Neuronal Networks in West Syndrome as Revealed by Source Analysis and Renormalized Partial Directed Coherence

Natia Japaridze · Muthuraman Muthuraman · Friederike Moeller · Rainer Boor · Abdul Rauf Anwar · Günther Deuschl · Urlich Stephani · Jan Raethjen · Michael Siniatchkin

Abstract West syndrome is a severe epileptic encephalopathy of infancy with a poor developmental outcome. This syndrome is associated with the pathognomonic EEG feature of hypsarrhythmia. The aim of the study was to describe neuronal networks underlying hypsarrhythmia using the source analysis method (dynamic imaging of coherent sources or DICS) which represents an inverse solution algorithm in the frequency domain. In order to investigate the interaction within the detected network, a renormalized partial directed coherence (RPDC) method was also applied as a measure of the directionality of information flow between the source signals. Both DICS and RPDC were performed for EEG delta activity (1–4 Hz) in eight patients with West syndrome and in eight patients with partial epilepsies (control group). The brain area with the strongest power in the given frequency range was defined as the reference region. The coherence between this reference region and the entire brain was computed using DICS. After that, the RPDC was applied to the source signals estimated by DICS. The results of electrical source imaging were compared to results of a previous EEG-fMRI study which had been carried out using the same cohort of patients. As revealed by DICS, delta activity in hypsarrhythmia was associated with coherent sources in the occipital cortex (main source) as well as the parietal cortex, putamen, caudate nucleus and brainstem. In patients with partial epilepsies, delta activity could be attributed to sources in the occipital, parietal and sensorymotor cortex. In West syndrome, RPDC showed the strongest and most significant direction of ascending information flow from the brainstem towards the putamen and cerebral cortex. The neuronal network underlying hypsarrhythmia in this study resembles the network which was described in previous EEG-fMRI and PET studies with involvement of the brainstem, putamen and cortical regions in the generation of hypsarrhythmia. The RPDC suggests that brainstem could have a key role in the pathogenesis of West syndrome. This study supports the theory that hypsarrhythmia results from ascending brainstem pathways that project widely to basal ganglia and cerebral cortex.

Keywords West syndrome · DICS · RDPC · EEG-fMRI

J. Natia and M. Muthuraman have contributed equally to this study.

N. Japaridze (✉) · F. Moeller · R. Boor · U. Stephani · M. Siniatchkin
Department of Neuropediatrics, Pediatric Hospital, Christian-Albrechts-University, Schwanenweg 20, 24105 Kiel, Germany
e-mail: n.japaridze@pedneuro.uni-kiel.de

M. Muthuraman · A. R. Anwar · G. Deuschl · J. Raethjen
Department of Neurology, Christian-Albrechts-University, Kiel, Germany

R. Boor · U. Stephani
Northern German Epilepsy Centre for Children and Adolescents, Schwentinental/OT Raisdorf, Kiel, Germany

A. R. Anwar
Digital Signal Processing and System Theory, CAU, Kiel, Germany

Introduction

West syndrome is a disabling, age-related epileptic encephalopathy which may be attributed to different aetiologies. This syndrome is characterised by a unique seizure type (infantile spasms), developmental delay, and a pathognomonic EEG pattern of hypsarrhythmia (Dulac

2001; Hrachovy and Frost 2003). The hypsarrhythmia is described as a mixture of giant abnormal, arrhythmic, and asynchronous electrical brain activity consisting of slow and sharp waves, multi-focal spikes, and polyspikes (Panayiotopoulos 2005). Despite a poor developmental outcome, treatment difficulties, and high association of West syndrome with severe encephalopathies, such as Lennox-Gastaut syndrome, the pathophysiological mechanisms of West syndrome are still poorly clarified. In particular, little is known about neuronal networks at the bases of hypsarrhythmia.

Studies on functional neuroimaging in West syndrome have revealed that the putamen, brainstem, and various cortical regions play an important role in the pathogenesis of hypsarrhythmia (Chugani et al. 1990; Chugani et al. 1992; Chiron et al. 1993; Haginoya et al. 2000; Hrachovy et al. 1981; Morimatsu et al. 1972; Metsahonkala et al. 2002; Neville 1972; Satoh et al. 1986; Hrachovy and Frost 2003). Using simultaneous EEG-fMRI recordings, Siniatchkin et al. (2007) demonstrated that the high-amplitude, slow cortical activity in hypsarrhythmia is associated with positive BOLD effects in the putamen and brainstem and that multifocal epileptiform discharges are correlated with positive BOLD effects in the occipital cortex and various other cortical areas. It is still unclear, however, which structures in the described network are primarily responsible for hypsarrhythmia. Because of a low temporal resolution and a limited sampling rate, it remains difficult to use PET, SPECT, and fMRI time series to demonstrate the temporal follow-up between structures involved in the hypsarrhythmia. The better temporal resolution of EEG allows better interpretation of different parts of neuronal networks, such as the separation of brain areas with the initial epileptic activity from regions of propagation (Groening et al. 2009; Vulliemoz et al. 2009; Siniatchkin et al. 2010) and better analysis of the relationship between activities in different brain regions (Schelter et al. 2009; Astolfi et al. 2007). However, due to the ambiguity of the underlying static electromagnetic inverse problem, EEG signals measured on the scalp surface do not directly indicate the location of the active neurons in the brain (Michel et al. 2004). In particular, electrical source imaging of brain activity generated in deep brain structures, such as the subcortical nucleus (e.g. thalamus), has not been possible in previous studies (Holmes 2008; Holmes et al. 2010; Holmes et al. 2004).

New solutions for the inverse problem of the EEG, which improve the localization power of the EEG substantially, have been developed, even for deep sources, thus enabling us to use EEG data to investigate the neuronal networks. Dynamic imaging of coherent sources (DICS) is one of these solutions. DICS is a source analysis method which is able to detect brain regions that are coherent with each other and a reference signal or region (Gross et al. 2001). It works in the frequency domain for EEG and magnetoencephalographic (MEG) data and is able to describe neuronal networks by imaging power and coherence of oscillatory brain activity using a spatial filter (Gross et al. 2001). Applied to different types of tremor and voluntary motor control, DICS was able to characterize networks including deep structures, such as the diencephalon (e.g. the thalamus) the cerebellum and the brainstem in MEG studies (Gross et al. 2001, 2002; Timmermann et al. 2003b, a; Sudmeyer et al. 2006; Schnitzler et al. 2006) as well as the thalamus (Moeller et al. 2012; Muthuraman et al. 2012a) and brain stem in recent EEG studies (Muthuraman et al. 2012b; Moeller et al. 2012). However, the interaction between the different network components cannot be resolved by DICS alone (Gross et al. 2002; Hellwig et al. 2000, 2001, 2003; Schack et al. 2003; Tass et al. 1998; Volkmann et al. 1996). In order to analyze the effective connectivity and informational flow between sources, the renormalized partial directed coherence (RPDC) is applied. The RPDC is a parametric technique that is thought to be capable of analyzing not only multivariate networks in neuroscience and to infer interrelations therein, but also to allow conclusions about causal dependencies based on Granger causality (Baccala and Sameshima 2001; Sameshima and Baccala 1999; Schelter et al. 2009).

The objective of this study was to elucidate on the network that generates the high-amplitude, slow wave activity in infants with infantile spasms and hypsarrhythmia using DICS and RPDC. In order to evaluate the specificity of pathogenetic mechanisms of hypsarrhythmia, these infants were compared with children suffering from complex partial seizures. In order to validate the results obtained with DICS, we compared the results of electrical source imaging with fMRI obtained previously from the same data sets of EEG-fMRI recordings (Siniatchkin et al. 2007).

Materials and Methods

Subjects

From our database of EEG-fMRI recordings we selected eight patients with infantile spasms and hypsarrhythmia (Group I, five cryptogenic and three symptomatic, mean age: 7.62 $\pm$ 2.87 months) and eight patients with drug-resistant focal epilepsies (Group II, three cryptogenic, five symptomatic, mean age: 20.75 $\pm$ 12.52 months). The age of the control group patients is not perfectly matched with the West syndrome group. We can justify this selection by the fact that our aim was to analyze the same patients and

