Children with well controlled epilepsy possess different spatio-temporal patterns of causal network connectivity during a visual working memory task

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Abstract Using spectral Granger causality (GC) we identified distinct spatio-temporal causal connectivity (CC) patterns in groups of control and epileptic children during the execution of a one-back matching visual discrimination working memory task. Differences between control and epileptic groups were determined for both GO and NOGO conditions. The analysis was performed on a set of 19-channel EEG cortical activity signals. We show that for the GO task, the highest brain activity in terms of the density of the CC networks is observed in α band for the control group while for the epileptic group the CC network seems disrupted as reflected by the small number of connections. For the NOGO task, the denser CC network was observed in θ band for the control group while widespread differences between the control and the epileptic group were located bilaterally at the left temporal-midline and parietal areas. In order to test the discriminative power of our analysis, we performed a pattern analysis approach based on fuzzy classification techniques. The performance of the classification scheme was evaluated using permutation tests. The analysis demonstrated that, on average, 87.6 % of the subjects were correctly classified in control and epileptic. Thus, our findings may provide a helpful insight on the mechanisms pertaining to the cognitive response of children with well controlled epilepsy and could potentially serve as “functional” biomarkers for early diagnosis.

Keywords Working memory · Epilepsy · Children · Spectral Granger causality · Causal connectivity networks · EEG · Classification · Early diagnosis

Introduction

Nowadays, it is estimated that epilepsy affects more than 65 million people worldwide (<http://www.epilepsyfoundation.org>). In Europe, around 6 million people are affected, a number which corresponds to a prevalence of about 8.2 per 1000 people (Cross 2011). Regarding children, it is estimated that worldwide around 10.5 million children suffer from active epilepsy; more than 80 % of those children live in developing countries (Guerrini 2006). Noteworthy is that epilepsy is about twice as common in children as in adults (Follett et al. 2012). Although for the majority of those children a stable remission can be achieved before adulthood, they are still at risk with respect to learning/educational problems (Stores 1978; Henriksen 1990; Pavlou and Gkampeta 2011; Dimitriadis et al. 2015), behavioral problems (Williams 2003), attention deficits (Mirsky et al. 2001; Hernandez et al. 2003; Alloway et al. 2006) as well as to reduction of memory capacity (Jambaqué et al. 1993; McCarthy et al. 1995).

Importantly, it has been shown that many of the above problems are closely related to impairments of Working Memory (WM), which is associated with basic cognitive functions including decision making (Toth and Lewis 1997), reasoning (Ruff et al. 2003), recognition (Bledowski et al. 2012), mental arithmetic (Swanson 2006) and reading (Gathercole et al. 2004, 2008). Furthermore, previous studies have shown that both visual and verbal WM is disturbed in various epilepsy types (Gülgönen et al. 2000; Chaix et al. 2006; Campo et al. 2009; Wagner et al. 2009;

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Luton et al. 2010). Here, by means of a visual one-back matching task, we intended to study not the visual modality but rather the WM disturbance in general that is specific for epilepsy.

Despite the rapid theoretical and technological progress advances in the field, the robust early diagnosis is still an open problem. Towards this aim various brain imaging approaches have been exploited including Electroencephalographic (EEG) recordings (Goodin et al. 1990; Smith 2005; Jan et al. 2001; Krause et al. 2008; Myatchin et al. 2009; Myatchin and Lagae 2011; Yang et al. 2012; van Diessen et al. 2013), Magnetoencephalography (MEG) (Colon et al. 2009), functional Magnetic Resonance Imaging (fMRI) (Gotman et al. 2005; Grouiller et al. 2011) and Proton MR spectroscopy (Kuzniecky et al. 2001) (for a review see also Bano et al. (2011)). Whereas well established neuroimaging analysis techniques such as ERP and event-related (de-)synchronization (ERS/ERD) have been applied to the analysis of the brain dynamics of normal and epileptic children (Jiruska et al. 2013; Klimesch 1999; Krause et al. 2008), significant work remains to be done towards the construction of the underlying anatomical and functional connectivity networks (FCN) (Sargolzaei et al. 2015b). Towards this direction, several studies have investigated the emerged FCN in epilepsy in adult populations; however, relatively fewer have been focused in pediatric populations (Sargolzaei et al. 2015a, b). To our knowledge there is no study that has examined the deployment of FCN across frequency bands for children with well controlled epilepsy as performing a WM task.

