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Title: INCREASED RESTING-STATE EEG FUNCTIONAL CONNECTIVITY IN BENIGN CHILDHOOD EPILEPSY WITH CENTRO-TEMPORAL SPIKES

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Highlights

1. Increased frontal and temporal EEGfC were found in BECTS in the beta band.

2. Increased beta EEGfC was maximal in left frontal lobe.

3. Increased broad-band EEGfC was found in the right parietal area.

4. Findings may be related to language and attention deficit reported in BECTS.

INCREASED RESTING-STATE EEG FUNCTIONAL CONNECTIVITY IN BENIGN CHILDHOOD EPILEPSY WITH CENTRO-TEMPORAL SPIKES

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Running title: EEG functional connectivity in BECTS

Abstract

Purpose: To explore intrahemispheric, cortico-cortical EEG functional connectivity (EEGfC) in benign childhood epilepsy with rolandic spikes (BECTS).
Methods: 21-channel EEG was recorded in 17 non-medicated BECTS children and 19 healthy controls. 180 seconds of spike- and artifact-free activity was selected for EEGfC analysis. Correlation of Low Resolution Electromagnetic Tomography- (LORETA-) defined current source density time series were computed between two cortical areas (region of interest, ROI). Analyses were based on broad-band EEGfC results. Groups were compared by statistical parametric network (SPN) method. Statistically significant differences between group EEGfC values were emphasized at $p<0.05$ corrected for multiple comparison by local false discovery rate (FDR).
Results: 1. Bilaterally increased beta EEGfC occurred in the BECTS group as compared to the controls. Greatest beta abnormality emerged between frontal and frontal, as well as frontal and temporal ROIs. 2. Locally increased EEGfC emerged in all frequency bands in the right parietal area.
Conclusions: Areas of increased EEGfC topographically correspond to cortical areas that, based on relevant literature, are related to speech and attention deficit in BECTS children.

Keywords: EEG functional connectivity, benign childhood epilepsy with centro-temporal spikes

1. Introduction

Benign epilepsy of childhood with centro-temporal spikes (BECTS) is a well-known epilepsy syndrome. Typical BECTS patients have very rare focal seizures and do not show neurological abnormalities in the interictal state. Their EEG records show centro-temporal interictal epileptiform discharges. Prognosis is excellent, terminal remission occurs in all cases by the age of 16 years. Therefore, BECTS has been classified as idiopathic focal epilepsy (ILAE 1989; Dalla Bernardina et al, 2002). The term "idiopathic" traditionally implies lack of "demonstrable anatomic lesions" (ILAE 1989). However, this notion has not been valid any longer. Structural and functional abnormalities were described in typical BECTS children: bilaterally increased grey matter volume in the frontal lobes and insula (Pardoe et al., 2013), extensive cortical thinning in frontal, central, parietal and temporal areas (Overvliet et al., 2013). Abnormal white matter was found in the frontal and temporal lobes (Lundberg et al., 1999). Decreased functional MRI (fMRI) connectivity was demonstrated between Broca's area and the sensorimotor network (Besseling et al, 2013). Subtle cognitive and language difficulties that occur in 28 to 53 per cent of BECTS children (Chahine and Mikati, 2006) further suggest the presence of abnormal cerebral structure. Importantly, these data refer to "typical" BECTS cases (ILAE 1989), not to the spectrum of atypical cases (Wirrel et al, 1995) and neurobiologically related conditions (Doose and Baier, 1989). The above-listed findings and new genetic results collectively disclosed that BECTS is a genetically determined, developmental condition (Gkampeta and Pavlou, 2012). However, the underlying cerebral abnormality of BECTS has not been thoroughly explored yet. Faulty genes presumably cause altered neuronal connectivity and increased excitability in cerebral networks (Gkampeta and Pavlou, 2012). If so, abnormal structural connectivity may predict abnormal functional connectivity (Honey et al, 2009). The aim of this study is to explore interictal, resting-state EEG functional connectivity (EEGfC) in untreated, typical BECTS children.