Table 1 Demographic and clinical data of the group I and II

Patients (gender)	Age	Etiology	EEG	Seizure types	AED
1(f)	6 months	Cryptogenic	Hypsarrhythmia	IS	Pyridoxal-5-phosphate, folic acid, VGB, cortisone,
2 (m)	12 months	Symptomatic[a]	Hypsarrhythmia	IS	VGB, VPA
3 (m)	11 months	Cryptogenic	Hypsarrhythmia	IS.	VPA,VGB, STM
4 (m)	6 months	Symptomatic[b]	Hypsarrhythmia	IS	VGB, VPA
5 (m)	12 months	Cryptogenic	Hypsarrhythmia	IS	VGB, LEV
6 (m)	6 months	Cryptogenic	Hypsarrhythmia	IS	VGB, STM
7 (m)	8 months	Cryptogenic	Hypsarrhythmia	IS	CBZ, VPA, VGB,
8 (f)	10 months	Symptomatic[c]	Hypsarrhythmia	IS, myoclonic seizures	TPM, LEV
9 (m)	10 months	Symptomatic[d]	Multifocal	CPS, SGTC	STM, TPM, VGB
10 (m)	24 months	Symptomatic[e]	Multifocal	CPS, atypical absences,	VPA, TPM, STM
11 (f)	19 months	Symptomatic[d]	Multifocal	Tonic seizures, atonic seizures, myoclonic, CPS,	VGB, OXC
12 (f)	6 years	Cryptogenic	Multifocal	Myoclonic, SGTC	VPA, LEV, LTG,
13 (m)	10 years	Symptomatic[f]	Predominantly left temporal	Atonic, atypical absences	VPA; LTG,
14 (m)	10 years	Cryptogenic	Multifocal	CPS, SGTC atypical absences	STM, LTG
15 (m)	1 years	Symptomatic[g]	Multifocal	CPS	OXC; CLN, PB
16 (f)	2 years	Cryptogenic	Multifocal	Tonic, myoclonic seizures	OXC, VPA

Note: Patients 1–8 had West syndrome, Patients 9–16 are from the control group of drug-resistant particle epilepsies

CPS complex partial seizures, *SGTC* secondary generalised tonic–clonic seizures, *IS* infantile spasms, *STM* sulthiame, *TPM* topiramate, *VGB* vigabatrin, *VPA* valproic acid, *OXC* oxcarbazepine, *LTG* lamotrigine, *CLN* clonazepam, *LEV* levetiracetam, *PB* phenobarbital

[a] Gliosis and encephalomalacia of the left supramarginal gyrus

[b] Focal cortical dysplasia in the left gyrus hippocampalis

[c] Gliosis and encephalomalacia in the occipital region

[d] Tuberose scleroses complex

[e] Perinatal asphyxia, HIE

[f] Gliosis and encephalomalacia after intracranial haemorrhage

[g] Primary microcephaly

same data sets that was analyzed for the previous EEG-fMRI study (Siniatchkin et al. 2007). The recruitment of younger patients with drug resistant focal epilepsies was impossible because of ethical concerns, and the eight selected patients were the youngest subjects from the sample of 86 investigated children with focal epilepsies (Siniatchkin et al. 2007). Clinical and demographical data of the patients are presented in Table 1. All patients were recruited from the Department of Neuropediatrics at the University Hospital of Schleswig-Holstein, Campus Kiel and the Northern German Epilepsy Centre for Children and Adolescents, Schwentinental/OT Raisdorf, Germany. In Group I clusters of infantile spasms were the main seizure type and EEG showed hypsarrhythmia in all patients (Fig. 1). Patients from Group II had partial, drug-resistant epilepsies of structural/metabolic or unknown cause. Drug resistance was defined as a failure of adequate trials of two tolerated and appropriately administered AED schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom (Kwan et al. 2010). Epilepsy was categorized as being of unknown aetiology, if clinical, laboratory and neuroradiological investigations failed to identify any causative factor. All patients from the control group had background EEG activity of diffuse, multifocal slow waves and epileptiform abnormalities (Fig. 2). Only one patient from Group II had a prominent focus in the left temporal region which was concordant with the location of the lesion. Diagnoses were made according to the ILAE 2001 classification scheme (Commission on Classification and Terminology of the International League against Epilepsy, 2001). The neurological examination and structural MRI (high-resolution 3T–T1, T2, FLAIR-T2, and diffusion-weighted imaging) were performed before inclusion in the study. Routine EEGs (21 electrodes in accordance with the International 10–20 system) were recorded 1–2 days before the EEG-fMRI investigation and were independently evaluated by at least two specialists who confirmed the type of EEG abnormality, i.e., hypsarrhythmia in Group

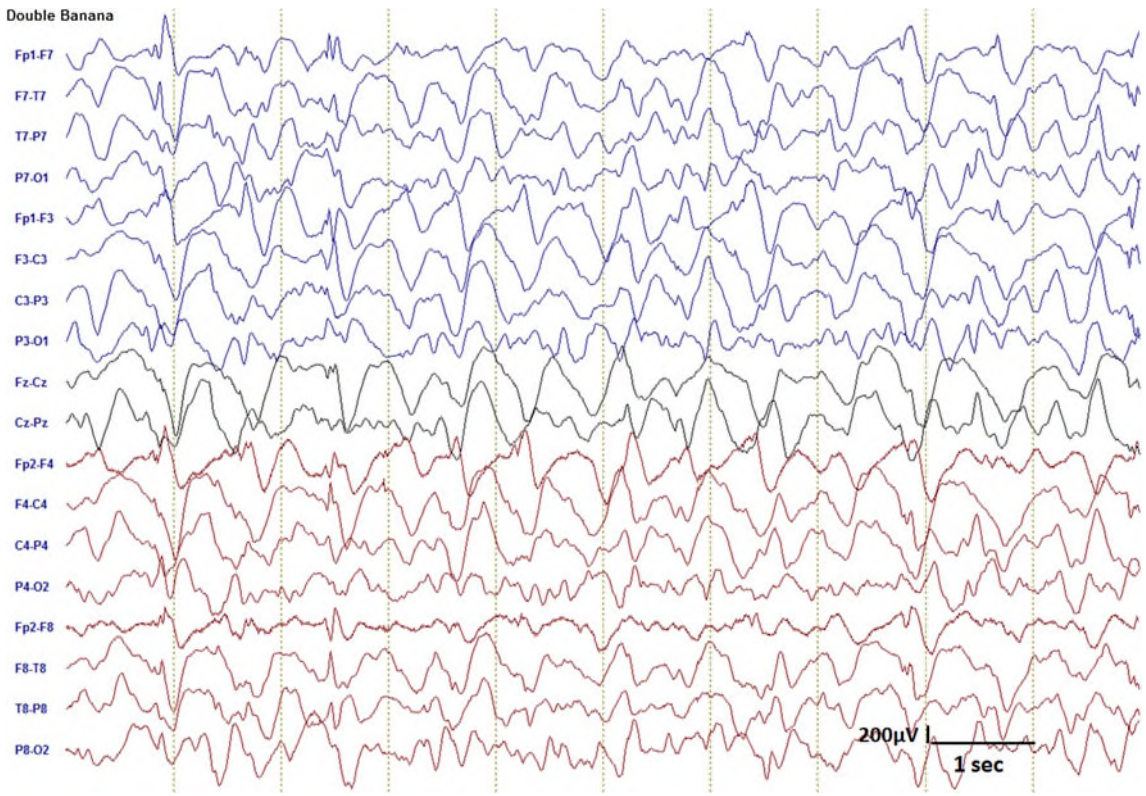

Fig. 1 EEG recording showing hypsarrhythmia with diffuse, bilateral, asynchronous high-amplitude slow waves in a 7-month old patient with cryptogenic West syndrome

I or multifocal, diffuse slow waves and epileptiform abnormalities in Group II. All patients had global developmental delay of various severities which was assessed by neurological examination and clinical scale (Denver Developmental Scale and Frankenburg and Bresnik 1998). All children were sedated with chloral hydrate 30 min before EEG-fMRI recordings which were performed when the children were asleep. A pediatrician was present throughout the examination.

The study was acknowledged by the Ethics Committee of the Faculty of Medicine, University of Kiel, Germany. All participants and their parents were instructed about the study, and written informed consent according to the Declaration of Helsinki (current version, 1996) on biomedical research involving human subjects (Tokyo amendment) was obtained.

EEG Recording

The EEG was continuously recorded during fMRI from 30 scalp sites (10–20 system plus FC1, FC2, CP1, CP2, FC5, FC6, CP5, CP6, TP9, TP10) with a reference located between Fz and Cz. Sintered Ag/AgCl ring electrodes with built-in 5 kOhm resistors were attached using the "Easy-Cap" (Falk-Minow Services, Herrsching-Breitbrunn, Germany), which is part of the MR-compatible, EEG recording system "BrainAmp-MR" (Brainproducts Co., Munich, Germany). Electrode impedance was kept below 10 kOhms. Two additional electrodes were placed on the infraorbital ridge of the left eye for recordings of the vertical electrooculography (EOG) and on the left perivertebral part of the lower back for acquisition of the electrocardiogram (ECG). Data were transmitted from the high-input impedance amplifier (250 Hz low-pass filter, 10 s time constant, 16-bit resolution, dynamic range of 16.38 mV).

Simultaneous EEG-fMRI Recordings and Data Processing

EEG was processed offline using the BrainVision Analyser software (Brain Products). Gradient artifacts due to electromagnetic distortion of the EEG through static and dynamic magnetic field during MR data acquisition and ballistocardiographic artifacts were removed using the averaged artifact subtraction (AAS) method described by Allen et al. (Allen et al. 2000, 1998). After artifact correction, the data were down-sampled to 250 Hz and were low-pass filtered at 75 Hz (Siniatchkin et al. 2007).