In this work, we employed spectral Granger causality (GC) to construct the emerged causal networks (CN) across frequency bands during a simple visual one-back matching WM task with GO and NOGO conditions for normal children and children with well controlled epilepsy. Our findings provide evidence of quadruple disassociation between groups and tasks of the spatio-temporal EEG cortical activation across frequency bands.

Materials and methods

Experimental procedure

Subjects

For this study, 21 children with established childhood epilepsy (range 6–16 years old; mean 11.43 years, $SD \pm 2.3$, 10 boys) were selected. All children were admitted to the neurophysiology laboratory at the Department of Paediatric Neurology, University Hospitals KU Leuven, for a 24-h video-EEG monitoring during which the WM experiment took place. The children had no anti-

epileptic treatment ($n = 3$) or were on standard anti-epileptic medication (monotherapy, $n = 15$, duotherapy, $n = 3$). Drug dosages were always within normal ranges. Visual inspection showed that none of the patients had structural brain abnormalities; MRI was done in 18 patients, showing normal findings in all cases. To avoid an acute effect of epileptic seizures on the child's performance, only patients with at least an 8 days seizure-free period preceding the test were included (see Myatchin et al. 2009). All children followed mainstream school and none had a history of learning problems. In the study group, children diagnosed with one out of two following epilepsy syndromes were included: benign rolandic epilepsy (BRE) ($n = 9$) and idiopathic generalized epilepsy (IGE) ($n = 12$, including childhood absence epilepsy ($n = 5$) and generalized epilepsy with tonic-clonic seizures ($n = 7$). Patients on monotherapy received valproic acid ($n = 7$), carbamazepine ($n = 4$), lamotrigine ($n = 3$) or sulthiame ($n = 1$). Patients on duotherapy received different drug combinations (see table at Myatchin et al. 2009).

As a control group we selected 25 age matched non-epileptic children (mean age 10.76 years, $SD \pm 3.4$, 17 boys), who did not display any school problem either. The study protocol was approved by the Ethical Committee of University Hospitals KU Leuven.

Design and stimuli

Children were instructed to observe a continuous stream of seven different figures presented one after the other in pseudo-random order at the middle of a computer monitor, which was located at a distance of 1.0 m from the subject's eyes. Everyday figures were used (horse, wardrobe, jacket, cake, comb, bunch of grapes, hammer), white with a black contour on a grey background, size $7.5 \text{ cm} \times 6.5 \text{ cm}$, visual angle $4^\circ 18' \times 3^\circ 02'$. Each stimulus was presented for 1.5 s, followed by a delay of 1.0 s, after which the next stimulus was presented. During the delay period a fixation point (dark-grey cross) was shown at the middle of the screen to facilitate eye fixation. Any figure identical to the one immediately preceding it was defined as a target stimulus (probability 0.30). Children were asked to respond to all targets by pressing a button with their dominant hand. Both accuracy and speed were stressed. The length of a single experimental block was 5 min; the block contained 120 trials, 36 of which were targets.

Children were seated comfortably in a dimly lit registration room and were instructed to avoid movements to reduce muscle artifacts in the EEG signal and to look at the middle of the computer screen to avoid unnecessary eye movements. The instruction for the task was given directly before the task and exercise trials were performed until task understanding by the child was ensured. During the

experiment, the experimenter sat out of sight of the child and no conversation was allowed.