Abbreviations: BECTS: benign childhood epilepsy with centro-temporal spikes; EEGfC: EEG functional connectivity; CSD: current source density; FD: false discovery rate; NC: normal (healthy) control; LORETA: low resolution electromagnetic tomography; LSC: LORETA Source Correlation; ROI: region of interest; SPN: statistical parametric network

2. Methods

2.1. Patients and control persons

The study design was approved by Research Ethics Committee of Kenézy Gyula County Hospital, Debrecen, Hungary. BECTS patients were enrolled at epilepsy outpatient services in Hungary. Clinical data and EEG records came from routine evaluation of children who had

been referred because of epileptic seizures. Evaluation included detailed medical history, pediatric and neurological investigations, routine blood and urine analysis and EEG (recorded in drug-free condition). Cranial MRI was indicated depending on the decision of the pediatric neurologist. Having finished the diagnostic procedure, EEG records of newly diagnosed, "typical" BECTS children (ILAE 1989) have got a code number and entered the investigation. Exclusion criteria were: EEG record that did not meet requirements of quantitative EEG analysis; very frequent spikes that masked background activity; any medical condition that is known to significantly interfere with EEG activity. No diagnostic evaluation or drug treatment was indicated, missed or postponed for study purposes.

The BECTS group (n = 17; 9 boys, 8 girls, aged 5.5-11.9, average: 8.5 years) was compared to a group of 19 healthy, normal control children (NC group; 10 boys, 9 girls, aged 6.0-11.9, average: 8.8 years). Unpaired t-test did not show statistically significant age difference between the groups (p=0.61). NC children were recruited from relatives of the medical staffs working at neurological departments. NC children were clinically healthy, without any developmental, neurological and psychiatric illness in medical history. Their waking EEG records were within normal limits, no abnormal slow wave activity or epileptiform potentials occurred. EEG was recorded and post-processed in the same way in patients and controls.

2.2. EEG recording and epoch selection

EEG recordings were carried out in the morning, after a night of sufficient sleep, in a semi-isolated room, with the same type of digital equipment, by trained personnel. Silver-silver chloride electrodes were placed according to the 10-20 system, fixed by appropriate adhesive and conductive gel. Electrode positions were not digitized. Impedances did not exceed 10 kOhm. 21-channel EEG was recorded from standard scalp sites and the earlobes against Fpz sampling reference. EEG was recomputed against a mathematical linked ears reference. Additional bipolar derivations were used to differentiate between EEG and eye movement potentials and to detect myogenic activity. In EEG derivations filters were set at 0.1 and 33.6 Hz, sampling rate was 256 per second, on-line digitization was 12 bit. 30 minutes EEG was recorded in the waking-relaxed, eyes-closed condition. The EEG technician controlled the state of vigilance and gently aroused the child when the posterior alpha rhythm disappeared.

The "best" 90 epochs (each 2 seconds, a total of 3 minutes EEG activity) were selected for EEGfC analysis by means of the NeuroGuide software Version 2.8. (www.appliedneuroscience.com). Our standard epoch selection protocol includes: 1. presence of continuous physiological alpha activity with alpha voltage maximum in posterior regions, 2. absence of artifacts, epileptiform potentials and other nonstationary elements, 3. absence of patterns indicating drowsiness or arousal. This electrographic definition of the relaxed-waking state refers to a narrow window of vigilance level (Bente, 1979). Post-spike periods of six seconds were excluded because the delayed effect of spikes that may interfere with EEG background activity (Clemens et al, 2009). We used two

reproducibility measures to minimize the effect of short- and long-term variability within the samples. Each sample showed at least 95 percent split-half and test-retest reliability (calculated as the average of the 19 channels). All steps of sampling and data analysis were the same for the patients and the controls. The selected epochs were revised by the senior author. NeuroGuide facilitated transmission of the samples to Low Resolution Electromagnetic Tomography (LORETA) software (Pascual-Marqui et al, 1994) and LORETA Source Correlation (LSC) software (Thatcher et al, 2007).

2.3. LORETA analysis

LORETA is a recently developed method to localize multiple distributed cortical sources of EEG activity in the three-dimensional space (Pascual-Marqui et al, 1994). In other words, LORETA demonstrates the synchronously activated EEG generators by computing their cortical localization from the scalp distribution of the electric field. The LORETA inverse solution is based on existing neuroanatomical and physiological knowledge and a mathematical constraint called smoothness assumption. LORETA computes the inverse solution within a three-shell spherical head model including scalp, skull, and brain. The brain compartment of this model was restricted to the cortical grey matter and hippocampus. The grey matter compartment is subdivided in 2394 voxels. LORETA computes current source density (ampers/ meters squared) for each voxel. For the sake of brevity, this is called "activity" as usual in the LORETA literature. Three-dimensional localization of voxels and cortical areas followed the Talairach coordinate system (Talairach and Tournoux, 1988). The consistency of LORETA with physiology and localization has been validated in physiological and pathological conditions (Pascual-Marqui et al, 2002). Comprehensive evaluation of the LORETA method is available in reviews (Plummer et al, 2008; Pascual-Marqui et al, 2009). In the present study we explored the frequency spectrum from 0.5 to 25.0 Hz by dividing it into four frequency bands (see Section 2.4).