The detailed description of simultaneous EEG and fMRI recordings, the protocol of MR artifact correction of the

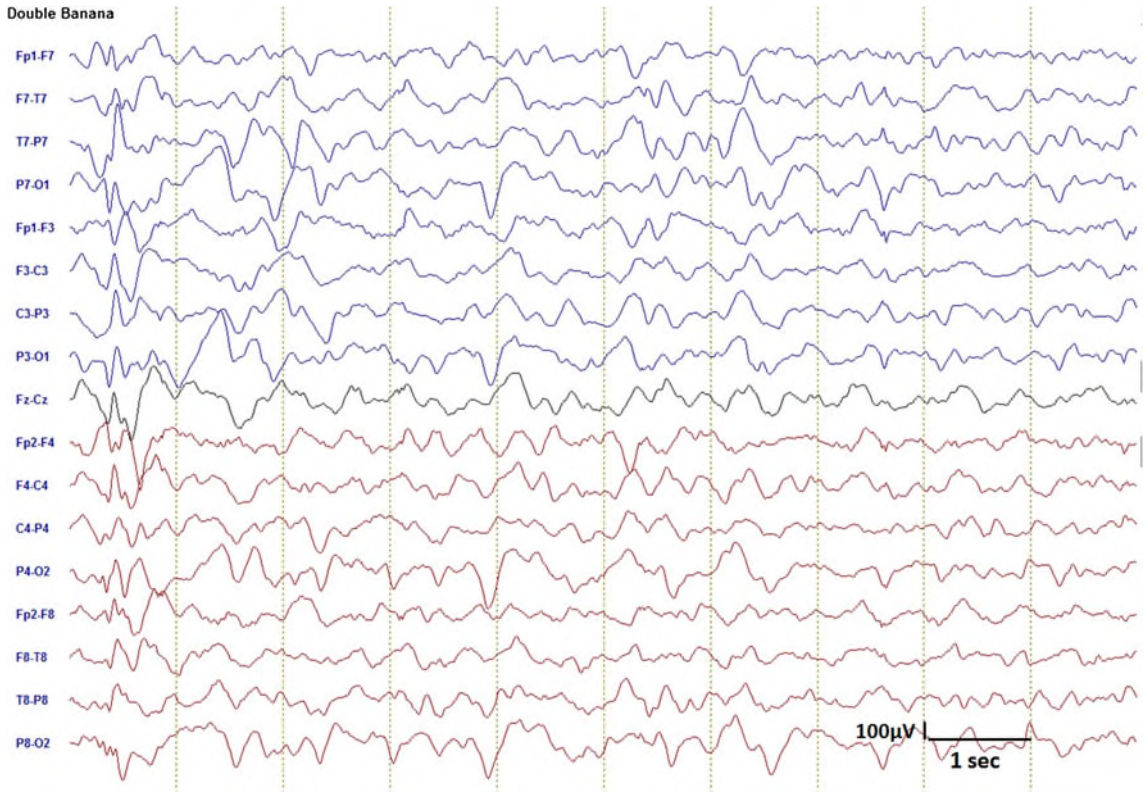

Fig. 2 EEG recording showing diffuse slowing of the background activity, with multifocal high amplitude delta-theta activity in a 10-month old patient with symptomatic resistant partial epilepsy

EEGs and fMRI analysis with the general linear model and canonical hemodynamic response function can be found in our previous publication (Siniatchkin et al. 2007).

EEG Analysis

Considering that slow wave activity and not epileptiform discharges has been proposed to specifically represent the hypsarrhythmia (Hrachovy and Frost 2003) and that high-voltage slow waves have been discussed to constitute a part of the neuronal process involved in the generation of spasms (Fusco and Vigevano 1993; Kobayashi et al. 2005), we decided to analyze high-amplitude, 1–4 Hz—delta waves in each patient from both groups.

Selection of EEG Epochs

For the DICS analyses, the EEG segments with the highest concentration of delta waves had to be chosen. For this reason estimation of a pooled time frequency power spectrum was performed (see Supplementary text 1). This method was chosen over the visual inspection and selection by an experienced neurophysiologist, in order to avoid subjective selectivity bias.

Source Analysis

DICS (Gross et al. 2001) was used to find the sources of epileptic activity in the brain. The DICS analysis was performed in a blinded fashion, so that the analyst did not know the patients' diagnoses. In order to locate the origin of specific EEG activity seen on the scalp, two problems need to be solved which are the forward and inverse problems. The forward problem is the computation of the scalp potentials for a set of neural current sources. It is solved by estimating the lead-field matrix with specified models for the brain. In this study, the brain was modeled by a complex, five-concentric-spheres model (Zhang 1995) with a single sphere for each layer corresponding to the white matter, grey matter, cerebral spinal fluid (CSF), skull and skin. In this multilayer anisotropic spheres the inner-most shell is considered to be anisotropic. If there is a dipole in the centre or in the surface of the sphere, the leadfields estimated due to these dipoles will not lead to any structural bias in there localization (Zhang 1995). Spherical models were used to localize brain stem sources in BAEP studies (Scherg and von Cramon 1985), as well as in our earlier studies in tremor (Muthuraman et al. 2012b) and in epilepsy patients (Moeller et al. 2012). The volume conductor model was created using standard T1 magnetic

resonance images (Zhang 1995). The template model created was then warped onto the standard head model. We used Fieldtrip, which is an open source software (Oostenveld et al. 2011). The head was modeled by entering the radius and the position of the sphere with the standard electrode locations. In order to map the current dipoles in the human brain to the voltages on the scalp, the lead-field matrix (LFM) needs to be calculated. The lead-field matrix was estimated using the boundary-element method (BEM) (Fuchs et al. 2002). The LFM contains information about the geometry and the conductivity of the model. For a complete description of the solution for the forward problem see Muthuraman et al. (2010b).

The inverse problem is the quantitative estimation of the properties of the neural current sources underlying the EEG activity. The neural activity is modeled as a current dipole or sum of current dipoles. The power and coherence at any given location in the brain can be computed using a linear transformation which in our case is the spatial filter (Drongelen et al. 1996). In this study, the linear constrained minimum variance (LMCV) spatial filter was used which relates the underlying neural activity to the electromagnetic field on the surface. The main aim of the LCMV method (Drongelen et al. 1996) was to design a bank of spatial filters that attenuates signals from other locations and only permits signals generated from a particular location in the brain. The DICS method employed a spatial filter algorithm (Drongelen et al. 1996) to identify the spatial power maximum or coherence in the brain for a particular frequency band. It uses a regularization parameter, which determines the spatial extent of source representation. For all analyses the same regularization parameter of $\alpha = 0.001$ was used so that the regularized DICS does not contain excessive contributions from noise. In terms of current distributions, regularization means that only those eigenleads are considered for the source analysis that correspond to the small eigenvalues, and thus are hard to measure in the data, which has sufficient signal-to-noise ratio (>20 dB). The second reason is that small eigenvalues are ignored in the estimation, which could lead to large computation errors in the vectors that are determined from the measurements. This value has been shown to yield reliable results in simulation studies and in MEG data (Kujala et al. 2008) and EEG data (Muthuraman et al. 2012b). The brain region representing the strongest power in a specific frequency band can subsequently be used as a reference region for cortico-cortical coherence analysis (Gross et al. 2001). In order to create topographic maps, the spatial filter is applied to a large number of voxels covering the entire brain using a voxel size of 5 mm. The individual maps of coherence were spatially normalized and interpolated on a standard T1 brain in SPM2. For a description of the spatial filter see Muthuraman et al. (2008).

For groups of patients, the brain source with the strongest power in the 1–4 Hz band was identified and defined as the reference region for further coherence analysis between brain areas. Since the coherence of a reference region with itself is always one, the reference region was projected out of the coherence matrix, and further coherent areas were found. In each subsequent step, the second strongest coherent source was considered as noise in order to locate the next correlated source. In this way, it was possible to locate very weak sub-cortical sources without the disturbance from the strongly correlated sources in the delta frequency band. The statistical significance of the identified coherent sources was tested by a within subject surrogate analysis. A Monte Carlo test of 100 random permutations was carried out, and the Monte Carlo p value ($\alpha = 0.05$) was calculated (Maris and Oostenveld 2007; Maris et al. 2007). This analysis was performed for each patient separately, followed by a grand average of the significant sources across all patients.

Once coherent brain areas were identified, their activity was extracted from the surface EEG by the spatial filter as described in Van Veen et al. (1997).

Directionality Analysis

Coherence analysis only reveals components that are common to two signals in the frequency domain. It does not give the direction of information flow between the two signals. In this study we applied renormalized partial directed coherence (RPDC) (Schelter et al. 2009) which is a technique performed in the frequency domain to detect the direction of information flow from one signal to the other and vice versa. The pooled time course of all the voxel source signals identified in a source were taken for the calculation of the RPDC. This method applies a multivariate (MVAR) modeling approach which uses an autoregressive process to obtain the coefficients of the signals in the frequency band of 1–4 Hz. In order to obtain these coefficients, the correct model order needs to be chosen which is estimated by minimizing the Akaike Information Criterion (AIC) (Akaike 1974) and gives the optimal order for the corresponding signal (Ding et al. 2000). After estimating the RPDC values, the significance level is calculated from the applied data using a bootstrapping method (Kaminski et al. 2001). In this manuscript the open source matrix laboratory (matlab) package ARFIT was used (Neumaier and Schneider 2001; Schneider and Neumaier 2001) to estimate the autoregressive coefficients from the spatially filtered source signals.

