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The physiological plausibility of time-varying Granger-causal modeling: Normalization and weighting by spectral power

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ABSTRACT

Time-varying connectivity methods are increasingly used to study directed interactions between brain regions from electrophysiological signals. These methods often show good results in simulated data but it is unclear to what extent connectivity results obtained from real data are physiologically plausible. Here we introduce a benchmark approach using multichannel somatosensory evoked potentials (SEPs) measured across rat cortex, where the structural and functional connectivity is relatively simple and well-understood. Rat SEPs to whisker stimulation are exclusively initiated by contralateral primary sensory cortex (S1), at known latencies, and with activity spread from S1 to specific cortical regions. This allows for a comparison of time-varying connectivity measures according to fixed criteria. We thus evaluated the performance of time-varying Partial Directed Coherence (PDC) and the Directed Transfer Function (DTF), comparing row- and column-wise normalization and the effect of weighting by the power spectral density (PSD). The benchmark approach revealed clear differences between methods in terms of physiological plausibility, effect size and temporal resolution. The results provide a validation of time-varying directed connectivity methods in an animal model and suggest a driving role for ipsilateral S1 in the later part of the SEP. The benchmark SEP dataset is made freely available.

Introduction

Sensory, cognitive and motor processing consists of dynamically coordinated activity in functional networks of brain regions. In such large-scale networks the activity in one region may drive activity in other regions, and which regions drive one another varies with time and task. A better understanding of directed interactions and their dynamics may help to better comprehend sensory and cognitive processing in both health and disease (Bressler and Seth, 2011; Bressler, 1995). Reliable time-varying methods are therefore needed that can identify from electrophysiological signals what the important drivers of cortical networks are, which regions they most strongly drive to, and how driving from each region varies with time.

Various time-varying methods exist that can model directed interactions from non-stationary electrophysiological recordings (Astolfi et al., 2008; Ding et al., 2000; Hesse et al., 2003; Hu et al., 2012; Lin et al., 2009; Milde et al., 2010; Porcaro et al., 2013; Sommerlade et al., 2012; van Mierlo et al., 2011; Wilke et al., 2007). Such methods may correctly represent directed interactions in simulated data but when applied to human data it is often unclear whether connectivity results correctly reflect the underlying physiology. This is because EEG and MEG signals at each electrode or source point reflect activity from multiple regions to unknown extents: the problem of volume conduction (Gómez-Herrero et al., 2008; Haufe et al., 2013; Nolte et al., 2004; Nunez and Srinivasan, 2006). In addition, large-scale human functional connectivity and its dynamics are not well-understood so that connectivity results cannot be easily compared to the underlying physiology, even in intracranial recordings.

We here use multichannel electrophysiological recordings from rats as a benchmark to test the performance of directed, time-varying connectivity methods. In rat cortex structural and functional connectivity are simpler than in human, and better understood because more direct electrophysiological measures are possible in animal models. After unilateral whisker stimulation the spatiotemporal dynamics of evoked activity follows a known pattern that reflects the underlying structural connectivity (Quairiaux et al., 2011). Rat SEPs can therefore provide a good benchmark to evaluate results from time-varying connectivity estimators, for three reasons in particular. Firstly, the SEP is entirely driven by the primary sensory cortex contralateral (cS1) to whisker stimulation (Farkas et al., 1999; Shuler et al., 2001). Secondly, activity in cS1 is known to start at around 5 ms after whisker stimulation and ceases at around 25 ms, as shown by intracranial recordings in anesthetized animals (Armstrong-James et al., 1992; Constantinople and Bruno, 2013; Quairiaux et al., 2011).

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Outside these latencies driving from cS1 to other regions is physiologically not plausible. Thirdly, cS1 has structural connections to specific regions in both hemispheres (Colechio and Alloway, 2009; Hoffer et al., 2003; Lee et al., 2011; Smith and Alloway, 2013; Zakiewicz et al., 2011). In line with structural connectivity, contralateral parietal and frontal sensory-motor regions become active immediately after cS1 (see Fig. 1, dark blue and orange traces).

Out of the numerous published Granger-causal methods we here selected time-varying PDC and DTF for comparison (Kaminski and Blinowska, 1991; Baccalá and Sameshima, 2001; Astolfi et al., 2008). These methods, based on multivariate autoregressive modeling, are variations within the Wiener–Granger causality theoretic framework, quantifying how activity at one region predicts activity at other regions (Bressler and Seth, 2011; Granger, 1969).

PDC is a linear multivariate method that separates direct from indirect connections and can correctly identify interactions even in relatively noisy data (Astolfi et al., 2006, 2007b; Baccalá and Sameshima, 2001; Fasoula et al., 2013; Florin et al., 2011). Stability and interpretability of PDC results are achieved through normalization. The original PDC definition normalizes the outgoing connection strengths from each region, a *column-wise* normalization that bounds the sum of the outflows per region to one (Baccalá and Sameshima, 2001). This bounding however, may compromise the sensitivity to outflows and therefore a normalization by inflows may be preferred. This *row-wise* normalization is part of the original DTF definition and has also been applied to PDC (Astolfi et al., 2007a; Kaminski and Blinowska, 1991; Kus et al., 2004). Row-wise normalized methods may be advantageous in studying neural systems because they allow more variability in outgoing connection strengths, but to our knowledge a direct comparison of the effects of row- and column-wise normalizations in real data is so far missing.

