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Tracking slow modulations in synaptic gain using dynamic causal modelling: Validation in epilepsy

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ABSTRACT

In this work we propose a proof of principle that dynamic causal modelling can identify plausible mechanisms at the synaptic level underlying brain state changes over a timescale of seconds. As a benchmark example for validation we used intracranial electroencephalographic signals in a human subject. These data were used to infer the (effective connectivity) architecture of synaptic connections among neural populations assumed to generate seizure activity. Dynamic causal modelling allowed us to quantify empirical changes in spectral activity in terms of a trajectory in parameter space — identifying key synaptic parameters or connections that cause observed signals. Using recordings from three seizures in one patient, we considered a network of two sources (within and just outside the putative ictal zone). Bayesian model selection was used to identify the intrinsic (within-source) and extrinsic (between-source) connectivity. Having established the underlying architecture, we were able to track the evolution of key connectivity parameters (e.g., inhibitory connections to superficial pyramidal cells) and test specific hypotheses about the synaptic mechanisms involved in ictogenesis. Our key finding was that intrinsic synaptic changes were sufficient to explain seizure onset, where these changes showed dissociable time courses over several seconds. Crucially, these changes spoke to an increase in the sensitivity of principal cells to intrinsic inhibitory afferents and a transient loss of excitatory–inhibitory balance.

Introduction

In this paper we test the hypothesis that systematic changes in observed cross spectral density of electroencephalographic signals can be explained in terms of fluctuations in key model parameters (such as the strength of recurrent inhibitory connections to specific neuronal populations) — and that slow fluctuations in one or more of these parameters can explain changes in brain activity. The methodological advance included here is the use of dynamic causal modelling (DCM) to provide biophysically informed characterisations of electrophysiological responses in terms of slow changes in synaptic efficacy. DCM is a Bayesian framework for comparing different hypotheses or network models of observed (neurophysiological) time series.

Although DCM has been validated in the context of event related responses (Garrido et al., 2009) and steady-state or induced responses (Moran et al., 2011a), it has not been used to track short-term fluctuations in synaptic efficacy. Our focus is therefore on the validity of DCM in recovering slow (pathophysiological) changes in synaptic connectivity from electrophysiological time series. We first establish face validity using physiologically realistic simulations (using the same model used to characterise our empirical data) and then apply the same procedure to real data, intracranial electroencephalography signals from an epileptic subject. This shows that DCM provides veridical estimates of how the data were generated and establishes the identifiability of the model used for subsequent empirical analyses. The empirical application provides a proof of principle that changes in synaptic efficacy can be measured at single subject level — and shows that pathophysiological changes beyond the seizure onset zone are necessary to explain seizure activity.

We chose epileptic seizure onset as a validation of this framework given the nature of the brain dynamics in this pathological condition. In patients affected by drug-resistant epilepsy and for which surgical

Abbreviations: DCM, dynamical causal modelling; SOZ, seizure onset zone; EEG, electroencephalography; CSD, cross spectral density

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treatment is thus sought, intracranial EEG is considered the gold standard for delineating the seizure onset zone (SOZ). Intracranial recordings allow one to characterise seizure activity with a high temporal resolution and track its temporal evolution. It should be noted that the onset of seizure activity may not be limited to the seizure onset zone but may be modulated – or be mediated by – distributed dynamics in brain networks.

The need to accurately track and quantify seizure dynamics has led to the development of multivariate time series analyses of signals recorded simultaneously (Pereda et al., 2005; Lehnertz, 1999). The fact that brain function involves distributed neuronal activity – and that this functional integration is modulated by cognitive or pathophysiological factors – motivates a focus on dynamical interactions not limited to the seizure onset zone but involving distal regions. Consequently, methods grounded in information theory and dynamical systems represent promising candidates, given their potential to describe the intricate pattern of dependencies in multivariate time series.

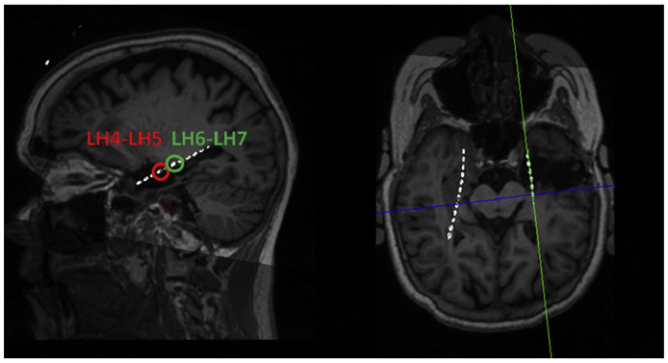

Fig. 1. Location of the two intracranial electrodes and sources considered in the dynamic causal modelling. The stereotactic trajectories of the electrodes are superimposed upon the individual structural MRI scan. The leftmost circle (LH4–LH5) corresponds to the first source — considered the onset zone, while the one on the right (LH6–LH7) indicates our second source.