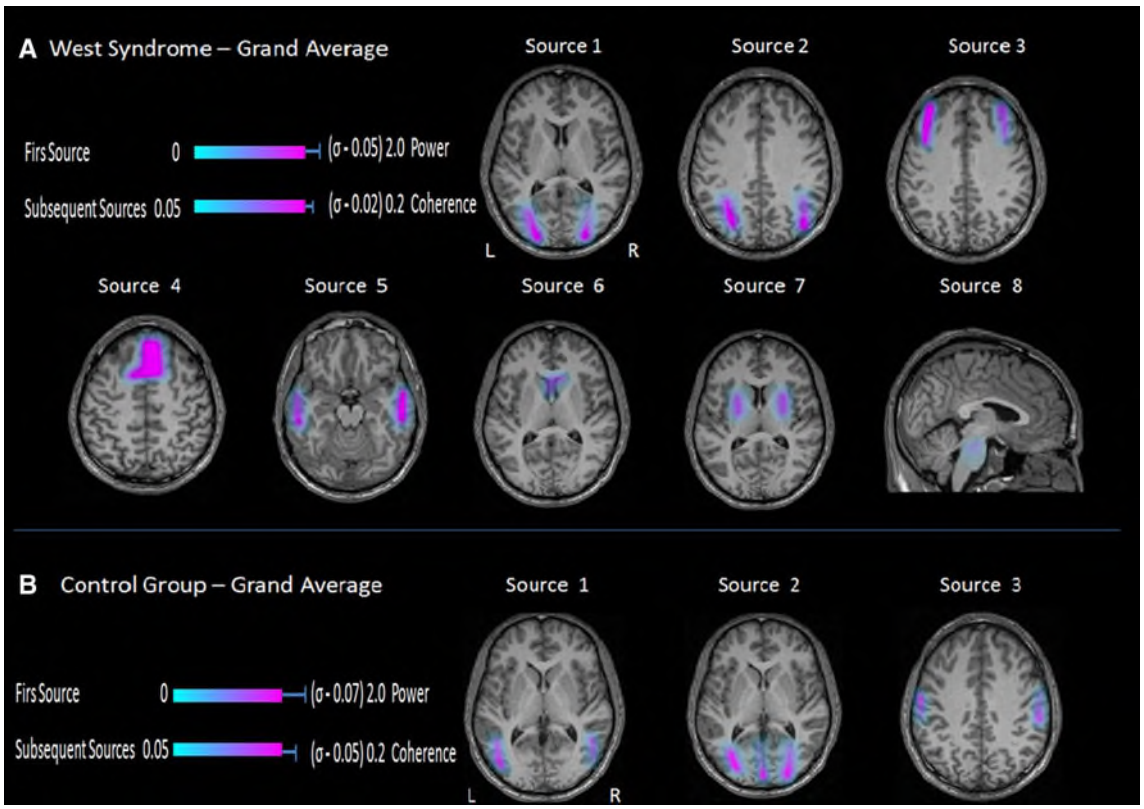

Fig. 3 DICS grand average analyses for the sources described in both groups. *Color bars* demonstrating the power and the coherence of the first source subsequent sources respectively. **a** West syndrome patients showing sources in cortical (occipital, parietal, and frontal) as well as in subcortical (lenticular nucleus, brainstem) regions. **b** Control group patients showing sources in cortical regions (occipital, parietal and frontal)

Results

DICS

West Syndrome Group

The grand average of the sources described by DICS analysis for the patients of both groups is shown in Fig. 3. (Results of DICS analyses for individual patients are shown in Supplementary Fig. 3). In patients with West syndrome, the source of the strongest power at the frequency band 1–4 Hz was detected in the occipital regions in all eight cases. Occipital sources were bilateral in six cases and unilateral in two cases (one on the right and one on the left side). The local maximum of this source varied slightly across the patients (Supplementary Fig. 3). This first source was defined as the reference region for further coherence analysis between brain areas. West syndrome cases commonly showed the common four sources coherent with the first source, and there were only small differences across the patients with respect to the local maxima of the sources (Supplementary Fig. 1). Sources with the strongest coherence with the reference source were found bilaterally in the parietal cortex (second source) in six patients and unilaterally in two patients. The next strongest coherence was detected in frontal regions in seven cases (five bilateral and two unilateral) and in bilateral temporal regions in only one case. Subsequent sources were detected in the putamen in all eight patients, whereas the last coherent source was found in the brainstem in all eight patients.

Control Group

In the control group, the source of the strongest power in the 1–4 Hz band was detected in temporal regions in all eight cases (six bilateral and two unilateral, respectively). The local maximum of these sources varied slightly across the patients (Supplementary Fig. 3). This first source was defined as the reference region for further coherence analysis between brain areas. The source with the strongest coherence with the reference source was found bilaterally in the occipital cortex (second source) of six patients and unilaterally in two patients. The third and the last coherent region in this frequency band were found in central regions

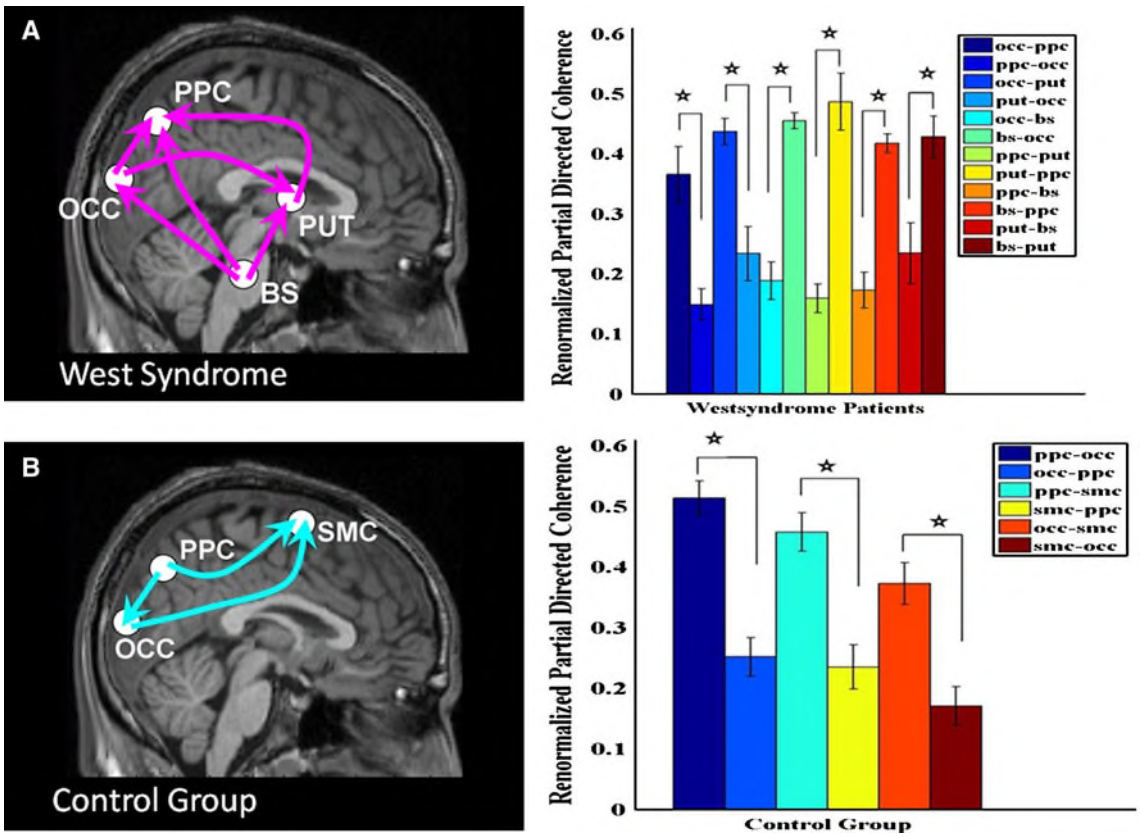

Fig. 4 The RPDC group analysis shows the direction of the informational flow between the sources estimated by the DICS analyses. **a** West syndrome group 4 sources which were detected in all West syndrome patients (occipital, parietal, putamen and brainstem) were used for the RPDC analysis. Figure shows the ascending informational flow from the brainstem towards the putamen and cortical regions. **b** Control group. All three identified sources were used for the further RPDC analysis. Figure shows the unspecific flow of information from the parietal cortex towards the occipital and frontal cortex. (OCC-occipital cortex, PPC-posterior parietal cortex, PUT-putamen, BS-brainstem, SMC-sensorimotor cortex). * The significant difference in the informational flow

in all eight cases (bilateral in six and unilateral in two cases, respectively).