EEG recordings

For the EEG recordings, 19 electrodes were placed according to the international 10–20 system at Fp1, Fp2, F3, F4, F7, F8, Fz, C3, C4, Cz, T3, T4, T5, T6, P3, P4, Pz, O1 and O2 positions. Additional four EOG electrodes were placed resulting in two EOG channels: horizontal EOG—two electrodes on the outer canthi of eyes, and vertical EOG—two electrodes above and below one eye. EOG channels allowed us to detect both vertical and horizontal eye movements and effectively remove them from EEG recording during subsequent preprocessing of the signal. Two linked mastoid electrodes were used as a reference.

Data pre-processing

EEG was sampled at a frequency of 1000 Hz with 12 bits A/D converter and amplified using a band-pass filter of 0.095–70 Hz. Notch filter was off. Registration of the digital EEG was made using the software program Brainlab 4.0 (OSG, Belgium). The impedance of all electrodes was monitored for each subject prior to recording and was always kept below 5 k Ω . Preprocessing of the continuous EEG was done off-line, using the EEGLAB v.5.02 toolbox (Matlab 7.0.4 platform). ECG channel was removed. Data were filtered with a 50 Hz digital low pass filter. Eye movement artifacts were marked and removed from the continuous signal without affecting the signal itself using an ICA-based algorithm (see Myatchin et al. 2009). EEG fragments containing other movement artifacts were removed. This resulted in an EEG signal clean from (eye) movement artifacts, which was then used for further analysis.

Afterwards, the continuous EEG signal was epoched according to the type of stimulus (Target and Non Target), with 750 ms pre-stimulus (delay period) and 1000 ms post-stimulus (presentation period of the second stimulus, where the motor responses had not yet taken place). Omitted Target trials (i.e. trials without correct motor response) and committed Non Target trials (i.e. trials with a wrong motor response) were excluded from the analysis. We then performed a down-sampling at 500 Hz and we applied a baseline correction by subtracting the mean value of the last 200 ms of the pre-stimulus period.

Overall, we ended up with 92 datasets (21 epileptic $\times$ 2 trial types + 25 control $\times$ 2 trial types) of 19 multi time-series, which were divided into four group types (Epileptic-Target (ET), Epileptic-Non Target (ENT), Control-Target (CT), Control-Non Target (CNT)).

Computational methodology

Spectral GC analysis

Generally, the study of brain connectivity can be accomplished either at the sensor-level or at the reconstructed source-level, yet, both of them hold certain caveats (see e.g. Palva and Palva (2012) for a critical review). On one hand, analysis at the signal-level can lead to artificial or spurious interactions due to mixing at the source level (Stam et al. 2007). On the other hand, source reconstruction reduces source-mixing effects but does not remove them completely (Palva and Palva 2012). Moreover source reconstruction introduces inherent ambiguities imposed by the ill-defined nature of the inverse problem (Dale et al. 2000; Kitzbichler et al. 2011).

In this study, also due to the limited number of electrodes (19), we have chosen to perform a Granger-causal connectivity analysis at the sensor-level (Seth 2008; Hu et al. 2012; Zhang et al. 2013). In particular, we employed the so-called spectral GC (Barrett et al. 2012; Brovelli et al. 2004; Dauwels et al. 2010; Ding et al. 2006; Protopapa et al. 2014), which is based on a Multivariate Autoregressive (MVAR) model, to construct the causal connectivity (CC) networks for all four group types (ET, ENT, CT, CNT).

