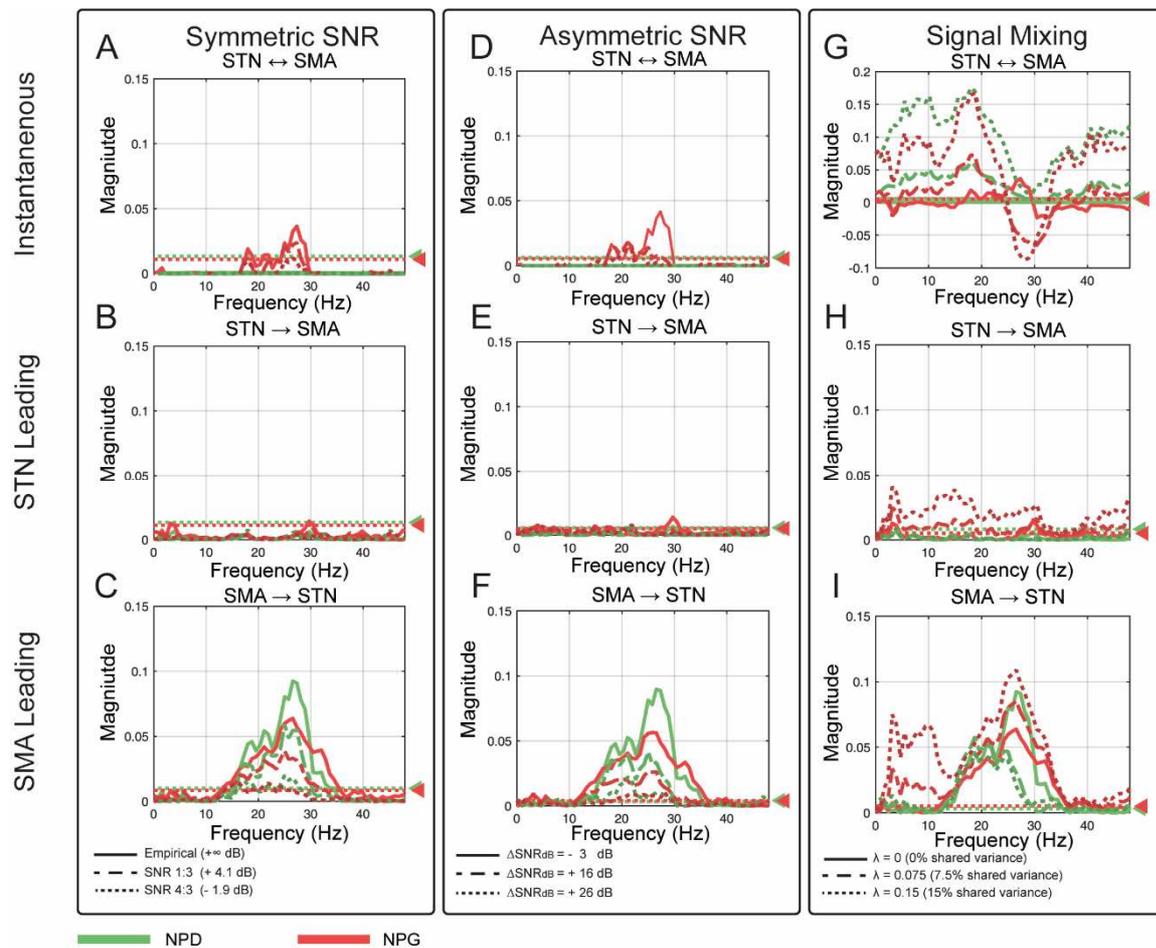
1182 **Figure 7 – Investigating the role of combined data confounds (instantaneous mixing and**  
 1183 **asymmetric signal-to-noise ratio;  $\Delta SNR_{XY}$ ) upon the accuracy of connectivity estimation when**  
 1184 **using non-parametric directionality, and non-parametric multivariate Granger causality.** The  
 1185 two measures were benchmarked against two sets of 24 realizations of a 3-node MVAR models  
 1186 comprising either one (top row), or two (bottom row) randomly placed connections. For each  
 1187 simulation 200s of data was simulated and divided into epochs of  $2^8$  samples. Simulated data is  
 1188 sampled at 200 Hz. All data is represented as a contour plot when varying first instantaneous mixing  
 1189 from 0% to 100% shared variance; and then adjusting the approximate asymmetric narrowband (45-  
 1190 55 Hz) SNR from -45 dB to 0 dB. **(A)** Benchmarking of mvNPG with simulations containing one  
 1191 randomly placed connection on a three-node network. **(B)** Same as for (A) but using NPD. **(C)**  
 1192 Benchmarking of mvNPG with simulations containing two randomly placed connections on a three-  
 1193 node network. **(D)** Same as for (C) but using NPD as the estimator.