RPDC

For the further RPDC analysis in patients with West syndrome, only those sources were used which were common for all West syndrome patients (occipital, parietal, putamen and brainstem). RPDC showed that the direction of information flow was significantly stronger from the brainstem towards the occipital, parietal regions and putamen, rather than vice versa. Also, the stronger RPDC was detected from the putamen towards the parietal regions and from the occipital regions toward the parietal region. See Fig. 4.

In the control group, all three sources were used for further RPDC analysis. RPDC showed that the direction of informational flow was significantly stronger from the temporal region (Source 1) towards the occipital region and precentral gyrus (Source 3). Also the stronger RPDC was detected from the occipital region towards the precentral gyrus (Fig. 4).

Discussion

Functional Connectivity in Hypsarrhythmia

Using the algorithm of DICS, we tried to describe the neuronal network underlying hypsarrhythmia by imaging power and coherence of oscillatory brain activity (Gross et al. 2001). Results of DICS analysis demonstrated that the high-amplitude slow activity within the hypsarrhythmia is attributed to coherent sources in occipital, frontal and parietal cortical regions, as well as in the basal ganglia and brainstem. In patients with partial epilepsies, the slow activity in the same frequency range was attributed to sources only in cortical regions (occipital, parietal, sensory-motor cortex). Therefore, we presume that the functionally related sources underlying hypsarrhythmia represent a specific network of this condition and might play an essential role in the pathogenesis of both infantile spasms and hypsarrhythmia.

In this study, we concentrated on the analyses of delta frequency band, considering that this is the most prominent

band seen in the West syndrome patients. High-voltage slow waves had been discussed to constitute a part of the neuronal process in the generation of spasms (Fusco and Vigevano 1993; Kobayashi et al. 2005). Slow wave activity has been proposed to specifically represent the hypsarrhythmia because this EEG phenomenon in some cases consists of either only high-voltage delta waves or a combination of delta waves and very little spike/sharp wave activity (Alva-Moncayo et al. 2002; Hrachovy and Frost 2003). Moreover, interictal slow wave activity has been associated with poor developmental outcome in West syndrome patients (Kramer et al. 1997). This high amplitude delta activity is one of the most homogeneous and constant findings in this group of patients.

The results of DICS analysis represented functional connectivity in hypsarrhythmia and were in line with EEG-fMRI results obtained from the same data sets. These fMRI results showed that multifocal epileptiform discharges within the hypsarrhythmia were associated with the complex and diverse pattern of cortical activations, whereas the high-amplitude slow activity in hypsarrhythmia correlated with BOLD signal changes in putamen and brainstem (Siniatchkin et al. 2007). Moreover, the results of this study are also consistent with results of previous PET and SPECT studies demonstrating significant metabolic changes in cortex, putamen and brainstem in patients suffering from infantile spasms (Chugani et al. 1990; Metsahonkala et al. 2002).

It is important to emphasize that all infants with hypsarrhythmia had the strongest source in the occipital cortex. These findings are supported by previous observations that the posterior cortex may be important in the pathogenesis of infantile spasms (Wenzel 1987; Guzzetta et al. 2002; Metsahonkala et al. 2002; Rando et al. 2005; Siniatchkin et al. 2007; Juhasz et al. 2001). It has been shown that visual abnormalities such as poor visual responsiveness, abnormal visual evoked potentials, and deficits in fixation shift can already be detected in the early stages of West syndrome or earlier (Wenzel 1987; Guzzetta et al. 2002; Rando et al. 2005). Focal posterior cortical hypometabolism has been found in a great proportion of children with the West syndrome (Chugani et al. 1990; Chiron et al. 1993; Jambaque et al. 1993; Metsahonkala et al. 2002). There is a discrepancy, however, concerning the relationship between the occipital cortex and pathological changes in hypsarrhythmia. In this study, the occipital source is related to the high-voltage slow activity. In contrast, our previous fMRI study demonstrated that the epileptic spikes are associated with BOLD signal changes in posterior brain regions. In the case of occipital cortex, both DICS and fMRI may appear complementary to each other. We suggest that the occipital cortex represents a common part of neuronal networks responsible for epileptiform discharges and high-amplitude slow activity. Unfortunately, these hypotheses have not been proven appropriately in the past. In this study, we did not analyze frequencies of epileptiform discharges. It is difficult to do such analyses from a methodological point of view because the spikes do not occur in a specific frequency range. In the fMRI study of Siniatchkin et al. (2007), the lack of association of high-amplitude slow activity with BOLD signal changes in the occipital cortex may be attributed either to an insufficient statistical power (only eight children were investigated) or a common variance of both regressors (epileptiform discharges and slow activity) which may have reduced sensitivity of the analysis. Whatever the explanation for discrepancies between studies may be, both studies demonstrated that the occipital cortex is an important node in the neuronal network of hypsarrhythmia.

Effective Connectivity in Hypsarrhythmia

It is poorly understood how the putamen, brainstem and occipital cortex within the described network of hypsarrhythmia are related to each other. Based on the DICS analysis we tried to describe interrelation and informational flow (effective connectivity) between different sources using the method of the RPDC (Schelter et al. 2009). In patients with West syndrome, RPDC showed that the strongest direction of influences could be an ascending informational flow from the brainstem towards the putamen and cerebral cortex.

Evidence from intracranial measurement, either from human or animal model, would fully clarify if there is any electrophysiological connection between brainstem and other cortical structures (Wilke et al. 2011, 2010). However, possibility of performing intracranial measurements in infants with West syndrome is restricted due to the ethical considerations. Our ffindings are supported by evidence suggesting that the brainstem is the area from which the spasms and the hypsarrhythmic EEG pattern arise (Chugani et al. 1992; Hrachovy et al. 1981; Morimatsu et al. 1972; Neville 1972; Satoh et al. 1986). Hrachovy and Frost (1989) had published a model of infantile spasms suggesting that disruption of certain monoaminergic or cholinergic areas within the region of the pontine reticular formation involved in the control of the sleep cycle could be the primary defect in this disorder. According to this model, the clinical seizures would result from phasic interference of descending brainstem pathways that control spinal reflex activity; whereas the activity in the ascending pathways from these same brainstem areas project widely to the cerebral cortex and could produce the characteristic EEG features and possibly disturbances of cognitive function (Hrachovy and Frost 2003). This hypothesis is based on the observation that patients with

infantile spasms have shorter REM sleep, a sleep phase during which the EEG normalizes and the number of spasms decreases. Brainstem serotonergic neurons are involved in sleep phases, and the depletion of serotonin may decrease REM sleep. Langlais and colleagues (1991) provided data supporting a serotonin dysfunction hypothesis by demonstrating reduced levels of 5-hydroxyindoleacetic acid (5-HIAA), a metabolite of serotonin, as well as decreased levels of homovanillic acid and 3-methoxy-4-hydroxyphenyl glycol (MHPG) in patients with infantile spasms. It is yet undetermined, whether these changes are the cause or a consequence of West syndrome.

Our results are in line with PET studies which had revealed focal or regional metabolic changes in the cortex of many infantile spasm patients (even in some patients with normal CT/MRI studies), significantly increased metabolic activity in the lenticular nuclei in the majority of subjects, and increased metabolic activity in the brainstem of some patients (Hrachovy and Frost 2003). Chugani et al. (2002, 1992) proposed that the primary dysfunction in infantile spasms is a focal or diffuse cortical abnormality, which, at a critical stage of development, triggers abnormal function of the serotonergic neurons in the raphe nuclei of the brainstem. Activation of the raphe-striatal pathway could then result in the observed hypermetabolic changes seen in the lenticular nuclei, whereas the raphe-cortical projections could be responsible for the hypsarrhythmic EEG pattern (Hrachovy and Frost 2003). Lado and Moshe (2002) have proposed another model suggesting that proconvulsant changes are necessary in both cortical and subcortical regions for the development of infantile spasms.