Spectral GC is a metric of the influence of signal y on x at a given frequency ω (Barrett et al. 2012) and it is calculated via: $GC_{y \rightarrow x}(\omega) = \ln \left(1 + \frac{H_{xy}(\omega)\sigma_{yy}H_{xy}^*(\omega)}{H_{xx}(\omega)\sigma_{xx}H_{xx}^*(\omega)} \right)$. Here, H is the inverse of the transfer matrix (the Fourier-transformed matrix of the model coefficients) and acquires the use of a linear regression model: $H(\omega) = \text{inv}[A(\omega)] = \text{inv} \left[I - \sum_{k=1}^p (e^{-i2\pi\omega t_0})^k A_k \right]$, where A_k are the model coefficients of the generalized Auto-Regressive (AR) model in time domain ($X(t) = \sum_{k=1}^p A_k X(t - kt_0) + E_x(t)$), with p being the number of lags included in the Multivariate Regression model (Blinowska et al. 2004) and t_0 the time between successive observations. σ_{xx} , σ_{yy} are the diagonal elements of the covariance matrix: $\Sigma \equiv \begin{pmatrix} \sigma_{xx} & \sigma_{xy} \\ \sigma_{yx} & \sigma_{yy} \end{pmatrix} = \text{cov} \begin{bmatrix} E_x(t) \\ E_y(t) \end{bmatrix}$, where $E_x(t)$ and $E_y(t)$ are the residual errors of the AR model in time domain.

We measured the CC between each pair of 19-channel EEG cortical activity signals at each frequency in the range of [1, 45] Hz. To reveal any time-varying causal interactions in this frequency range, the analysis was performed on sliding time-windows. The range of each window was set at 500 ms and the sliding step was set at 20 ms. The selection of the size of time window was based on the requirement for stationarity and adequate frequency and

time resolution. Thus, we ended up with 39 sliding-windows (13 in pre-stimulus and 26 in post-stimulus period).

The previous step (time-windowing) along with differencing ensured the stationarity of our data, which was tested via the Kwiatkowski–Phillips–Schmidt–Shin test at a critical level of 0.01 (Kwiatkowski et al. 1992). The model-order (number of lags) p is estimated via the Bayesian Information Criterion (BIC) (Schwarz 1978). In our computations we allowed p to range between 1 and 20. As a result, the values of p s ranged between 9 and 19 (mean at 12), which are consistent to previous studies (e.g. Barnett and Seth 2011; Keil et al. 2009; Nicolaou et al. 2012; Protopapa et al. 2014).

At the final step of the analysis, we tested whether the derived GC pairwise values at each time-window were statistically significant across frequencies. Thus, we adopted a random permutation approach (Brovelli et al. 2004; Bollimunta et al. 2008) by constructing 100 surrogate data via rearranging the time-windows (for each trial separately) and calculating their GC-values (Seth 2010). Only the GC-values that were higher from the 95 % of the GC-values of the surrogate data were considered as statistically significant. Here, in order to address the problem of multiple comparisons, we adopted false discovery rate (FDR) approximation (Benjamini and Hochberg 1995).

To obtain the so-called “band-limited GC” (Barrett et al. 2012), we coarse-grained our data into five frequency bands [δ (1–4 Hz), θ (4–7 Hz), α (8–12 Hz), β (13–30 Hz) and γ (30–45 Hz)] via: $GC_{y \rightarrow x}(\omega_1, \omega_2) = \frac{1}{\omega_2 - \omega_1} \int_{\omega_1}^{\omega_2} GC_{y \rightarrow x}(\omega) d\omega$,

with $[\omega_1, \omega_2]$ being the frequency range of each frequency band. Thus, for each group type, subject, frequency band and sliding-window, we had a 19 dimensional matrix, which contained the significant pair-wise directed GC-values between all nodes.

All the above calculations were performed using Seth’s Granger causality Connectivity Analysis toolbox implemented in MATLAB (Seth 2010). Due to the large quantity of datasets and the significantly high computational demands we parallelized the procedure exploiting a 48 Quatro Core LINUX cluster with 3.2 GHz Intel Xeons and 48 GB RAM.