2.4. Analysis of resting-state EEG functional connectivity

The covariance of the activity of LORETA-localized sources is a useful alternative for correlating quantitative EEG variables measured at scalp electrodes and offers a deeper understanding of intrahemispheric cortico-cortical connectivity (Thatcher et al., 2007; Schoffelen and Gross, 2009). The LSC software computes temporal covariance or correlation of LORETA-defined CSD between two cortical areas (region of interest, ROI), across the selected 2-seconds epochs over the investigated sample. Pearson product correlation coefficient (r) is a valid measure of oscillator coupling, especially when a relatively long interval of time is analyzed, as in this study. Authors who compared the sensitivity and reliability of several methods have concluded that Pearson correlation is a robust method, sensitive to all the investigated coupling parameters, and does not require any specific assumptions about the model (Wendling et al., 2009). Given the 19 scalp electrodes, the effect of the point spread on CSD estimates was minimized by clustering voxels into 33 ROIs

within each hemisphere. ROIs were pre-defined by the LSC software. Each ROI corresponded to a cortical gyrus and comprised voxels that belong to that gyrus, as defined by Talairach coordinates. Fig.1. shows the flowchart of computing asymmetric EEGfC matrices (Clemens et al., 2013a). This figure indicates that, EEGfC between two ROIs is characterized by two correlation coefficients. In order to avoid the asymmetry, we have generated a set of symmetric source correlation matrices from the average of the two correlation coefficients between ROIs: R_{ghbs} , stand for group ($g \in \{bers, nc\}$), hemisphere ($h \in \{left, right\}$), band ($b \in \{delta, theta, alpha, beta\}$) and subject indices ($s = 1 \ldots N_g$) respectively.

A single element of an R_{ghbs} matrix was denoted by r^e_{ghbs} (where e represents a connection between two regions). The number of rows and columns are equal with the number of ROIs (N=33) and with the number of correlation coefficients M=N (N-1)/2 (M=528). All analyses were based on broad-band results of four frequency bands (delta: 0.5-3.0 Hz, theta: 3.5-7.0 Hz; alpha: 7.5-12.0 Hz; beta: 12.5-25.0 Hz).

2.5. Statistical inference of connections

Statistical parametric network (SPN) terminology has been introduced recently (Ginestet and Simmonds, 2011). In our study, we generated population and state differential SPNs which provide a statistical method to infer differences of connections. SPNs were calculated from R_{ghbs} matrices, using M mixed-effect models: $r^e_{ghbs} = X^e_{ghb}\beta^e + Z^e_s b^e_s + \varepsilon^e_{ghbs}$, where r are the correlation coefficients of interest, β is a vector of fixed effect (group, hemisphere and band) which does not vary over subjects, b is the subject-specific random effects (subject, age-group) and ε are the residuals. Two age-groups were defined: a younger (age < 9 years) and an elder (age ≥ 9 years) one. The matrices X and Z contain the fixed-effect and the random-effect components of the introduced linear model. The effect of the group factor was evaluated for all bands by post-hoc Tukey test which produced t^e_{hb} t-values for all edges, hemispheres and bands. These t-values were stored in N x N SPN matrices for visualization and for statistical inference. SPN were evaluated by home-developed BrainNetTools software BrainCON (www.minipetct.com/braincon; Spisák et al., 2013). Statistically significant differences between group EEGfC values were emphasized at $p<0.05$ corrected for multiple comparison by local false discovery rate (FDR), (Efron, 2004; 2007). The circular plot of SPN was generated by the circos software package (Krzywinski 2009).

2.6. Limitations of localization accuracy

LORETA source localization is a key feature of subsequent connectivity analysis. The use of 19 electrodes means spatial undersampling and decreases localization accuracy.