Materials and methods

This report introduces the concepts and procedures that allow one to estimate slow changes in synaptic parameters that may underlie changes of brain states. Its focus is on describing the approach and providing some face validation (showing it does what it says it does). This validation uses data from a single patient to provide plausible model architectures and parameters – that were used to create synthetic data. We then invert models of those data – to ensure we can recover the (known) parameters. In subsequent publications we will apply this analysis to examine its reproducibility and predictive validity in patient cohorts.

We used data recorded from a patient (female, 50 years old) with refractory epilepsy who had a total of three epileptic seizures during video-EEG monitoring. The patient was implanted at Ghent's University Hospital with 52 intracranial contacts monitoring eight regions of interest according to the following configuration: bilateral occipito-hippocampal depth electrodes with 12 contacts each (Left: LH1–LH12, Right: RH1–RH12); four subdural strips with four contacts each, monitoring the anterior temporo-basal and the posterior temporo-basal region (Left: anterior LTA 1–LTA4 and posterior LTM1–LTM4, Right: anterior RTA1–RTA4 and posterior RTM1–RTM4) and two subdural strips of six contacts each, monitoring the temporo-lateral region (Left: LTP1–LTP6, Right: RTP1–RTP6). Based on the invasive video-EEG monitoring the ictal onset zone was localized to the left hippocampus, primarily involving LH2–4. The patient underwent a selective amygdalo-hippocampectomy in 2007 and has been seizure free since that time.

The data were epoched to a segment starting 20 s before electroencephalographic seizure onset (pre-ictal). The segment included the whole duration of seizure activity, which varied over the three seizures from 229 to 262 s. The beginning and the end of the seizure were marked by epileptologists. The sampling frequency of the EEG recordings was 256 Hz and a band pass filter was applied to the data (0.5 Hz–48 Hz). The intracranial data were re-referenced by applying a bipolar montage corresponding to a series of overlapping bipolar derivations (acting as spatial filter).

Our analysis focused on two sources of activity: a primary source within the subsequently resected area, whose activity was confirmed to be part of the seizure onset zone after postsurgical follow-up (LH4–LH5) and a second source (LH6–LH7) lying just outside the area of resection (Fig. 1). 10 s of activity before and after seizure onset were modelled, where each segment was partitioned into nine contiguous windows with 50% (1 s) overlap, for a total of 18 time windows.

Dynamic causal modelling

Dynamic causal modelling (DCM) is an established procedure in the analysis of functional magnetic resonance imaging in brain mapping (Daunizeau et al., 2011; Friston et al., 2012) and is now being used increasingly for the characterisation of electrophysiological time series. DCM is used to identify the connectivity architectures and connection strengths in distributed networks using (observable) measurements of (hidden) neuronal activity. It is essentially a Bayesian model comparison scheme that allows one to evaluate competing hypotheses (or architectures) in terms of their Bayesian model evidence or marginal likelihood. Having established the best model architecture, Bayesian estimates of the model parameters provide a quantitative characterisation of effective connectivity and other (synaptic) parameters. There is an extensive literature on the validation of DCM ranging from face validation studies (David et al., 2006) to validation in terms of multimodal measurements (David et al., 2008a), pharmacological manipulations (Moran et al., 2011a, 2011b) and psychophysical constructs (Brown and Friston, 2012). Its predictive validity has been established in a number of studies in terms of pathophysiology (Boly et al., 2011).

Quantifying the effective connectivity between coupled neuronal sources corresponds to inferring the causal relationships among them, in relation to a model of those dependencies (Stephan et al., 2007). The nodes of dynamical causal models can reflect different regions in the brain that are connected by (extrinsic) forward and backward connections according to the laminar specificity established by Felleman and Van Essen (1991). Different models can be used within DCM depending on the question of interest and the most informative data features at hand (Moran et al., 2013).

The analysis described in this section uses standard procedures developed in DCM for cross spectral density (CSD) (Friston et al., 2012), which is a generalisation of DCM for steady state responses. The CSD is the Fourier transform of the cross-correlation function, which summarizes the activity and statistical dependencies among channels in frequency space. It can be thought of as reporting the correlations at each frequency. Usually, DCM for CSD is applied to a single cross spectrum (for a given time series). However here, we model successive time windows; effectively summarizing the time series with its time–frequency decomposition. The reason that we choose these (cross spectral) data features is that they contain information about the underlying connectivity that can be accessed through estimating the spectral density (second-order statistics) of endogenous activity. This contrasts with modelling of the time series per se, which would require the time-dependent (first-order statistics) endogenous input (e.g., the input associated with a stimulus in the event related potential studies).

This DCM has been applied in several contexts previously. Technical details can be found in Moran et al. (2007, 2009) and its applications to in vivo synaptic assays are described in Moran et al. (2011a, 2011b). In brief, parameter estimation uses standard (variational) Bayesian model inversion, where the forward or generative model predicts cross spectral responses from models of coupled neuronal masses. These models