Construction of the causal connectivity networks

Our first aim was to detect for each group type (ET, ENT, CT and CNT) any statistically significant differences of each connection from the pre-stimulus period, which, for all practical reasons, consists the baseline period of our visuo-spatial WM task. To reveal the differences between networks, we employed the non parametric Wilcoxon test (with the significant threshold set at 0.05) across subjects between all

the GC-values of the pre-stimulus period and the GC-values of each sliding-window. Here, given that each time the same GC-values of the pre-stimulus period were compared, the problem of multiple comparisons was raised and to accommodate it we applied the so called cluster-based permutation algorithm (Maris and Oostenveld 2007). Specifically, we repeated the aforementioned procedure 200 times by performing the non-parametric Wilcoxon test between the pre-stimulus GC-values the GC-values of each sliding-window of the surrogate data [random permutation in time of the original data (GC series)]. We then calculated the length of the sequential significant GC-values of the original data and rejected it as noise when it was smaller than the 95 % of the length distribution of the significant permuted sequential points. We note here that none sliding-window of the pre-stimulus period was computed to be significant.

Consequently, for each one of the group types and at each sliding-window, we were able to construct the binary directed causal networks with edges obtained from the statistically significant different from the baseline sequential GC-values. If the distribution (over subjects) of GC-values between a pair of electrodes was determined to differ significantly from that of the pre-stimulus period then this connection was set to 1; otherwise it was set to 0.

Our second and most important aim was to detect any statistically significant differences between the group types. Thus, we proceeded with four planned comparisons between the group types, namely (1) CT versus CNT, (2) ET versus ENT, (3) CT versus ET and (4) CNT versus ENT. We applied the non-parametric Wilcoxon test at each sliding-window, frequency band and pair of electrodes between the GC-values of each group type that were found statistically significant different compared to the pre-stimulus period. The significant threshold was set at 0.02 corrected with FDR. If there was no statistically significant difference between the distributions of GC-values then the connection was set zero. If a statistically significant difference was found and simultaneously the median of the distribution of GC-values of the first group type [CT in (1), ET in (2), CT in (3) and CNT in (4)] was greater (lower) than that of the second group type [CNT in (1), ENT in (2), ET in (3) and ENT in (4)] then the connection was set to +1 (−1).

The above analysis resulted to the construction of four binary directed networks whose connections represent statistically significant differences between the group types that pertain to the specific comparison.

Classification of subjects-performance evaluation of the resulting network patterns

To test the discriminative power of the proposed methodology between control and epileptic children, we proceeded as follows.

For each subject we computed the causal networks, whose connections were statistically significant different from those of the pre-stimulus period. To do so, at each time-window we accepted as statistically significant different connections only those whose GC-value were outliers when compared to the distribution of GC-values within the pre-stimulus period. For this test, we used the Dixon's Q-test (Dean and Dixon 1951) with a 99 % confidence interval. We then implemented a pattern analysis (see e.g. Zeng et al. 2012) approach to evaluate the performance of the discriminative power of the statistical measures of the resulting networks.

Here, the classification of each subject in the control or in the epileptic group was performed using the fuzzy-kNN algorithm (Keller et al. 1985), which assigns a membership value in the interval $[0, 1]$ reflecting the subject's membership in each group. The membership value is computed as a function of the distances of each subject's network characteristics and its corresponding k-nearest neighbor's network characteristics. Other approaches such as support vector classification (Zeng et al. 2012) can be also employed.

Due to the relatively limited number of subjects (21 epileptic children and 25 healthy children), we used the

leave-one-out cross-validation technique to estimate the generalization ability of our classifier (Zeng et al. 2012). To validate the performance of our classifier we employed a permutation procedure. In particular, we permuted 10,000 times the labels (control/epileptic) of our training set and accepted as correct classifications only those whose membership value to the correct group was greater than the 95 % of the permuted membership values.