## 1194 9.8 Figure 8 (COLOR)



1196 **Figure 8 – The effects of incomplete signal observation upon estimation of directed functional**  
 1197 **connectivity: non-parametric Granger causality (NPG); non-parametric directionality (NPD);**  
 1198 **and NPD conditioned on reference signal Z (NPD(Z)).** Simulations investigate the connectivity of  
 1199  $X \rightarrow Y$  and the influence of propagation involving a tertiary node  $Z$ . We simulate incomplete  
 1200 sampling of  $Z$  by modifying its signal-to-noise ratio (SNR) via the addition of Gaussian white noise  
 1201 and then standardizing the variance equal to 1. **(A and D) Serial propagation** – signals propagate  
 1202 from  $X \rightarrow Z \rightarrow Y$ . The results of changing the SNR of  $Z$  are shown in panel D. Simulations  
 1203 demonstrate that dFC estimation with NPD/NPG are constant. At complete signal observation (SNR  
 1204 1:0;  $+\infty$  dB), conditioning removes the estimate of dFC. With increasing SNR, the attenuation is  
 1205 diminished to the point where conditioning has no effect. **(B and E) Feedforward connectivity** –  
 1206 signals propagate to feedforward to the tertiary node:  $X \rightarrow Y \rightarrow Z$ . We find that conditioning has a  
 1207 weak effect (panel E), and the attenuation of NPD(Z) for estimation of  $X \rightarrow Y$  is again reduced by  
 1208 decreasing SNR of  $Z$ . **(C and F) Recurrent connectivity** – a further connection is added to the model  
 1209 to complete a cyclic path in the network:  $X \rightarrow Z \rightarrow Y \rightarrow X$ . Decreasing the SNR of  $Z$  results in an  
 1210 increased estimation of NPG in  $X \rightarrow Y$  (panel F). We again find that that increased completeness of  
 1211 observation of  $Z$  results in an increase in the efficacy of NPD(Z) in determining tertiary (non-direct)  
 1212 signal routing.

## 1213 9.9 Figure 9 (COLOR)



1214

1215 **Figure 9 – Testing for the confounding effects of symmetric and asymmetric SNR, and**  
 1216 **instantaneous signal mixing upon estimation of directed functional connectivity in experimental**  
 1217 **data recorded in patients with Parkinson’s disease.** Empirical data is comprised of local field  
 1218 potentials recorded from the STN and a virtual electrode localized to the SMA, computed from  
 1219 whole-head magnetoencephalography. Signals were analysed for dFC using the instantaneous  
 1220 components (first row); STN → SMA (second row); and SMA → STN (third row) parts of the NPD  
 1221 (green) and NPG (red). Empirical data is indicated by bold line; low by the dotted (···); and high  
 1222 degrees by the dashed (---). (A-C) The effect of modulating the overall SNR of the signals equally.  
 1223 We used a range of narrowband (14-31 Hz) SNRs: 1:1 (+∞ dB; bold); 4:3 (+4.1 dB; ---); and 1:3 (-  
 1224 1.9 dB; ···). (D-F) The effect of modulating the SNR of the strongest signal (STN) only. We used a  
 1225 range of  $\Delta\text{SNR}_{\text{STN}}$ : -3 dB (bold); +16 dB (---); and +26 dB (···). (G-I) The effect of modulating the  
 1226 degree of instantaneous mixing between signals. We simulated a degree of signal mixing:  $\lambda = 0$  (0%  
 1227 shared variance; bold);  $\lambda = 0.075$  (7.5% shared variance; ---); and  $\lambda = 0.15$  (15% shared variance; ···).

1228 **10 Appendices**1229 **10.1 List of External Toolboxes Used in Analysis, Statistics, and**  
1230 **Plotting**

- 1231 1. BSMART toolbox- Hualou Liang, Steven Bressler, Mingzhou Ding (Cui et al. 2008):  
1232 <http://www.brain-smart.org/>
- 1233 2. Fieldtrip toolbox- Donders Insitute, Radboud University (Oostenveld et al. 2011a):  
1234 [www.fieldtriptoolbox.org/](http://www.fieldtriptoolbox.org/)
- 1235 3. Linspecer - David Kun: <https://github.com/davidkun/linspecer>
- 1236 4. Neurospec 2.11 toolbox- David Halliday, University of York: <http://www.neurospec.org/>
- 1237 5. SPM 12 toolbox- UCL, Wellcome Centre for Human Neuroscience:  
1238 <https://www.fil.ion.ucl.ac.uk/spm/>

1239

1240 **10.2 Table of MVAR Coefficients****Simulating Common Drive, Signal-to-noise, instantaneous mixing (figure 1, 2, 4, 5C)***Transfer Matrix*

$$A_1 = \begin{bmatrix} 0.5 & 0 & 0 \\ 0 & 0.5 & 0 \\ 0 & 0 & 0.5 \end{bmatrix}$$

$$A_2 = \begin{bmatrix} -0.5 & 0 & 0 \\ 0.5 & -0.5 & 0 \\ 0 & 0 & -0.5 \end{bmatrix}$$

$$A_3 = \begin{bmatrix} 0.5 & 0 & 0 \\ 0 & 0.5 & 0 \\ 0.5 & 0 & 0.5 \end{bmatrix}$$

*Noise Covariance Matrix*

$$\epsilon = \begin{bmatrix} 0.3 & 0 & 0 \\ 0 & 0.3 & 0 \\ 0 & 0 & 0.3 \end{bmatrix}$$

**Simulating Asymmetric Signal-to-noise (figure 3, 5A, 5B)***Transfer Matrix*

$$A_1 = \begin{bmatrix} 0.5 & 0 \\ 0 & 0.5 \end{bmatrix}$$

$$A_2 = \begin{bmatrix} -0.5 & 0.35 \\ 0.35 & -0.5 \end{bmatrix}$$

$$A_3 = \begin{bmatrix} 0.5 & 0 \\ 0 & 0.5 \end{bmatrix}$$

*Noise Covariance Matrix*

$$\epsilon = \begin{bmatrix} 0.3 & 0 \\ 0 & 0.3 \end{bmatrix}$$

**Simulating Incomplete Signals for Conditioning: Serial (figure 8A, D)***Transfer Matrix*

$$A_1 = \begin{bmatrix} 0.5 & 0 & 0 \\ 0 & 0.5 & 0 \\ 0 & 0 & 0.5 \end{bmatrix}$$

