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Review

Probabilistic functional tractography of the human cortex

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ABSTRACT

Single-pulse direct electrical stimulation of cortical regions in patients suffering from focal drug-resistant epilepsy who are explored using intracranial electrodes induces cortico-cortical potentials that can be used to infer functional and anatomical connectivity. Here, we describe a neuroimaging framework that allows development of a new probabilistic atlas of functional tractography of the human cortex from those responses. This atlas is unique because it allows inference *in vivo* the directionality and latency of cortico-cortical connectivity, which are still largely unknown at the human brain level. In this technical note, we include 1535 stimulation runs performed in 35 adult patients. We use a case of frontal lobe epilepsy to illustrate the asymmetrical connectivity between the posterior hippocampal gyrus and the orbitofrontal cortex. In addition, as a proof of concept for group studies, we study the probabilistic functional tractography between the posterior superior temporal gyrus and the inferior frontal gyrus. In the near future, the atlas database will be continuously increased, and the methods will be improved in parallel, for more accurate estimation of features of interest. Generated probabilistic maps will be freely distributed to the community because they provide critical information for further understanding and modelling of large-scale brain networks.

Contents

Introduction . . . 0
Materials and methods . . . 0
Clinical procedure and data acquisition . . . 0
Functional tractography methods . . . 0
Preprocessing of IEEG signals . . . 0
Statistical significance and latency of responses . . . 0
Maps of functional tractography . . . 0
Software implementation and atlas sharing . . . 0
Results . . . 0
Single subject analysis . . . 0
Group analysis . . . 0
Patients . . . 0
Atlas spatial sampling . . . 0
Sensitivity analysis . . . 0
Probabilistic functional tractography of PSTG-IFG . . . 0
Discussion . . . 0
Acknowledgments . . . 0
Conflict of interest statement . . . 0
References . . . 0

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Introduction

Epilepsy surgery requires intracranial electrodes in 25–50% of the cases, either at the surface (grids, strips) or deep inside the brain (stereo-electroencephalography, SEEG) (Spencer et al., 2008), in order to delineate from the intracranial electroencephalogram (IEEG) the cortical areas where seizures start and rapidly propagate (David et al., 2011). For clinical reasons, it is also possible to use direct electrical stimulation (DES) of the cortex in a given region using a bipolar derivation of two adjacent electrodes and to record electrophysiological responses with the other electrodes. In addition to induced changes of behaviour or perception used for functional mapping (Selimbeyoglu and Parvizi, 2010), after discharges or abnormal responses can be elicited for mapping epileptic circuits (David et al., 2008; Kahane et al., 1993; Valentín et al., 2002), but also cortico-cortical evoked potentials (CCEPs) that resemble physiological responses (Catenoix et al., 2005; 2011; Koubeissi et al., 2012; Lacruz et al., 2007; Matsumoto et al., 2004, 2007, 2011; Rosenberg et al., 2009; Wilson et al., 1990). Because CCEPs are usually composed of a sharp deflection followed by a slow wave, they can be used to estimate neuroanatomical functional pathways to and from the site of stimulation by the quantification of the strength and latency of the first response component recorded at every electrode.

CCEPs are obtained in response to brief current stimulations, of pulse-width usually below 3 ms (David et al., 2010). Amplitude and spatial extent of CCEPs depend on the stimulation energy E per time unit (1 s), which can be approximated to Pwf for a monophasic stimulation of pulse width w at frequency f where P is the power of stimulation. Assuming pure resistive coupling between tissue and electrodes of impedance Z, P is equal to $\frac{V^2}{Z}$ for a stimulation at voltage amplitude V (usually below 10 V) or to I^2Z for a stimulation at current amplitude I (usually below 10 mA). Strong activations are thus obtained with large pulse-width and amplitude of stimulation, but delivered energy also critically depends on the electrode impedance, and in general on the physical properties of the electrode/tissue interface that are in fact also capacitive (Franks et al., 2005).

Available methods of analysis of DES responses for connectivity inference are based on the visual analysis of the stimulation-related averaged CCEP. Usually, significant responses are detected when the averaged CCEP amplitude increase is above twice the standard deviation of background activity (Catenoix et al., 2005, 2011; Lacruz et al., 2007; Rosenberg et al., 2009; Wilson et al., 1990). It has also been proposed to use a geometrical analysis of the N1 component, and of the N2 component if present (Koubeissi et al., 2012; Matsumoto et al., 2004, 2007, 2011). Latency of responses are defined either at the start of the slope (Rosenberg et al., 2009) or at the peak (Matsumoto et al., 2004) of the first CCEP component.

