Clinical Neurophysiology 121 (2010) 1726–1739

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Clinical utility of distributed source modelling of interictal scalp EEG in focal epilepsy

C. Plummer [a,b,*], M. Wagner [c], M. Fuchs [c], S. Vogrin [a], L. Litewka [a], S. Farish [b], C. Bailey [d], A.S. Harvey [d,e], M.J. Cook [a,b]

[a] Centre for Clinical Neurosciences and Neurological Research, St. Vincent's Hospital, 5th Floor Daly Wing, 35 Victoria Parade, Fitzroy, Victoria 3065, Australia
[b] Department of Medicine, University of Melbourne, Grattan Street, Parkville, Victoria 3052, Australia
[c] Compumedics Neuroscan, Heussweg 25, 20255 Hamburg, Germany
[d] Department of Neurology, Royal Children's Hospital, Flemington Road, Parkville, Victoria 3052, Australia
[e] Department of Paediatrics, University of Melbourne, Grattan Street, Parkville, Victoria 3052, Australia

ARTICLE INFO

Article history:
Accepted 3 April 2010
Available online 8 May 2010

Keywords:
EEG source localization
Distributed modelling
Dipole
BFEC
MTLE
Focal epilepsy

ABSTRACT

Objective: Assess the clinical utility of non-invasive distributed EEG source modelling in focal epilepsy.
Methods: Interictal epileptiform discharges were recorded from eight patients – benign focal epilepsy of childhood (BFEC), four; mesial temporal lobe epilepsy (MTLE), four. EEG source localization (ESL) applied 48 *forward–inverse–subspace* set-ups: *forward* – standardized, leadfield-interpolated boundary element methods (BEMs, BEMi), finite element method (FEMi); *inverse* – minimum norm (MNLS), L1 norm (L1), low resolution electromagnetic tomography (LORETA), standardized LORETA (sLORETA); *subspace* – whole volume (3D), cortex with rotating sources (CxR), cortex with fixed sources (CxN), cortex with fixed extended sources (patch). Current density reconstruction (CDR) maxima defined 'best-fit'.
Results: From 19,200 CDR parameter results and 2304 CDR maps, the dominant variables on best-fit were inverse model and subspace constraint. The most clinically meaningful and statistically robust results came with sLORETA–CxR/patch (lower Rolandic in BFEC, basal temporal lobe in MTLE). Computation time was inverse model dependent: sub-second (MNLS, sLORETA), seconds (L1), minutes (LORETA).
Conclusions: From the largest number of distributed ESL approaches compared in a clinical setting, an optimum modelling set-up for BFEC and MTLE incorporated sLORETA (inverse), CxR or patch (subspace), and either BEM or FEMi (forward). Computation is efficient and CDR results are reproducible.
Significance: Distributed source modelling demonstrates clinical utility for the routine work-up of unilateral BFEC of the typical Rolandic variety, and unilateral MTLE secondary to hippocampal sclerosis.

1. Introduction

The increasing sophistication of the distributed modelling method for EEG source localization (ESL) has heightened debate on its clinical translatability to routine epilepsy practice. Even dipole modelling (an allied field boasting more clinical studies to date) remains largely tied to the research domain (Plummer et al., 2008). Indeed, the distributed model can be regarded as a three-dimensional latticework of multiple, point-like dipole models; each dipole carries its own orientation, location, and strength per time instant (also termed CDR, 'current density reconstruction') (Wagner et al., 2001).

One theoretical advantage held by distributed (over dipole) modelling is that its algorithms address the inverse problem with fewer lead-in assumptions, or 'priors', mainly in respect of the number of sources that explain the measured EEG signal. Due to the ill-posed nature of the inverse problem however, (Helmholtz, 1853), solutions are highly under-determined (Fuchs et al., 1999). Post-process constraints are needed to arrive at a 'best-fit' solution. The mathematical tools employed to do this is essentially what distinguishes one distributed modelling algorithm from another. Constraints may also be anatomically informed (subspace constraint) whereby the three-dimensional solution space is specified (cortical versus head space).

While there is a body of work in the biophysics literature on the application of distributed modelling to experimental simulations (Baillet and Garnero, 1997; Grova et al., 2006; Kim et al., 2002; Nummemnaa et al., 2007), comparatively little work has assessed the usefulness of this technology in a systematic way in the routine

* Corresponding author at: Centre for Clinical Neurosciences and Neurological Research, St. Vincent's Hospital, 5th Floor Daly Wing, 35 Victoria Parade, Fitzroy, Victoria 3065, Australia. Tel.: +61 392883045; fax: +61 392883350.
E-mail address: chris.plummer@svhm.org.au (C. Plummer).

1388-2457/$36.00
doi:10.1016/j.clinph.2010.04.002

clinical epilepsy setting. There are several immediate issues. First, much like functional Magnetic Resonance Imaging (f-MRI), CDR maps are typically threshold-set in order to curb the display of those elements of the map that are more likely to be representing noise. However, no standardized or agreed-upon threshold value has been determined to date. The second practical issue is that distributed modelling is generally more computationally demanding than is the case for dipole modelling. This is effectively why, at least at present, CDR solutions can only be calculated for the net distributed current per time instant, making it difficult for the investigator to tease apart activity that might be coming from multiple sources that overlap in space and time during the course of a spike or seizure discharge (Scherg et al., 1999). Third, while constraining the solution to a particular subspace within the volume conductor (or forward model) might minimize the final fit error in respect of the individualized cortical anatomy, it should be emphasized that however spatially constrained the final fit becomes, little will be gained if the choice of the forward or inverse model is inappropriate in the first place. And fourth, most clinical ESL studies select a particular source modelling set-up (a forward–inverse modelling combination with or without a subspace constraint) and test its performance across a particular patient cohort (a series of lesion positive epilepsy surgery cases for instance). ESL studies which compare the performance of multiple different types of distributed modelling approaches across the same patient cohort are genuinely lacking in the clinical literature. To our knowledge, the present study incorporates the largest number of distributed modelling set-ups to have been cross-examined in the clinical setting.