*Noise Covariance Matrix*

$$\epsilon = \begin{bmatrix} 0.3 & 0 & 0 \\ 0 & 0.3 & 0 \\ 0 & 0 & 0.3 \end{bmatrix}$$

$$A_2 = \begin{bmatrix} -0.5 & 0 & 0 \\ 0 & -0.5 & 0 \\ 0 & 0 & -0.5 \end{bmatrix}$$

$$A_3 = \begin{bmatrix} 0 & 0 & 0 \\ 0.3 & 0 & 0 \\ 0 & 0.3 & 0 \end{bmatrix}$$

**Simulating Incomplete Signals for Conditioning: Feedforward (figure 8B, E)***Transfer Matrix**Noise Covariance Matrix*

$$A_1 = \begin{bmatrix} 0.5 & 0 & 0 \\ 0 & 0.5 & 0 \\ 0 & 0 & 0.5 \end{bmatrix}$$

$$A_2 = \begin{bmatrix} -0.5 & 0 & 0 \\ 0 & -0.5 & 0 \\ 0 & 0 & -0.5 \end{bmatrix}$$

$$A_3 = \begin{bmatrix} 0.5 & 0 & 0 \\ 0 & 0.5 & 0 \\ 0.3 & 0 & 0.5 \end{bmatrix}$$

$$\epsilon = \begin{bmatrix} 0.3 & 0 & 0 \\ 0 & 0.3 & 0 \\ 0 & 0 & 0.3 \end{bmatrix}$$

**Simulating Incomplete Signals for Conditioning: Recurrent (figure 68, F)***Transfer Matrix**Noise Covariance Matrix*

$$A_1 = \begin{bmatrix} 0.5 & 0 & 0 \\ 0 & 0.5 & 0 \\ 0 & 0 & 0.5 \end{bmatrix}$$

$$A_2 = \begin{bmatrix} -0.5 & 0 & 0 \\ 0 & -0.5 & 0 \\ 0 & 0 & -0.5 \end{bmatrix}$$

$$A_3 = \begin{bmatrix} 0 & 0.3 & 0 \\ 0 & 0 & 0.3 \\ 0.3 & 0 & 0 \end{bmatrix}$$

$$\epsilon = \begin{bmatrix} 0.3 & 0 & 0 \\ 0 & 0.3 & 0 \\ 0 & 0 & 0.3 \end{bmatrix}$$

1241

1242 **10.3 Permutation Testing for Significance Thresholds**

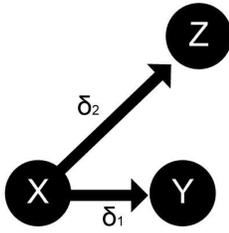
1243 Estimates of interactions between signals can give rise to non-zero values in the absence of any  
 1244 interaction. To check whether an observed value of an estimator is statistically significant, its value  
 1245 can be compared against a distribution of the same index estimated from surrogate data (Theiler et al.  
 1246 1992). This surrogate data must preserve the statistics of the individual signals whilst removing the  
 1247 property to be tested, namely the interactions between them. Once a null distribution is obtained,  
 1248 (rank-order) significance thresholds can be calculated from the corresponding percentiles of the  
 1249 surrogate distribution (e.g. a  $P = 0.01$  threshold can be estimated from the 99<sup>th</sup> percentile).

1250 Many possibilities exist for the generation of surrogates and methods range from the very simple  
 1251 permutation of the time series samples, up to increasingly complex surrogates that aim to maintain  
 1252 nonlinear features of the individual signals (for reviews see: Lancaster et al. 2018; Pereda et al. 2005).  
 1253 All methods will fall short at capturing all confounding properties of the individual generators of the  
 1254 signals including the phase randomization method (Zalesky and Breakspear 2015).

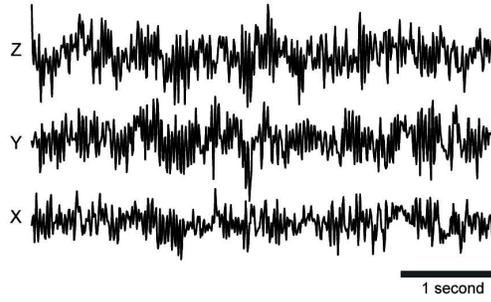
1255 In this work we use a phase randomization approach. We maintain the original FFTs of the signals but  
1256 randomize the phase of the individual Fourier components. To do this we generate a vector of random  
1257 phases  $\Psi$  uniformly sampled on the interval  $[0, 2\pi]$  for  $N/2$  samples and multiply the first half of the  
1258 FFT by  $\exp(i\Psi)$ . The remainder of the FFT is then the horizontally flipped complex conjugate of the  
1259 first half. This method ensures that the overall expected value of the magnitude of the averaged  
1260 spectral estimate is equal to zero. See Lancaster et al. (2018) for a discussion of this method and  
1261 Breakspear and Terry (2002) for application to assessing interdependence of neurophysiological  
1262 signals.