Results

Figure 1 depicts with solid lines (for visualization purposes) the discrete temporal evolution of the total degree of the CC networks for each group type (ET: orange, ENT: red, CT: grey, CNT: blue) at each one of the five frequency bands (δ , θ , α , β and γ). The CT group exhibits higher network activity (as reflected by the total degree) in α band (max $\sim 75^\circ$). Indeed, the total degree in α band appears to be approximately the double compared to that of other frequency bands but also to the other group types for a large period of time during the post-stimulus period (grey bars: 2, 3, 4). The CNT group exhibits higher network

Fig. 1 Sub-graphs of temporal evolution of the total degree of the CCN for all group types [ET (orange line), ENT (red line), CT (grey line) and CNT (blue line)] which correspond to five common frequency bands (δ , θ , α , β and γ). Five grey-bars separate the post-

stimulus period to five time-intervals of 80 ms duration (1: [35, 115] ms, 2: [135, 215] ms, 3: [235, 315] ms, 4: [335, 415] ms, 5: [435, 515] ms). (Color figure online)

activity mainly in θ band (max $\sim 65^\circ$), but also in δ and β band (max $\sim 45^\circ$), for a period that lasts around 200 ms (grey bars: 1, 2 for δ , θ and grey bars: 2, 3 for β band). The ET group exhibits relatively small total degrees in all frequencies bands ($\sim 10^\circ$) with the exception of β band which exhibits a rather high activity (max $\sim 42^\circ$) at ~ 300 ms within the post-stimulus period (grey bar: 3). Finally, the ENT group possess higher network activity at ~ 300 ms in α band (max $\sim 40^\circ$) (grey bars: 3, 4) and in β band (max $\sim 35^\circ$) (grey bar: 3). The CC networks for all group types are remarkable sparse at γ band.

Figures 2, 3, 4 and 5 illustrate both the discrete total degree of the CC networks of statistically significant differences among group types (top figure) and their corresponding topographic maps (bottom figure) depicting the spatial distribution of the average significant differences, over the corresponding time periods for δ , θ , α , β bands. The topographic maps were created with the aid of Field-Trip (Oostenveld et al. 2011).

Differences between CT and CNT

Profound differences were found in all bands (except that of γ band) (Figs. 2, 3, 4, 5). In δ and θ bands the maximum difference was observed at the beginning (Figs. 2, 3 top), while in α at the end (Fig. 4 top) and in β mainly in the middle (Fig. 5 top) of the post-stimulus period. In δ band, the CNT CCN (compared to the CT) exhibited significantly higher degree nodes mainly at right parieto-occipital and left frontal brain areas [Fig. 2, bottom-1st line (1–3 maps)]. In θ band, the CNT network was denser at the right parieto-occipital and left temporal-midline brain areas compared to the CT's CCN (Fig. 3, bottom-1st line [1–3 maps]), while the CT CCN exhibits higher degree nodes with a narrower focus at the left midline and right midline channels [Fig. 3, bottom-1st line (4–5 maps)]. In α band, the CT CCN appears to be denser at frontal and right-midline channels [Fig. 4, bottom-1st line (4–5 maps)]. Finally, in β band the CNT network exhibits higher degree nodes at the left-

Fig. 2 δ band. *Top* temporal evolution of the total degree of the CCN whose connections represent statistically significant differences in the GC distributions for each pair of electrodes for the 4 group comparisons: CT versus CNT (grey line), ET versus ENT (blue line), CT versus ENT (black line) and CNT versus ENT (red line). The post-stimulus period is divided into five characteristic time intervals

of 80 ms duration (1: [35, 115] ms, 2: [135, 215] ms, 3: [235, 315] ms, 4: [335, 415] ms, 5: [435, 515] ms) are marked with grey bars. *Bottom* topographic maps of node degrees which correspond to 1, 2, 3, 4 and 5 time intervals marked with grey bars. (Color figure online)

Fig. 3 θ band. *Top* temporal evolution of the total degree of the CC networks whose connections represent statistically significant differences for the 4 group comparisons: CT versus CNT (grey line), ET versus ENT (blue line), CT versus ENT (black line) and CNT versus ENT (red line). The post-stimulus period is divided into five

characteristic time intervals of 80 ms duration (1: [35, 115] ms, 2: [135, 215] ms, 3: [235, 315] ms, 4: [335, 415] ms, 5: [435, 515] ms) are marked with grey bars. *Bottom* topographic maps of node degrees which correspond to 1, 2, 3, 4 and 5 time intervals marked with grey bars. (Color figure online)

midline brain area extending throughout the post-stimulus period [Fig. 5, bottom-1st line (2–5 maps)].