Methodological Considerations

The localization of bioelectrical sources in deep brain structures may appear rather adventurous and ominous. Therefore, we were very careful in drawing conclusion from our results and tried to prove validity of sources in deep brain structures using different methods and arguments. Indeed, thalamic and brainstem activities are far away from sensors located on the scalp and the signal from these sources may be too weak. However, some arguments support the notion that brain stem activity may be measured on the scalp. For example brainstem auditory evoked potentials had been measured clinically using EEG and intracranial recordings which clearly show the detectability of brainstem potentials in humans (Scherg and von Cramon 1985; Curio et al. 1987; Curio and Oppel 1988; Legatt 2002; Moller et al. 1995) and in monkeys (Legatt et al. 1986; Moller and Burgess 1986). Moreover, in tremor oscillatory networks, brainstem was found using DICS in patients with essential tremor in MEG study (Schnitzler et al. 2009) and in EEG study with high signal-to-noise ratio (SNR) data (Muthuraman et al. 2012b). The signal from brainstem evoked potentials and from tremor activity are much lower and less synchronized than the epileptic activity studied. Therefore, the probability to detect activity originating from brainstem for epileptiform discharges or high amplitude delta activity with high SNR is higher than for the other types of brain activity. High amplitude Delta waves investigated in this study also have a higher overall relative SNR in the EEG (32.78 $\pm$ 6.02 dB) (see Supplementary text 3) and only those EEG epochs were chosen which had a relative SNR greater than 20 dB. In the study of Moeller et al. (2012) DICS was applied to different types of generalized epileptiform discharges and showed cortical and thalamic involvement which was in line with the EEG-fMRI data obtained previously from the same data sets. Even though DICS was used to characterize neuronal networks including subcortical structures in a number of neurological disorders (Gross et al. 2001, 2002; Timmermann et al. 2003a, b; Sudmeyer et al. 2006; Schnitzler et al. 2006), it has been a matter of debate whether subcortical sources can be detected in EEG signals recorded from the skull surface. An important concern might be that DICS is locating artificial midline sub-cortical sources due to distributed activity in the cortex. However, the simulation described by Moeller et al. (2012) demonstrated that DICS does not locate any artificial sources. A second concern could be that the application of inverse algorithms to 32-channel EEG is unable to correctly locate sources in the deep structures of the brain like the thalamus, cerebellum, and brainstem. Simulation I, however, indicated that the deep sources like the brainstem could be identified when there is higher signal to noise ratio and a certain dipole orientation exists (see Supplementary Fig. 2 and Supplementary text). The reason for this is the spatial extent of the electrode configurations on the head from 8 to 64 channels which does not contain any electrodes on the posterior region below the inion and the more frontal part above the eyelids in the simulation. In all West syndrome subjects, the dipole orientation of the brainstem source was identified with a 32-channel configuration pointing towards the cortex at an angle of 90°. This dipole orientation can be explained by anatomical evidence of vertically running corticospinal and corticopontine fibers from the cortex to the pontine nuclei (Leergaard et al. 2007) and by additional evidence from the BAEP dipole analysis that the brain stem dipoles are vertically oriented (Scherg and von Cramon 1985; Plourde et al. 2008; Paquereau et al. 1994; Riedel et al., 2002).

Another point supporting the fact that the brainstem source was found in all West syndrome subjects is the spatial filtering approach that has been extensively tested earlier with different electrode configurations from the standard 10–20 system to 32 channels. It has been

described that the standard sphere head model will have better accuracy with the source located in the center of the sphere with certain dipole orientations depending on the spatial extent of the electrodes in Van Veen et al. (1997).

It is important to emphasize that this is the first study using scalp EEG identifying brainstem sources in infant patients. This could be an additional advantage given the reduced density of the skull in pediatric patients. It may be suggested that the localization of deep sources is easier in infants than in young children (Glass et al. 2004; Wolters et al. 2004). However, this assumption is speculative and has to be proven in further studies.

The possibility to detect brainstem activity may be supported by methodological advantages of DICS. In the DICS source analysis the first strongest source is used as reference to find the network of sources. In each subsequent step, the second strongest coherent source is considered as noise in order to locate the next correlated source. In this way, it is possible to locate very weak subcortical sources without the disturbance from the strongly correlated sources in the delta frequency band. (Muthuraman et al. 2012b; Moeller et al. 2012).

We are aware of difficulties to detect brainstem activity; therefore, we used another neuroimaging method to validate data—EEG-fMRI. The EEG-fMRI results of the same data sets showed that multifocal epileptiform discharges within the hypsarrhythmia were associated with the complex and diverse pattern of cortical activations, whereas the high-amplitude slow activity in hypsarrhythmia correlated with BOLD signal changes in the putamen and brainstem (Siniatchkin et al. 2007). Thus, we were able to directly compare the results of coherent source analysis (DICS) to EEG-fMRI results in the same events and patients. The comparison revealed a high correspondence between the methods applied. Nevertheless, considering the mismatches between electrophysiological signals and BOLD signals, due to their different underlying mechanisms, the previous EEG-fMRI study cannot fully support the point that there is electrophysiological activity in brainstem. The best way to validate sources is to find correspondence with intracranial recordings; however, in case of brain stem it is difficult to do (brainstem does not belong to usual target of deep brain stimulation and does not generate seizures).

We would like to point out some limitations in our analysis. Firstly, we focused only on the high-amplitude slow activity, considering that this is the most prominent band seen in the West syndrome patients, and did not analyze neuronal networks associated with epileptiform discharges in hypsarrhythmia. Therefore, our considerations concerning mechanisms of hypsarrhythmia are limited to this phenomenon. Secondly, the DICS has two major limitations as applied in this paper. First, the estimation of the source activity is done by using a single dipole as the underlying model and this is susceptible to the presence of highly correlated sources (Schoffelen et al. 2008). The highly correlated sources are difficult to localize and separate using the traditional beamformer analyses. Due to this reason, in the current method after the first, strongest coherent source is found the corresponding identified voxels are taken out of the source matrix so that in the next step of the source analysis these voxels are considered as noise. In this way the next strongest coherent source can be identified and separated from other coherent sources. The second limitation is that the standard head model was used with standard electrode locations. To increase the localization accuracy of the sources, the individual electrode locations can be used in the estimation of the individual lead field matrix. The localization accuracy of the sources can be improved by using the boundary element and finite element methods to build realistic-shaped head models with the individual MRI and electrode location from the subjects.

Compared to other studies which demonstrated sources in brainstem (Scherg and von Cramon 1985; Curio et al. 1987; Curio and Oppel 1988; Legatt 2002; Moller et al. 1995; Schnitzler et al. 2009; Muthuraman et al. 2012b) our study is the first which used external validation technique. This study may be considered as one among others, which provide evidence for the brainstem sources. Moreover, we would like emphasize the important aspect of physiological significance of the described activity: sources in the brainstem were specifically accounted to the West syndrome in which the brain stem pathology was repeatedly discussed and found in earlier studies (Chugani et al. 1990; Metsahonkala et al. 2002). Thus, the described sources make sense from physiological point of view and enable making a prior physiological constraints about the expected activity. Importantly, in the control group we did not find brainstem sources, although the activity analyzed was similar in both groups. If the brain stem source represents an artifact of the analysis of high amplitude delta waves, it is difficult to explain why this artifact was found only in children with West syndrome, and is not generally related to delta.

Conclusion

The study shows that EEG-based coherent source analysis is a powerful technique to map oscillatory activity. Consistent with the EEG-fMRI results, the sources in the cortical regions, as well as in subcortical structures were detected in West syndrome patients, whereas in control group only sources in the cortical structures were found. RPDC in West syndrome patients showed that the strongest direction of information flow could be an ascending flow

from the subcortical structures broadly projecting towards the cortical regions.

Acknowledgments We are very grateful patients, parents and colleagues who contributed to the study. The funding for the study was provided by Deutsche Forschungsgemeinschaft (DFG). The study was conducted in the frames of D3 and D2 subproject of Sonderforschungsbereich (SFB) 855.

Conflict of interest None of the authors has any conflict of interest to disclose.

Ethical Publication Statement We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

References

Akaike H (1974) A new look to the statistical model identification. IEEE Trans Autom Control 19(6):716–723

Allen PJ, Polizzi G, Krakow K, Fish DR, Lemieux L (1998) Identification of EEG events in the MR scanner: the problem of pulse artifact and a method for its subtraction. Neuroimage 8(3): 229–239. doi:10.1006/nimg.1998.0361

Allen PJ, Josephs O, Turner R (2000) A method for removing imaging artifact from continuous EEG recorded during functional MRI. Neuroimage 12(2):230–239. doi:10.1006/nimg.2000.0599

Alva-Moncayo E, Diaz-Leal MC, Olmos-Garcia De Alba G (2002) Electroencephalographic discoveries in children with infantile massive spasms in Mexico. Rev Neurol 34(10):928–932

Astolfi L, Cincotti F, Mattia D, Marciani MG, Baccala LA, de Vico FF, Salinari S, Ursino M, Zavaglia M, Ding L, Edgar JC, Miller GA, He B, Babiloni F (2007) Comparison of different cortical connectivity estimators for high-resolution EEG recordings. Hum Brain Mapp 28(2):143–157. doi:10.1002/hbm.20263

Baccala LA, Sameshima K (2001) Partial directed coherence: a new concept in neural structure determination. Biol Cybern 84(6): 463–474

Chiron C, Dulac O, Bulteau C, Nuttin C, Depas G, Raynaud C, Syrota A (1993) Study of regional cerebral blood flow in West syndrome. Epilepsia 34(4):707–715

Chugani HT (2002) Pathophysiology of infantile spasms. Adv Exp Med Biol 497:111–121

Chugani HT, Shields WD, Shewmon DA, Olson DM, Phelps ME, Peacock WJ (1990) Infantile spasms: I. PET identifies focal cortical dysgenesis in cryptogenic cases for surgical treatment. Ann Neurol 27(4):406–413. doi:10.1002/ana.410270408