Journal Pre-proof

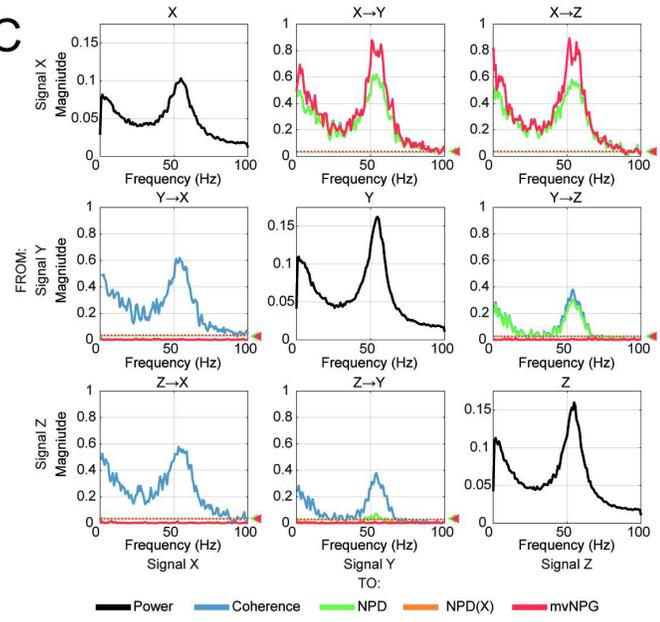
A



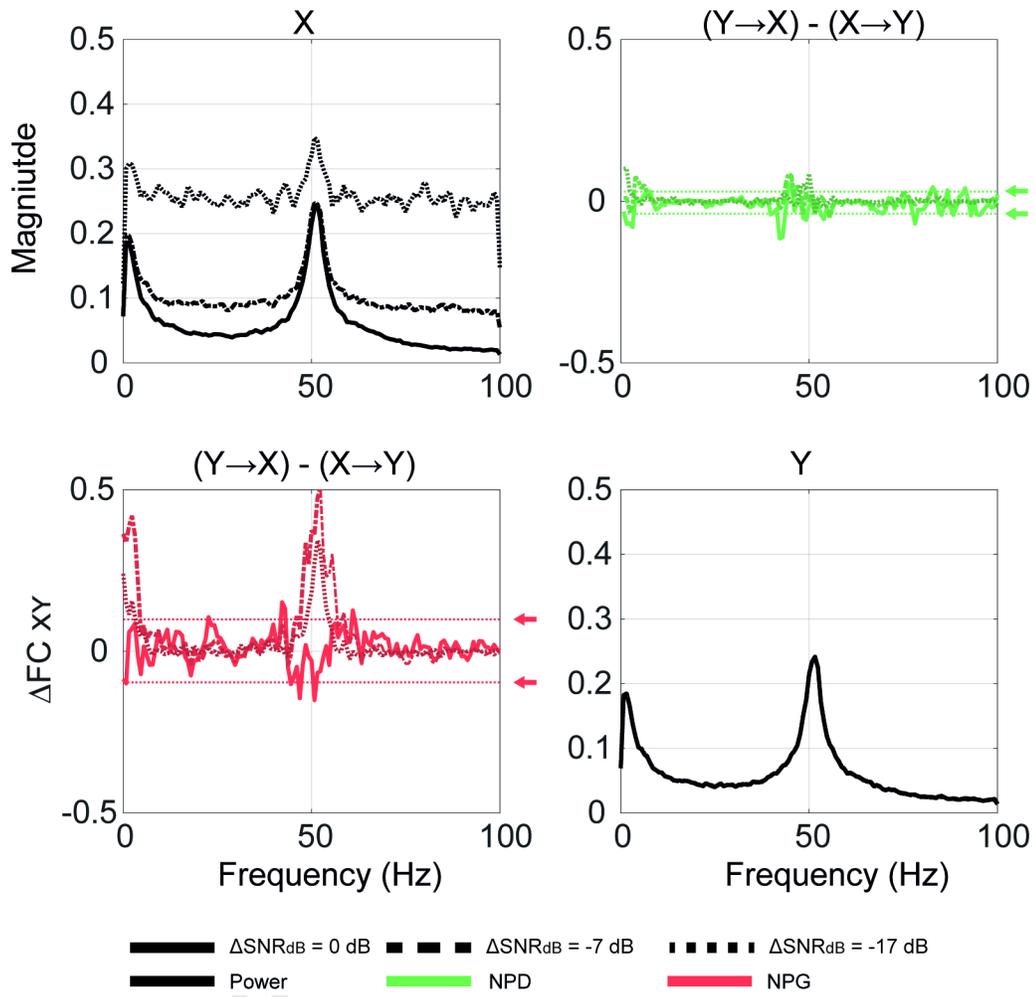
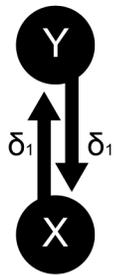
B