Because IEEG electrodes sparsely sample the brain, DES group studies are often limited to a small number of patients and/or of regions. Similarly to neuroimaging studies however, it has been proposed to normalise patients' brain into a stereotactic space, such as proposed by Talairach and Tournoux (1988) or Montreal Neurological Institute (MNI), in order to summarise electrophysiological data between patients (Catenoix et al., 2011; Matsumoto et al., 2011; Rosenberg et al., 2009). Here, we propose to extensively develop this approach in order to develop an atlas of human brain connectivity derived from DES data. It can be thought of as an atlas of "functional tractography", a term originally proposed in Matsumoto et al. (2007), as a distinction from "anatomical fibre tractography" that is studied in human by brain diffusion tensor imaging (DTI) (Jones, 2008). Building a new atlas of functional tractography is relevant because several thousands of patients have now been stimulated in many epilepsy centres worldwide, using grids, strips or depth electrodes, and putting together parts of those data in a common framework should certainly allow for reaching nearly full coverage of the cortex. Below, we demonstrate the feasibility of the approach using SEEG data from Grenoble University Hospital recorded in 35 patients. We will continue including other patients in our database in the next few years. Eventually, the DES atlas will be made freely available for usage by the community for different purposes (*e.g.* studying cortico-cortical human connectivity *in vivo*, validating or improving other non invasive connectivity methods such as diffusion tractography, studying propagation pathways of epileptic seizures and their relationships with cognitive networks).

Materials and methods

Clinical procedure and data acquisition

Patients included in this study (n = 35) were fully informed and gave their consent to undergo invasive recordings and stimulation as part of the presurgical evaluation of their drug-resistant epilepsy, in addition to more standard exams (high resolution structural magnetic resonance imaging — MRI, video-EEG monitoring, neuropsychological testing). SEEG recordings and DES at 1 Hz were performed according to the routine procedure used at Grenoble University Hospital to better delineate the brain areas to be resected (Kahane et al., 1993, 2004). Ten to 17 semirigid intracerebral electrodes (mean: 13.6 ± 1.8) were implanted per patient, unilaterally (n = 26) or bilaterally (n = 9), in various cortical areas depending on the suspected origin of seizures. Each electrode was 0.8 mm in diameter and included 5, 10, 15 or 18 leads 2 mm in length, 1.5 mm apart (Dixi Medical, Besançon, France), depending on the target region. A preoperative stereotaxic MRI and a stereotaxic teleradiography matched with Talairach and Tournoux's atlas (Talairach and Tournoux, 1988) were used to assess anatomical targets. Implantation of the electrodes was performed in the same stereotaxic conditions, with the help of a computer-driven robot (Neuromate, ISS). The location of the electrode contacts was subsequently reported on a stereotaxic scheme for each patient and defined by their coordinates in relation to the anterior commissure/posterior commissure plane. They were finally expressed in the MNI coordinate system to allow group analyses. When an anatomical MRI with SEEG electrodes was available, MNI coordinates were directly obtained from the MRI and its nonlinear transform defined by the brain normalisation procedure of the Statistical Parametric Mapping 8 software (SPM8, Wellcome Department of Imaging Neuroscience, University College London, www.fil.ion.ucl.ac.uk/spm). When it was not (for patients implanted before 2009 in our centre, 17 of the 35 patients included in this report), electrode repositioning in the MNI space was based on the use of coronal and sagittal teleradiographic images of the stereotactic scheme of each patient and was composed of the following steps (Lachaux et al., 2005): (1) The anterior and posterior commissures were detected in teleradiographic images and used to define the Talairach and Tournoux coordinate system (Talairach and Tournoux, 1988); (2) External anatomical landmarks (most lateral and most anterior–posterior points of the brain) were used to proceed to a linear scale adjustment to correct for size differences between patient's brain and Talairach's reference brain, with an additional scale factor to transform Talairach's coordinates into the MNI space; (3) For every patient, anatomical locations of electrodes were confirmed or slightly adjusted manually by visually comparing their positions in the MNI canonical brain to the anatomical structures initially targeted by the neurosurgeon.

SEEG recordings were performed using a video-EEG monitoring system (Micromed, Treviso, Italy) that allowed for simultaneously recording up to 256 monopolar contacts, so that a large range of mesial and cortical areas, as well as fissural cortices, was sampled for each patient. Sampling rate was either 256 or 512 Hz, with an acquisition band-pass filter between 0.1 and 90 Hz or between 0.1 and 200 Hz respectively, depending on amplifier capacities at the date of recordings. Data were acquired using a referential montage with reference electrode chosen in the white matter. All other recording sites were

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