Shortcomings of the three-shell model (as compared to more sophisticated models) and disregarding individual cerebral anatomy and the spatial relationship of the electrodes to gyri and sulci were further sources of imprecise localization (Michel et al., 2004). Therefore, EEGfC group differences were computed between ROIs (output data of the LSC software) but were described, graphically demonstrated and discussed at the lobar level. This approach is usual in the neuroimaging literature (Anderson and Hamandi, 2011).

3. Results

3.1. Clinical and laboratory findings, visual EEG analysis

BECTS patients had one to three, non-provoked seizures. Clinical and laboratory findings were within normal limits. Based on medical history and parents' narrative, the children had no remarkable difficulties in school performance, behaviour and social functioning. EEG background activity was within normal limits. Typical central spikes or sharp waves with aftercoming slow wave (for the sake of brevity: spikes) were found in all records. Immediate activation of spikes appeared in all patients when the first EEG signs of drowsiness occurred. 14 children displayed spikes with voltage maximum in T3/T4 derivations, three children in C3/4 leads. 10 children had right-sided, 4 had left-sided and 3 had bilateral-independent spikes. The characteristic dipolar field at the main negative phase of the spike was demonstrable in all cases. Cranial MRI was carried out in 10 children, no abnormal findings emerged.

3.2. EEG functional connectivity findings

In this section the term “increased” EEGfC always refers to the BECTS group (as compared to the NC group), if not otherwise specified. All EEGfC values were increased in the BECTS group.

Our main finding was increased EEGfC in the beta band (Fig. 2.). Maximum beta abnormality emerged between frontal and frontal ROIs, followed by EEGfC between frontal and temporal ROIs. The number of abnormal beta EEGfC values decreased in rostro-caudal direction in the both hemispheres. Beta EEGfC was greater within the left fronto-temporal areas than in the mirror region in the right hemisphere. On the other hand, more abnormal EEGfC values emerged in temporal and parietal regions of the right hemisphere than in the left one.

In addition to increased beta EEGfC, increased delta and alpha EEGfC emerged between several left frontal ROIs. Furthermore, we found increased EEGfC in the right parietal area in all frequency bands.

4. Discussion

4.1. General remarks

As far as is known, this is the first study addressing EEG-based, resting-state functional connectivity in a group of typical BECTS patients as compared to a healthy control group. We demonstrated increased intrahemispheric, cortico-cortical connectivity in several areas. The great majority of our findings was confined to the beta band.

Nonstationary physiological and abnormal events may interfere with resting-state functional connectivity (Centeno and Carmichael, 2014). Having circumvented vigilance- and spike-related effects as far as possible (see Section 2.2) we believe that the results in fact reflect the core baseline EEGfC abnormality of the BECTS group.

Because of the multicenter approach we could not evaluate speech and other cognitive functions by neuropsychological methods. Therefore, this discussion is centered on topographical correspondence between our findings and already published, neuroimaging and neuropsychological findings that characterize typical BECTS. Relevant neurophysiological aspects are discussed as well. According to the BECTS literature, dysfunction of three cortical areas unequivocally contributes to BECTS. Out of them, two showed abnormal EEGfC in this study (see Sections 4.2-4.4).

Increased EEGfC and lack of decreased EEGfC is in accord with the genetic-developmental etiology of BECTS (Gkampeta and Pavlou, 2012). As far as this area is explored, non-developmental disorders with diffuse or gross focal lesions show decreased EEG connectivity (Leocani and Comi, 1999; Guggisberg et al, 2008; Alstott et al., 2009). On the other hand, increased and decreased EEGfC may coexist in developmental cerebral disorders (Marosi et al, 1992). Genetically determined developmental disorders are expected to affect both hemispheres. Bilaterality of BECTS pathology is supported by bilateral and alternating spikes that may occur in a single record and repeated recordings. Unilateral spiking in the waking state frequently becomes bilateral in slow wave sleep. This means that laterality of spiking is a random-like and state-dependent feature of BECTS.

4.2. Abnormal EEGfC in frontal areas

We demonstrated abnormally increased neuronal coupling between frontal and frontal, frontal and temporal ROIs. Most abnormalities emerged in the beta band. The results are topographically concordant with decreased hemodynamic coupling between left frontal areas (Besseling et al. 2013). Decreased hemodynamic coupling together with increased electrical coupling (EEGfC) is common finding in focal epilepsy (Centeno and Carmichael, 2014). The hemodynamic and EEGfC abnormalities are presumably pathophysiologically related to a specific language deficit, the neuropsychological endophenotype of BECTS (Smith et al., 2012). A further argument for this relationship is that beta activity shows the strongest relationship to language function (Spironelli and Angrilli, 2010). Also structural abnormalities are predominant in left frontal and temporal areas in BECTS (Lundberg et al, 1999; Overvliet

et al, 2013; Pardoe et al, 2013). Topographical correspondence of these findings suggests that they are interrelated.