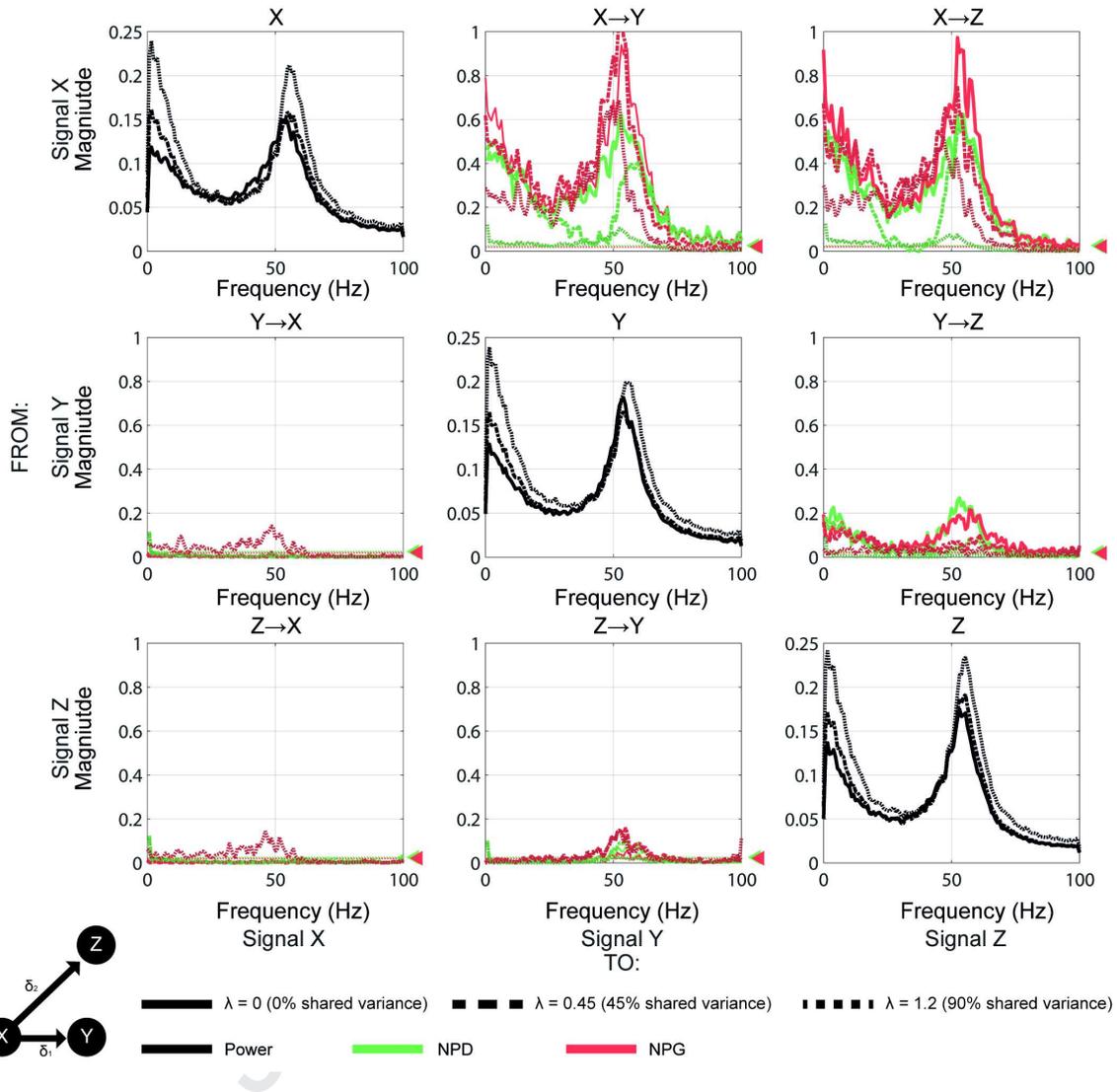


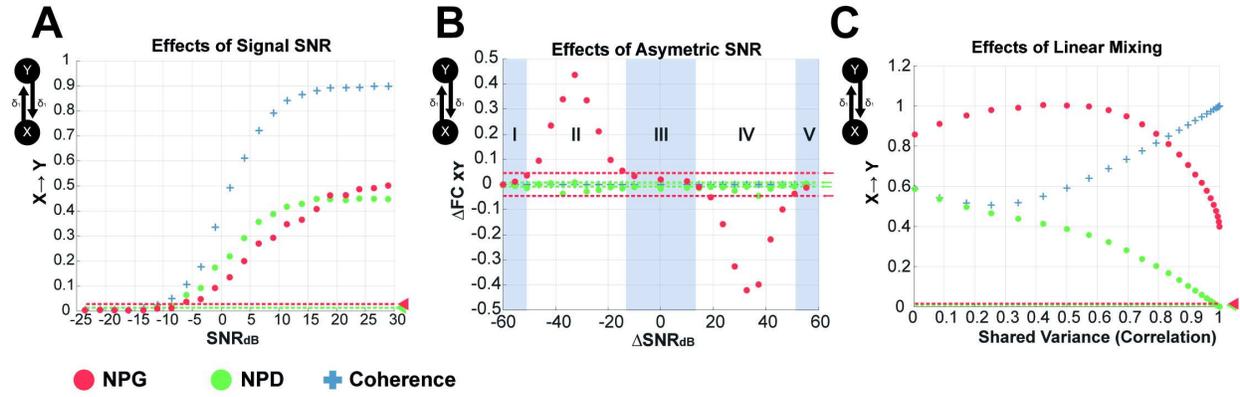
C

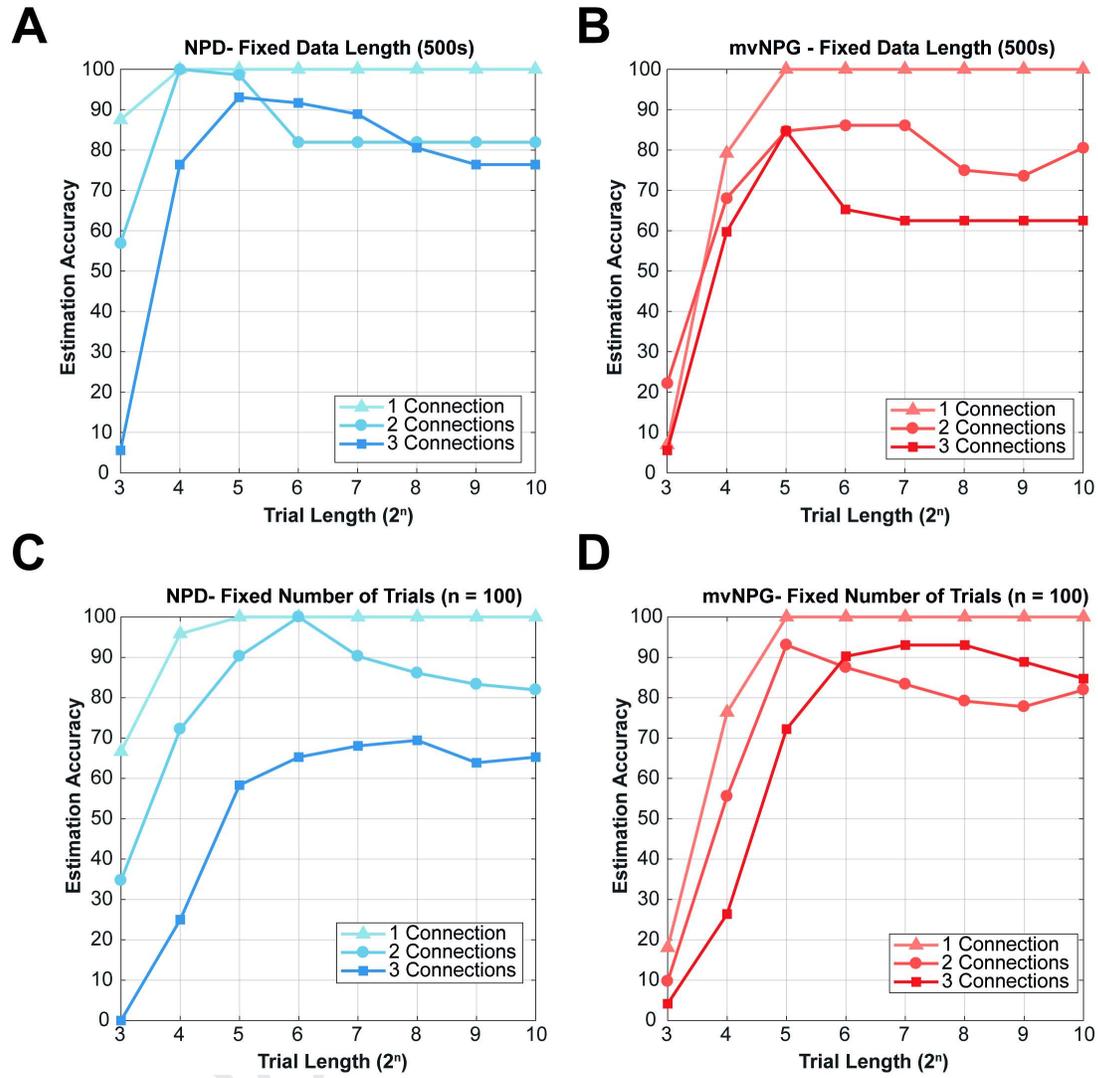


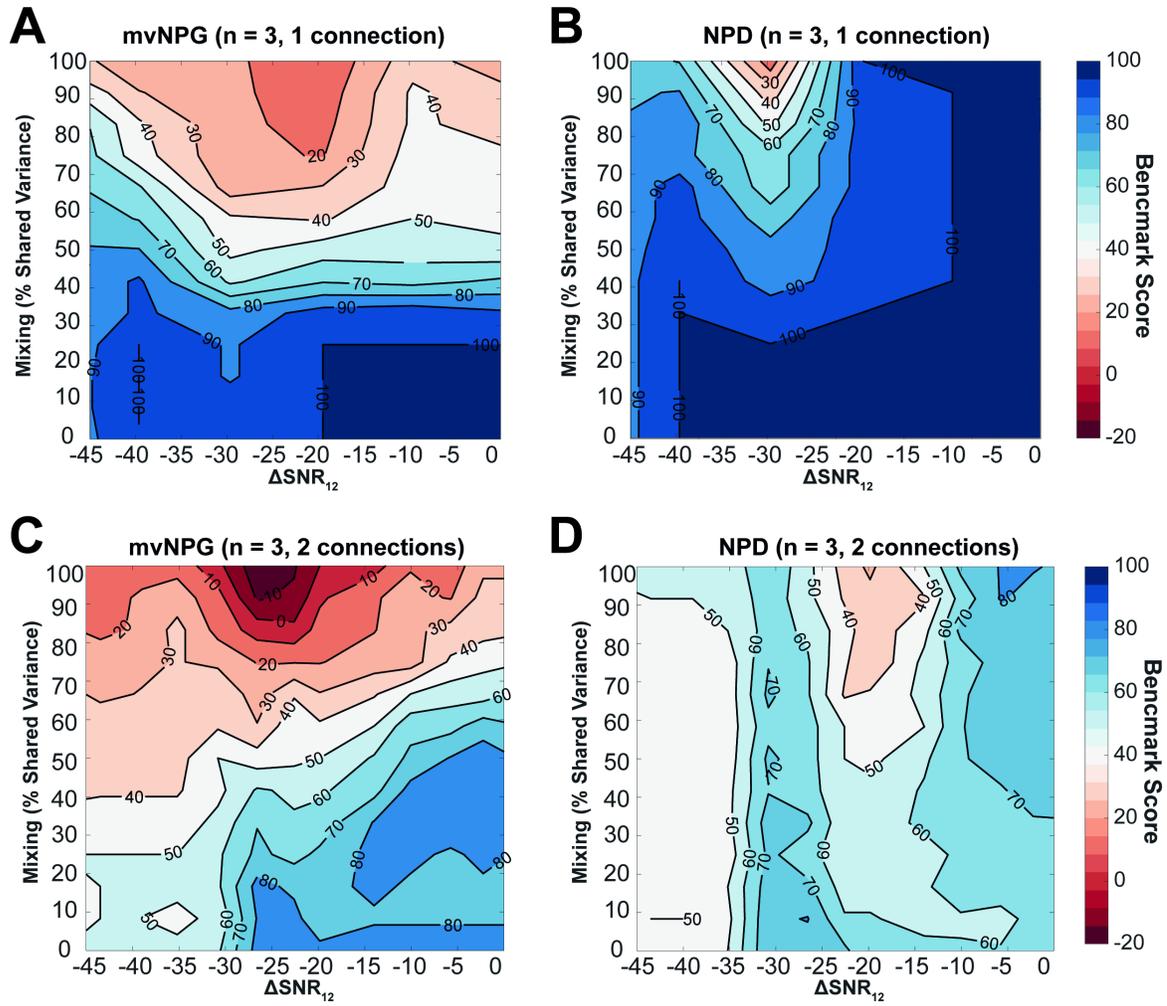


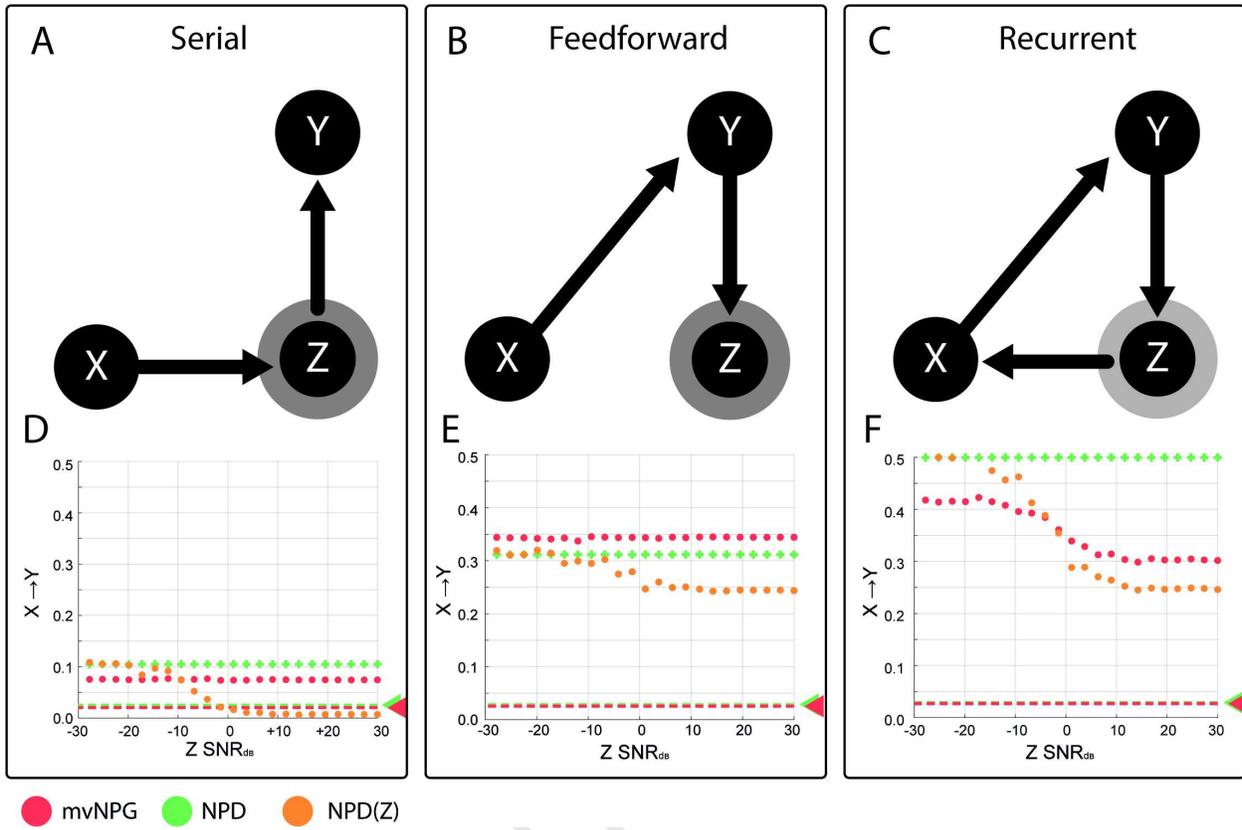


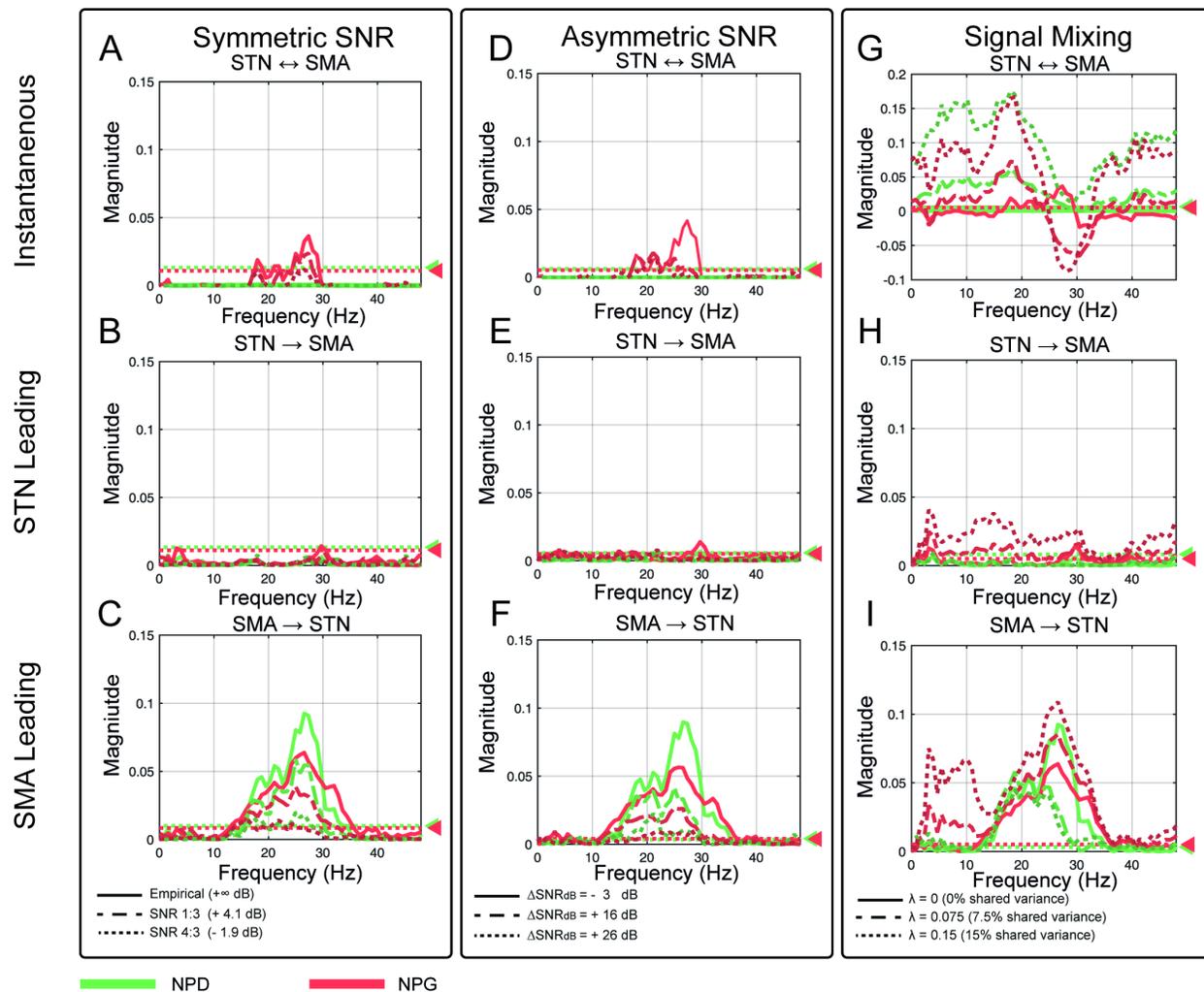












## 1.1 Table of MVAR Coefficients

Simulating Common Drive, Signal-to-noise, instantaneous mixing (figure 1, 2, 4, 5C)	
Transfer Matrix	Noise Covariance Matrix
$A_1 = \begin{bmatrix} 0.5 & 0 & 0 \\ 0 & 0.5 & 0 \\ 0 & 0 & 0.5 \end{bmatrix}$ $A_2 = \begin{bmatrix} -0.5 & 0 & 0 \\ 0.5 & -0.5 & 0 \\ 0 & 0 & -0.5 \end{bmatrix}$ $A_3 = \begin{bmatrix} 0.5 & 