A chief criticism of ESL generally, and of distributed modelling in particular, is that the mathematical constraints that may be applied to solve the inverse problem are not known to genuinely mirror actual electrophysiological behaviour. The algorithms that underpin the various distributed modelling approaches are technically loaded and, while these methods have produced encouraging results in the relatively high signal-to-noise environment of the simulated experiment when the true source configuration is known, their translatability to the routine clinical setting remains largely undefined. This is the primary motivation for the present study. More directly, what difference is made to the final distributed fit if the BEMi is used instead of the FEMi forward model; if LORETA is used instead of the sLORETA inverse model; or if CxR is used instead of the patch subspace constraint? How reproducible are the results? Are the results clinically meaningful when the number of electrodes applied is only in the order of 19–21, as is often the case for routine interictal EEG recordings? Is the modelling too cumbersome and time costly to carry out for prospective use in clinical practice?

We have selected benign focal epilepsy of childhood (BFEC), the prototypic idiopathic focal epilepsy, and mesial temporal lobe epilepsy (MTLE), the prototypic symptomatic focal epilepsy, in the present study for two reasons. They represent two of the most common types of epilepsy encountered in routine clinical practice and they are arguably the most well characterized epilepsies in the field of non-invasive ESL at this point in time (Wong, 1998; Ebersole, 2000; Huiskamp et al., 2004; Pataraia et al., 2005; Ebersole and Hawes-Ebersole, 2007; Plummer et al., 2007).

2. Methods

2.1. Patients and EEG recordings

Eight patients underwent interictal scalp EEG – four with benign focal epilepsy of childhood with centrotemporal spikes (BFEC), 6–10 years (mean 8.5 years); four with unilateral mesial temporal lobe epilepsy (MTLE), 12–16 years (mean 14.3 years) secondary to hippocampal sclerosis on Magnetic Resonance Imaging (MRI) and histopathology (Engel class 1, 5–7 year follow-up). Stereotypic interictal epileptiform discharges (IEDs) of a single morphology and topography were present on visual assessment of the EEG in each patient (30-min 19-electrode recordings BFEC; prolonged 21-electrode pre-operative scalp recordings MTLE). International 10–20 electrode positions (Jasper, 1958) were used for both groups with accurate scalp measurement. In MTLE, two extra electrodes were placed at points one-third the distance from the outer canthus to the external auditory meatus (T1, T2) (Binnie et al., 1982). Standard 10 mm gold plated disc electrodes (pure silver cast cup, two millimetre central port) were attached to the scalp with SLE Collodion Adhesive® and injected with high conductivity electrode gel (Parker Signa Gel®). Recordings were at 256 Hz digital acquisition (16 bit ADC resolution) were performed with Compumedics ProFusion® software; 0.15 Hz (high pass) and 105 Hz (low pass) hardware filters. Study approval by the Ethics in Human Research Committees of the Royal Children's Hospital and St. Vincent's Hospital, Melbourne. Informed consent was obtained in all cases.

2.2. EEG source localization (ESL)

EEG recordings were uploaded to *Scan 4.3*® (Neuroscan®, El Paso, Texas, USA) for analysis (common average reference at vertex). Single IEDs were epoched from −200 ms to +500 ms relative to the spike peak and uploaded to *CURRY 5.0*® (Compumedics®, Melbourne, Australia). Notch 50 Hz and bandpass 0.5–70 Hz filters were applied. Mean and incremental (every four milliseconds) SNR calculations for the spike interval were based on the pre-spike interval (identical number of noise sampling points per ESL operation). Electrode positions were label match co-registered using predefined electrode locations for the three Montreal Neurological Institute (MNI)-based realistic models. The interval for ESL analysis was marked from spike onset-to-peak latency using a butterfly plot (see Supplementary Figures S1 and S2). Spike onset was defined by the first significant deflection (surface positive or negative) from baseline and spike peak was defined by the peak (surface negative) amplitude of the last overlapping spike waveform on the butterfly plot. Mean global field orthogonal signal components of the spike with an SNR >1.0 identified by principal component analysis (PCA) underwent independent component analysis (ICA). The five single spikes for each patient were later electrographically averaged based on automated detection and overlay of surface-negative maxima. Averaged IEDs were subjected to the same ESL operation as described for single IEDs. A total of 48 *forward–inverse–subspace* modelling set-ups (Fig. 1) were derived from three *forward* models (Fuchs et al., 2002) – standardized boundary element method (BEMs), leadfield-interpolated boundary element method (BEMi), leadfield-interpolated finite element method (FEMi); four *inverse* models – minimum norm least squares (MNLS) (Fuchs et al., 1999), minimum L1 norm (L1) (Wagner et al., 1998), low resolution electromagnetic tomography (LORETA) (Pascual-Marqui et al., 1994), standardized LORETA (sLORETA) (Pascual-Marqui, 2002); four *subspace* constraints – whole volume (3D), cortex with rotating sources (CxR), cortex with fixed sources normal to cortex (CxN), cortex with fixed extended sources using a 20 millimetre patch (patch) (Wagner et al., 2001).

2.3. Results analysis (quantitative)

Each CDR map was quantified by seven output parameters describing the spatiotemporal behaviour of that mini-dipole (as one of several thousand mini-dipoles per CDR map) that reached the highest current density (*cdmax*) at some time-point during