Chugani HT, Shewmon DA, Sankar R, Chen BC, Phelps ME (1992) Infantile spasms: II. Lenticular nuclei and brain stem activation on positron emission tomography. Ann Neurol 31(2):212–219. doi:10.1002/ana.410310212

Curio G, Oppel F (1988) Intraparenchymatous ponto-mesencephalic field distribution of brain-stem auditory evoked potentials in man. Electroencephalogr Clin Neurophysiol 69(3):259–265

Curio G, Oppel F, Scherg M (1987) Peripheral origin of BAEP wave II in a case with unilateral pontine pathology: a comparison of intracranial and scalp records. Electroencephalogr Clin Neurophysiol 66(1):29–33

Ding M, Bressler SL, Yang W, Liang H (2000) Short-window spectral analysis of cortical event-related potentials by adaptive multivariate autoregressive modeling: data preprocessing, model validation, and variability assessment. Biol Cybern 83(1):35–45

Drongelen W, Yuchtman M, VanVeen BD, van Huffelen AC (1996) A spatial filtering technique to detect and localize multiple sources in the brain. Brain Topogr 9(1):39–49

Dulac O (2001) What is West syndrome? Brain Dev 23(7):447–452. doi:10.1016/S0387-7604(01)00268-6

Fuchs M, Kastner J, Wagner M, Hawes S, Ebersole JS (2002) A standardized boundary element method volume conductor model. Clin Neurophysiol 113(5):702–712

Fusco L, Vigevano F (1993) Ictal clinical electroencephalographic findings of spasms in West syndrome. Epilepsia 34(4):671–678

Glass RB, Fernbach SK, Norton KI, Choi PS, Naidich TP (2004) The infant skull: a vault of information. Radiographics 24(2): 507–522. doi:10.1148/rg.24203510524/2/507

Groening K, Brodbeck V, Moeller F, Wolff S, van Baalen A, Michel CM, Jansen O, Boor R, Wiegand G, Stephani U, Siniatchkin M (2009) Combination of EEG-fMRI and EEG source analysis improves interpretation of spike-associated activation networks in paediatric pharmacoresistant focal epilepsies. Neuroimage 46(3):827–833. doi:10.1016/j.neuroimage.2009.02.026

Gross J, Kujala J, Hamalainen M, Timmermann L, Schnitzler A, Salmelin R (2001) Dynamic imaging of coherent sources: studying neural interactions in the human brain. Proc Natl Acad Sci USA 98(2):694–699. doi:10.1073/pnas.98.2.69498/2/694

Gross J, Timmermann L, Kujala J, Dirks M, Schmitz F, Salmelin R, Schnitzler A (2002) The neural basis of intermittent motor control in humans. Proc Natl Acad Sci USA 99(4):2299–2302. doi:10.1073/pnas.03268209999/4/2299

Guzzetta F, Frisone MF, Ricci D, Rando T, Guzzetta A (2002) Development of visual attention in West syndrome. Epilepsia 43(7):757–763. doi:10.1046/j.1528-1157.2002.34601.x

Haginoya K, Kon K, Yokoyama H, Tanaka S, Kato R, Munakata M, Yagi T, Takayanagi M, Yoshihara Y, Nagai M, Yamazaki T, Maruoka S, Iinuma K (2000) The perfusion defect seen with SPECT in West syndrome is not correlated with seizure prognosis or developmental outcome. Brain Dev 22(1):16–23. doi:10.1016/S0387-7604(99)00081-9

Hellwig B, Haussler S, Lauk M, Guschlbauer B, Koster B, Kristeva-Feige R, Timmer J, Lucking CH (2000) Tremor-correlated cortical activity detected by electroencephalography. Clin Neurophysiol 111(5):806–809. doi:10.1016/S1388-2457(00)00248-0

Hellwig B, Haussler S, Schelter B, Lauk M, Guschlbauer B, Timmer J, Lucking CH (2001) Tremor-correlated cortical activity in essential tremor. Lancet 357(9255):519–523. doi:10.1016/S0140-6736(00)04044-7

Hellwig B, Schelter B, Guschlbauer B, Timmer J, Lucking CH (2003) Dynamic synchronisation of central oscillators in essential tremor. Clin Neurophysiol 114(8):1462–1467. doi:10.1016/S1388-2457(03)00116-0

Holmes MD (2008) Dense array EEG: methodology and new hypothesis on epilepsy syndromes. Epilepsia 49:3–14. doi:10.1111/j.1528-1167.2008.01505.x

Holmes MD, Brown M, Tucker DM (2004) Are "generalized" seizures truly generalized? Evidence of localized mesial frontal and frontopolar discharges in absence. Epilepsia 45(12):1568–1579. doi:10.1111/j.0013-9580.2004.23204.x

Holmes MD, Quiring J, Tucker DM (2010) Evidence that juvenile myoclonic epilepsy is a disorder of frontotemporal corticothalamic networks. Neuroimage 49(1):80–93. doi:10.1016/j.neuroimage.2009.08.004

Hrachovy RA, Frost JD Jr (1989) Infantile spasms. Pediatr Clin N Am 36(2):311–329

Hrachovy RA, Frost JD Jr (2003) Infantile epileptic encephalopathy with hypsarrhythmia (infantile spasms/West syndrome). J Clin Neurophysiol 20(6):408–425

Hrachovy RA, Frost JD Jr, Kellaway P (1981) Sleep characteristics in infantile spasms. Neurology 31(6):688–693

Jambaque I, Chiron C, Dulac O, Raynaud C, Syrota P (1993) Visual inattention in West syndrome: a neuropsychological and neurofunctional imaging study. Epilepsia 34(4):692–700

Juhasz C, Chugani HT, Muzik O, Chugani DC (2001) Neuroradiological assessment of brain structure and function and its implication in the pathogenesis of West syndrome. Brain Dev 23(7):488–495. doi:10.1016/S0387-7604(01)00295-9

Kaminski MDM, Truccolo WA, Bressler SL (2001) Evaluating causal relations in neural systems: Granger causality, directed transfer function and statistical assessment of significance. Biol Cybern 85(2):145–157

Kobayashi K, Oka M, Inoue T, Ogino T, Yoshinaga H, Ohtsuka Y (2005) Characteristics of slow waves on EEG associated with epileptic spasms. Epilepsia 46(7):1098–1105. doi:10.1111/j.1528-1167.2005.63004.x

Kramer U, Sue WC, Mikati MA (1997) Hypsarrhythmia: frequency of variant patterns and correlation with etiology and outcome. Neurology 48(1):197–203

Kujala J, Gross J, Salmelin R (2008) Localization of correlated network activity at the cortical level with MEG. Neuroimage 39(4):1706–1720. doi:10.1016/j.neuroimage.2007.10.042

Kwan P, Arzimanoglou A, Berg AT, Brodie MJ, Allen Hauser W, Mathern G, Moshe SL, Perucca E, Wiebe S, French J (2010) Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia 51(6):1069–1077. doi:10.1111/j.1528-1167.2009.02397.x

Lado FA, Moshe SL (2002) Role of subcortical structures in the pathogenesis of infantile spasms: what are possible subcortical mediators? Int Rev Neurobiol 49:115–140

Langlais PJ, Wardlow ML, Yamamoto H (1991) Changes in CSF neurotransmitters in infantile spasms. Pediatr Neurol 7(6):440–445

Legatt AD (2002) Mechanisms of intraoperative brainstem auditory evoked potential changes. J Clin Neurophysiol 19(5):396–408

Legatt AD, Arezzo JC, Vaughan HG Jr (1986) Short-latency auditory evoked potentials in the monkey. II. Intracranial generators. Electroencephalogr Clin Neurophysiol 64(1):53–73

Maris E, Oostenveld R (2007) Nonparametric statistical testing of EEG- and MEG-data. J Neurosci Methods 164(1):177–190. doi:10.1016/j.jneumeth.2007.03.024

Maris E, Schoffelen JM, Fries P (2007) Nonparametric statistical testing of coherence differences. J Neurosci Methods 163(1):161–175. doi:10.1016/j.jneumeth.2007.02.011

Metsahonkala L, Gaily E, Rantala H, Salmi E, Valanne L, Aarimaa T, Liukkonen E, Holopainen I, Granstrom ML, Erkinjuntti M, Gronroos T, Sillanpaa M (2002) Focal and global cortical hypometabolism in patients with newly diagnosed infantile spasms. Neurology 58(11):1646–1651

Michel CM, Murray MM, Lantz G, Gonzalez S, Spinelli L, Grave de Peralta R (2004) EEG source imaging. Clin Neurophysiol 115(10):2195–2222. doi:10.1016/j.clinph.2004.06.001

Moeller F, Muthuraman M, Stephani U, Deuschl G, Raethjen J, Siniatchkin M (2012) Representation and propagation of epileptic activity in absences and generalized photoparoxysmal responses. Hum Brain Mapp. doi:10.1002/hbm.22026

Moller AR, Burgess J (1986) Neural generators of the brain-stem auditory evoked potentials (BAEPs) in the rhesus monkey. Electroencephalogr Clin Neurophysiol 65(5):361–372