0 & 0 \\ 0 & 0.5 & 0 \\ 0.5 & 0 & 0.5 \end{bmatrix}$	$\epsilon = \begin{bmatrix} 0.3 & 0 & 0 \\ 0 & 0.3 & 0 \\ 0 & 0 & 0.3 \end{bmatrix}$
Simulating (A)symmetric Signal-to-noise (figure 3, 5A, 5B)	
Transfer Matrix	Noise Covariance Matrix
$A_1 = \begin{bmatrix} 0.5 & 0 \\ 0 & 0.5 \end{bmatrix}$ $A_2 = \begin{bmatrix} -0.5 & 0.35 \\ 0.35 & -0.5 \end{bmatrix}$ $A_3 = \begin{bmatrix} 0.5 & 0 \\ 0 & 0.5 \end{bmatrix}$	$\epsilon = \begin{bmatrix} 0.3 & 0 \\ 0 & 0.3 \end{bmatrix}$
Simulating Incomplete Signals for Conditioning: Serial (figure 8A, D)	
Transfer Matrix	Noise Covariance Matrix
$A_1 = \begin{bmatrix} 0.5 & 0 & 0 \\ 0 & 0.5 & 0 \\ 0 & 0 & 0.5 \end{bmatrix}$ $A_2 = \begin{bmatrix} -0.5 & 0 & 0 \\ 0 & -0.5 & 0 \\ 0 & 0 & -0.5 \end{bmatrix}$ $A_3 = \begin{bmatrix} 0 & 0 & 0 \\ 0.3 & 0 & 0 \\ 0 & 0.3 & 0 \end{bmatrix}$	$\epsilon = \begin{bmatrix} 0.3 & 0 & 0 \\ 0 & 0.3 & 0 \\ 0 & 0 & 0.3 \end{bmatrix}$
Simulating Incomplete Signals for Conditioning: Feedforward (figure 8B, E)	
Transfer Matrix	Noise Covariance Matrix
$A_1 = \begin{bmatrix} 0.5 & 0 & 0 \\ 0 & 0.5 & 0 \\ 0 & 0 & 0.5 \end{bmatrix}$ $A_2 = \begin{bmatrix} -0.5 & 0 & 0 \\ 0 & -0.5 & 0 \\ 0 & 0 & -0.5 \end{bmatrix}$ $A_3 = \begin{bmatrix} 0.5 & 0 & 0 \\ 0 & 0.5 & 0 \\ 0.3 & 0 & 0.5 \end{bmatrix}$	$\epsilon = \begin{bmatrix} 0.3 & 0 & 0 \\ 0 & 0.3 & 0 \\ 0 & 0 & 0.3 \end{bmatrix}$
Simulating Incomplete Signals for Conditioning: Recurrent (figure 6C, F)	
Transfer Matrix	Noise Covariance Matrix

$$A_1 = \begin{bmatrix} 0.5 & 0 & 0 \\ 0 & 0.5 & 0 \\ 0 & 0 & 0.5 \end{bmatrix}$$

$$A_2 = \begin{bmatrix} -0.5 & 0 & 0 \\ 0 & -0.5 & 0 \\ 0 & 0 & -0.5 \end{bmatrix}$$

$$A_3 = \begin{bmatrix} 0 & 0.3 & 0 \\ 0 & 0 & 0.3 \\ 0.3 & 0 & 0 \end{bmatrix}$$

$$\epsilon = \begin{bmatrix} 0.3 & 0 & 0 \\ 0 & 0.3 & 0 \\ 0 & 0 & 0.3 \end{bmatrix}$$

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