PDC is a measure in the frequency domain that quantifies to what degree a power change at frequency *f* predicts a power change in another region at *f*. That is, PDC represents a directional *rate of change* in the spectral power between two regions: large $PDC_{(f)}$ indicates that increased spectral power in the source region yields a large increase in the destination region (Schelter et al., 2009). However, the PDC calculation is independent of the signal spectral power, and therefore large PDC can occur from regions that show little spectral power, and vice versa. PDC values therefore lack a clear physiological interpretation (Baccalá and Sameshima, 2001; Faes et al., 2012). To increase the physiological interpretability we weigh PDC values by the instantaneous power spectral density (PSD) in the source region. This weighting reflects the fact that activity in a source region is necessary, but not sufficient, in order for the source region to effectively drive activity in

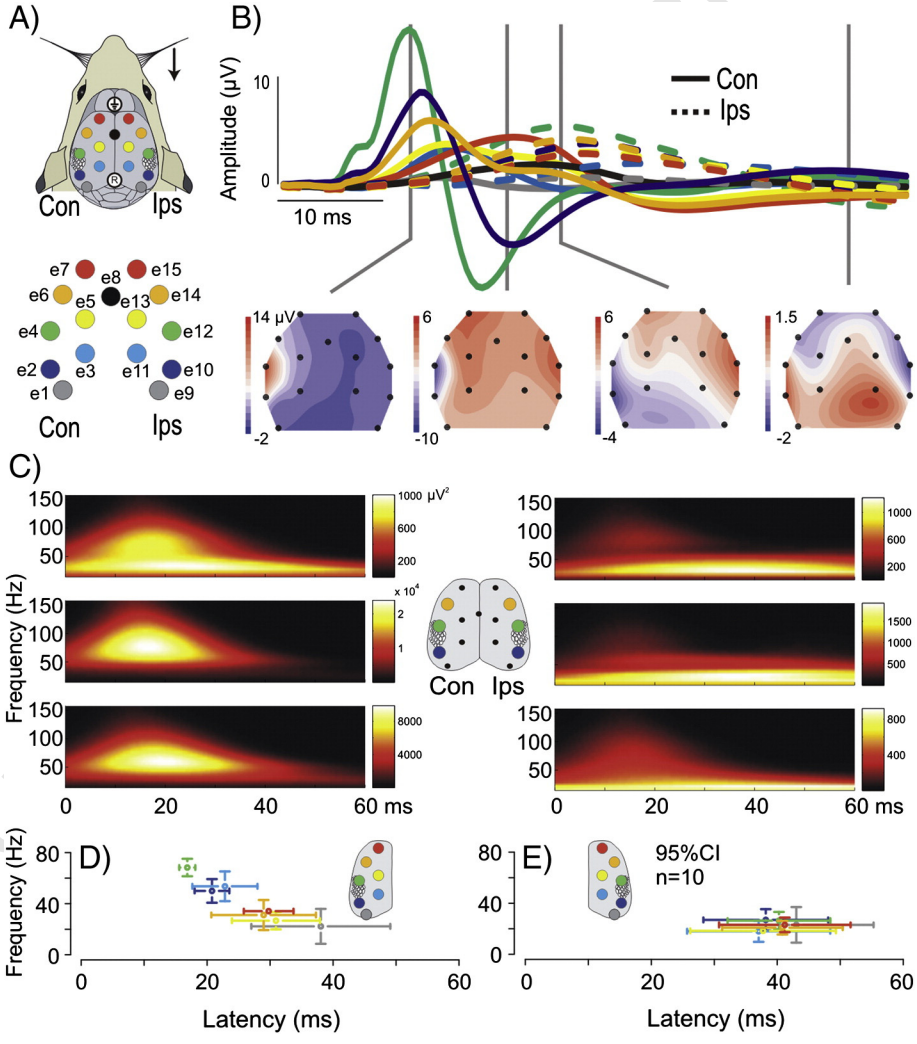

Fig. 1. Large-scale SEP mapping after whisker stimulation (A) A multi-electrode grid placed on the skull bone recorded unilateral SEPs across cortex. The hemisphere contralateral (Con) to stimulation is shown on the left, ipsilateral (Ips) on the right. The electrode layout is shown below with color-coding used in all plots. (B) In the grand-average SEP (n = 10), the maximum voltage peak over cS1 (e4, dark green; mean 13.9 ms, 95% bootstrapped confidence intervals (CI) 13.1–14.9 ms) was quickly followed by peak activity over more parietal (e2, dark blue; 15.4 ms, CI 14.2–16.2 ms), frontal areas (e6, orange; 15.6 ms, CI 14.4–16.4 ms). At middle latencies the maximal activity was measured over iS1 (e12, green dotted line; 29.0 ms, CI 26.5–31.4 ms). Topographic layouts of the voltage potential (2D spline interpolation) are plotted below to illustrate large-scale activity spread. (C) Shows time-frequency plot of the SEP for three nearby electrodes.

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