Moller AR, Jho HD, Yokota M, Jannetta PJ (1995) Contribution from crossed and uncrossed brainstem structures to the brainstem auditory evoked potentials: a study in humans. Laryngoscope 105(6):596–605. doi:10.1288/00005537-199506000-00007

Morimatsu Y, Murofushi K, Handa T, Shinoara T, Shiraki H (1972) Pathology in severe physical and mental disabilities in children–with special reference to 4 cases of nodding spasm. Shinkei Kenkyu No Shimpo 16(3):465–470

Muthuraman M, Raethjen J, Hellriegel H, Deuschl G, Heute U (2008) Imaging coherent sources of tremor related EEG activity in patients with Parkinson's disease. Conf Proc IEEE Eng Med Biol Soc 2008:4716–4719. doi:10.1109/IEMBS.2008.4650266

Muthuraman M, Heute U, Deuschl G, Raethjen J (2010) The central oscillatory network of essential tremor. Conf Proc IEEE Eng Med Biol Soc 2010:154–157. doi:10.1109/IEMBS.2010.5627211

Muthuraman M, Tamas G, Hellriegel H, Deuschl G, Raethjen J (2012a) Source analysis of Beta-synchronisation and cortico-muscular coherence after movement termination based on high resolution electroencephalography. PLoSOne 7(3):e33928

Muthuraman M, Heute U, Arning K, Anwar AR, Elble R, Deuschl G, Raethjen J (2012b) Oscillating central motor networks in pathological tremors and voluntary movements. What makes the difference?. NeuroImage. doi:10.1016/j.neuroimage.2012.01.088

Neumaier A, Schneider T (2001) Estimation of parameters and eigenmodes of multivariate autoregressive models. ACM Trans Math Softw 27(1):27–57

Neville BG (1972) The origin of infantile spasms: evidence from a case of hydranencephaly. Dev Med Child Neurol 14(5):644–647

Oostenveld RFP, Maris E, Schoffelen JM (2011) FieldTrip: open source soft ware for advanced analysis of MEG, EEG, and invasive electrophysiological data. Comput Intell Neurosci. doi:10.1155/2011/156869

Panayiotopoulos CP (2005) Epileptic encephalopathies in infancy and early childhood in which the epileptiform abnormalities may contribute to progressive dysfunction. In: Panayiotopoulos CP (ed) The epilepsies. Seizures, syndromes and management, 2010/09/08 edn. Bladon Medical Publishing, Oxfordshire. doi:NBK2606 [bookaccession]

Paquereau J, Meurice JC, Neau JP, Ingrand P, Patte F (1994) Auditory brain-stem responses (ABRs) in sleep respiratory disorders. Eur J Clin Invest 24(3):156–160

Plourde G, Garcia-Asensi A, Backman S, Deschamps A, Chartrand D, Fiset P, Picton TW (2008) Attenuation of the 40-hertz auditory steady state response by propofol involves the cortical and subcortical generators. Anesthesiology 108(2):233–242. doi:10.1097/01.anes.0000299839.33721.6d

Rando T, Baranello G, Ricci D, Guzzetta A, Tinelli F, Biagioni E, La Torre G, Epifanio R, Signorini S, Fazzi E, Mercuri E, Cioni G, Guzzetta F (2005) Cognitive competence at the onset of West syndrome: correlation with EEG patterns and visual function. Dev Med Child Neurol 47(11):760–765. doi:10.1017/S0012162205001593

Riedel H, Kollmeier B (2002) Auditory brain stem responses evoked by lateralized clicks: is lateralization extracted in the human brain stem? Hear Res 163(1–2):12–26. doi:S0378595501003628

Sameshima K, Baccala LA (1999) Using partial directed coherence to describe neuronal ensemble interactions. J Neurosci Methods 94(1):93–103

Satoh J, Mizutani T, Morimatsu Y (1986) Neuropathology of the brainstem in age-dependent epileptic encephalopathy: especially of cases with infantile spasms. Brain Dev 8(4):443–449

Schack B, Hesse W, Moller E, Arnold M (2003) The use of time-variant EEG Granger causality for inspecting directed interdependencies of neural assemblies. J Neurosci Methods 124(1):27–44. doi:10.1016/S0165-0270(02)00366-7

Schelter B, Timmer J, Eichler M (2009) Assessing the strength of directed influences among neural signals using renormalized partial directed coherence. J Neurosci Methods 179(1):121–130. doi:10.1016/j.jneumeth.2009.01.006

Scherg M, von Cramon D (1985) A new interpretation of the generators of BAEP waves I–V: results of a spatio-temporal dipole model. Electroencephalogr Clin Neurophysiol 62(4):290–299

Schneider T, Neumaier A (2001) Algorithm 808: ARfit: a Matlab package for the estimation of parameters and eigenmodes of multivariate autoregressive models. ACM Trans Math Softw 27(1):58–65

Schnitzler A, Timmermann L, Gross J (2006) Physiological and pathological oscillatory networks in the human motor system. J Physiol Paris 99(1):3–7. doi:10.1016/j.jphysparis.2005.06.010

Schnitzler A, Münks C, Butz M, Timmermann L, Gross J (2009) Synchronized brain network associated with essential tremor as revealed by magnetoencephalography. Mov Disord 24(11): 1629–1635

Schoffelen JM, Oostenveld R, Fries P (2008) Imaging the human motor system's beta-band synchronization during isometric contraction. Neuroimage 41(2):437–447. doi:10.1016/j.neuroimage.2008.01.045

Siniatchkin M, van Baalen A, Jacobs J, Moeller F, Moehring J, Boor R, Wolff S, Jansen O, Stephani U (2007) Different neuronal networks are associated with spikes and slow activity in hypsarrhythmia. Epilepsia 48(12):2312–2321. doi:10.1111/j.1528-1167.2007.01195.x

Siniatchkin M, Groening K, Moehring J, Moeller F, Boor R, Brodbeck V, Michel CM, Rodionov R, Lemieux L, Stephani U (2010) Neuronal networks in children with continuous spikes and waves during slow sleep. Brain 133(9):2798–2813. doi:10.1093/brain/awq183

Sudmeyer M, Saleh A, Wojtecki L, Cohnen M, Gross J, Ploner M, Hefter H, Timmermann L, Schnitzler A (2006) Wilson's disease tremor is associated with magnetic resonance imaging lesions in basal ganglia structures. Mov Disord 21(12):2134–2139. doi:10.1002/mds.21136

Tass P, Rosenblum MG, Weule J, Kurths J, Pikovsky A, Volkmann J, Schnitzler A, Freund HJ (1998) Detection of n:m phase locking from noisy data: application to magnetoencephalography. Phys Rev Lett 81(15):3291–3294

Timmermann L, Gross J, Butz M, Kircheis G, Haussinger D, Schnitzler A (2003a) Mini-asterixis in hepatic encephalopathy induced by pathologic thalamo-motor-cortical coupling. Neurology 61(5):689–692

Timmermann L, Gross J, Dirks M, Volkmann J, Freund HJ, Schnitzler A (2003b) The cerebral oscillatory network of parkinsonian resting tremor. Brain 126(Pt 1):199–212

Van Veen BD, van Drongelen W, Yuchtman M, Suzuki A (1997) Localization of brain electrical activity via linearly constrained minimum variance spatial filtering. IEEE Trans Biomed Eng 44(9):867–880. doi:10.1109/10.623056

Volkmann J, Joliot M, Mogilner A, Ioannides AA, Lado F, Fazzini E, Ribary U, Llinas R (1996) Central motor loop oscillations in parkinsonian resting tremor revealed by magnetoencephalography. Neurology 46(5):1359–1370

Vulliemoz S, Thornton R, Rodionov R, Carmichael DW, Guye M, Lhatoo S, McEvoy AW, Spinelli L, Michel CM, Duncan JS, Lemieux L (2009) The spatio-temporal mapping of epileptic networks: combination of EEG-fMRI and EEG source imaging. Neuroimage 46(3):834–843

Wenzel D (1987) Evoked potentials in infantile spasms. Brain Dev 9(4):365–368

Wilke C, van Drongelen W, Kohrman M, He B (2010) Neocortical seizure foci localization by means of a directed transfer function method. Epilepsia 51(4):564–572. doi:10.1111/j.1528-1167.2009.02329.x

Wilke C, Worrell G, He B (2011) Graph analysis of epileptogenic networks in human partial epilepsy. Epilepsia 52(1):84–93. doi:10.1111/j.1528-1167.2010.02785.x

Wolters CH, Anwander A, Maess B, Macleod RS, Friederici AD (2004) The influence of volume conduction effects on the EEG/MEG reconstruction of the sources of the Early Left Anterior Negativity. Conf Proc IEEE Eng Med Biol Soc 5:3569–3572. doi:10.1109/IEMBS.2004.1404003

Zhang Z (1995) A fast method to compute surface-potentials generated by dipoles within multilayer anisotropic spheres. Phys Med Biol 40(3):335–349