We found increased bilateral beta band connectivity. This finding is consistent with bihemispheric fMRI activation of language areas in BECTS children, as compared to selective, left hemispheric activation of healthy controls (Lillywhite et al, 2009). Partial shift of left-hemispheric speech functions to the right hemisphere may reflect compensatory efforts of the brain. We suggest that also increased beta EEGfC might reflect compensatory plasticity changes. Increased EEGfC within the epileptogenic zone and between the epileptic zone and the mirror region in the other hemisphere has been interpreted as compensatory change in epilepsy patients (Bettus et al, 2011).

4.3. Abnormal EEGfC in the parietal area

Increased EEGfC emerged within the right parietal area. This abnormality was topographically limited but involved the entire investigated frequency spectrum, so it should be considered as neurophysiologically important. It topographically corresponds to the superior parietal area, an important node of the attention network. Attention deficit due to superior parietal dysfunction is part of neuropsychological profile of BECTS (Kavros et al, 2008, Smith et al, 2012).

4.4. No abnormal EEGfC in the central area

It was surprising that EEGfC was normal in the central region that generates spikes and seizures in BECTS (Legarda et al, 1994; Kamada et al., 1998; Pataraia et al., 2008). BECTS differs from the rest of focal epilepsies in this respect. Greatest connectivity abnormality usually appears between the seizure onset zone and the rest of the brain (Certeno and Carmichel, 2014). Furthermore, interictal spiking was reported to increase local cortical gene expression, leading to formation of abnormal connectivity (Rakhade et al, 2007). However, these findings stem from pharmacoresistant, severe focal epilepsies. Why BECTS did not show abnormal connectivity in the ictogenic and spiking region remains hidden. Relationship of connectivity abnormality, etiology and severity of the disease should be investigated systematically.

Intuitively, lack of abnormal EEGfC may correspond to lack of MRI abnormality in the central region (Overvliet et al, 2013; Pardoe et al, 2013). However, abnormal functional connectivity was reported in lesional and nonlesional focal epilepsy alike. So, further investigations are necessary to understand real structure-function relationship in BECTS.

4.5. Further considerations

Diffuse, increased theta phase stability emerges in the course of epileptogenesis and persists thereafter in a focal epilepsy model (Ge et al, 2013). Robust, diffuse increase of cortico-cortical theta EEGfC characterizes human, cryptogenic and symptomatic focal

epilepsies (Douw et al, 2010). Neurophysiological background of this phenomenon is not known. So, we can not explain why we did not detect it in BECTS.

However, further neurophysiological differences exist between BECTS and the rest of focal epilepsies. It is possible that they might help to solve this dilemma. First, slow wave sleep promotes interictal spiking in several focal epilepsy patients but not in all (Foldvary-Schafer and Grigg-Damberger, 2006). On the contrary, alpha-dropout (the first EEG sign of drowsiness) and slow wave sleep cause immediate and obligatory provocation of spikes in all BECTS children (Dalla Bernardina et al, 1982). Second, cyclic alternating patterns of slow sleep modulate spike frequency in lesional focal epilepsies but not in BECTS (Terzano et al, 1991). Together, these findings indicate that neurophysiological coupling between global brain state regulation and spike activation is dissimilar in BECTS and the rest of focal epilepsies. Given that also spontaneous theta activity is generated by two, interactive diffuse projection systems (septal-hippocampal-cortical and thalamo-cortical), the lack of diffuse theta EEGfC might be interpreted as lack of coupling between the ictogenic area and these projection systems.

4.6. Limitation of the study

For technical limitations, see Section 2.6. From the clinical point, routine clinical evaluation is not sensitive enough to detect subtle speech and attention deficit. Due to the lack of neuropsychological testing, we could not correlate EEGfC abnormalities with speech and attention scores. We propose that multimodal investigations (clinical, EEG, structural and functional imaging, neuropsychological evaluation) should be carried out in the same cohort of BECTS children in order to get deeper insight into the developmental abnormality underlying this condition (Uludag and Roebroeck, 2014). Furthermore, investigations must be carried in brief time window and in the same period of the disease (onset, active phase, remitted) because structural abnormalities (Overvliet et al, 2013; Pardoe et al, 2013), individual EEGfC patterns (Clemens et al, 2013b) and some of the neuropsychological deficit may decrease as a function of time (Kavros et al, 2008; Monjauze et al, 2011; Smith et al, 2012).

5. Conflicts of interest

None of the authors have any conflicts of interest to disclose.

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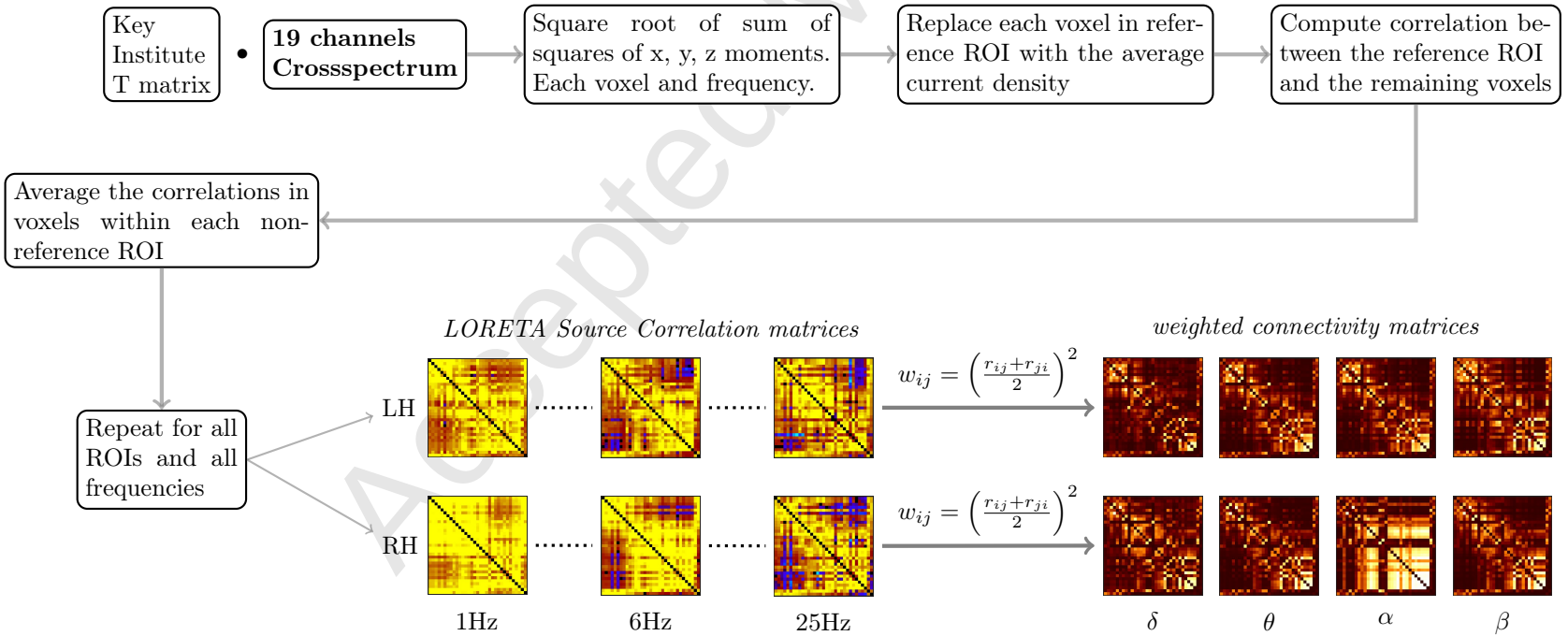
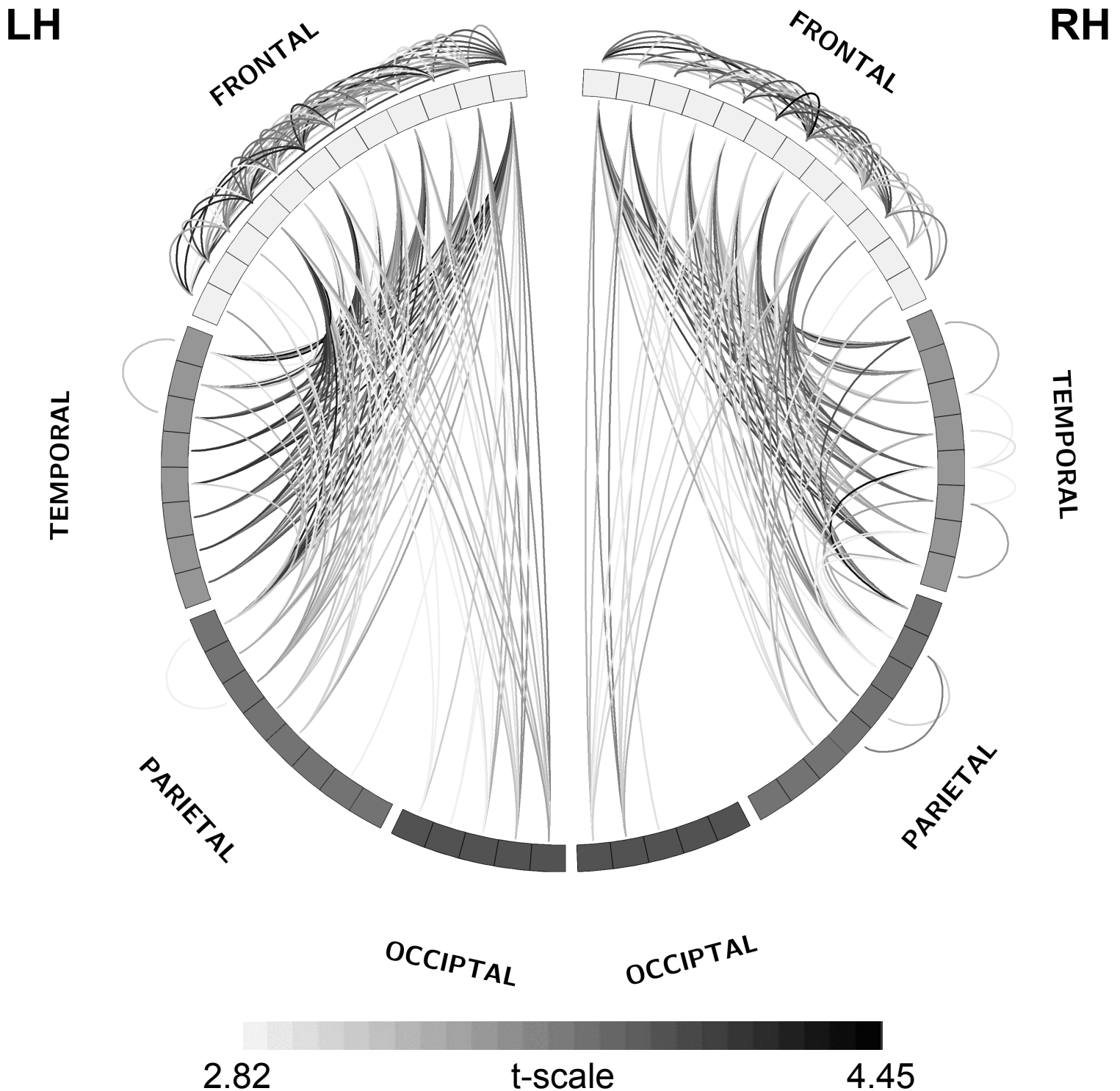
6. Legends to Figures

Fig. 1. Flowchart of LORETA source correlation computing method demonstrates the evaluation of Loreta Source Correlation (top row) of the left (LH) and right (RH) hemispheres for 1-25Hz narrow bands (bottom middle). The elements of algorithm and their titles were drawn after Thatcher et al. (2007) with permission of the author. The broad band averaged 2nd power of regional correlation coefficients – stored in weighted connectivity matrix - were used as measurement of connectivity strength between regions (bottom, right).

Fig. 2. EEG functional connectivity in the beta frequency band. Group differences are demonstrated by circular graph. Higher level brain regions (frontal, temporal, parietal, and occipital) of the left and right hemispheres are arranged in the segmented circular track. Left and right hemisphere connectivity is demonstrated in left and right parts of the figure, respectively. Inter-lobar connections are demonstrated inside the circle, intra-lobar connections are outside. Greyscale shows Student-t values within the range of 2.82-4.45.




LH
RH
FRONTAL
FRONTAL
TEMPORAL
TEMPORAL
PARIETAL
PARIETAL
OCCIPTAL
OCCIPTAL
2.82
t-scale
4.45