Differences between ET and ENT

Differences were found mainly in α and β bands (Figs. 4, 5). In both bands the maximum difference was observed at the end of the post-stimulus period (Figs. 4, 5 top). In α band, the ENT network (compared to the ET) exhibited significantly higher degree nodes mainly at left parieto-occipital and left frontal brain areas [Fig. 4, bottom-2nd line (4–5 maps)]. The ET network (compared to the ENT) was denser mainly at the frontal and left midline brain areas in β band [Fig. 5, bottom-2nd line (3–5 maps)].

Differences between CT and ET

Differences here were found mainly in α and β bands (Figs. 4, 5). In both bands the maximum difference was observed at the end of the post-stimulus period (Figs. 4, 5 top). The most profound differences were in α band, where

the CT network exhibited profoundly higher degree nodes in a wide range of channels including left midline, parieto-occipital, right midline and frontal brain areas [Fig. 4, bottom-3rd line (3–5 maps)].

Differences between CNT and ENT

Here, similar differences to the CT versus CNT group-type were observed. In particular, in δ and θ bands the maximum difference was observed at the beginning (Figs. 2, 3 top), in α at the end (Fig. 4 top) and in β mainly in the middle (Fig. 5 top) of the post-stimulus period. In δ band, the CNT CCN exhibited significantly higher degree nodes mainly at right parieto-occipital and central midline brain areas [Fig. 2, bottom-4th line (1–4 maps)]. In θ band, the CNT CCN was denser mainly at the right parieto-occipital and left temporal-midline brain areas [Fig. 3, bottom-4th line (1–3 maps)]. In β band the CNT network exhibits higher degree nodes mainly at left-midline brain area extending throughout the post-stimulus period [Fig. 5, bottom-4th line (1–5 maps)]. Less

Fig. 4 α band. *Top* temporal evolution of the total degree of the CC networks of the CCN whose connections represent statistically significant differences for the 4 group comparisons: CT versus CNT (grey line), ET versus ENT (blue line), CT versus ET (black line) and CNT versus ENT (red line). The post-stimulus period is divided

into five characteristic time intervals of 80 ms duration (1: [35, 115] ms, 2: [135, 215] ms, 3: [235, 315] ms, 4: [335, 415] ms, 5: [435, 515] ms) are marked with grey bars. *Bottom* topographic maps of node degrees which correspond to 1, 2, 3, 4 and 5 time intervals marked with grey bars. (Color figure online)

widespread differences (compared to δ and θ bands) were observed also in α band, where the CCN of the CNT group type was denser at left-midline channels [Fig. 4, bottom-4th line (4 map)], while the ENT's CCN exhibits higher degree nodes at left frontal channels [Fig. 4, bottom-4th line (4 map)].

Classification results-discriminative power

The results indicate that a “good” variable that could serve as potential discriminator between groups could be the total degree (see Fig. 1). Indeed, regarding for example the GO task, the total degree is striking larger in the control group at α band for the period $\sim$ [135, 415] ms; for the NOGO task, the total degree of the epileptic group is significantly bigger at θ band for the period $\sim$ [35, 215] ms. Based on this global variable, the proposed classification scheme achieved an average accuracy of 87.6 % (at 95 % using permutation). In particular, the classification scheme resulted to 88 % for the CT, 71.2 % for the ET, 96 % for the CNT and 95.2 % for the ENT group.

Discussion

One of the main targets in connectomics is the identification of distinct spatio-temporal patterns in the topology of the brain network activities, which would enhance our understanding of the mechanisms that pertain to brain function, and/or serve as potential “bio-markers” for early diagnosis and monitoring of neurological disorders. Depending on the target, the sought connectivity pattern can be anatomic (structural), functional and/or effective (causal) (for a review see e.g. Friston 2011; Smith et al. 2013).

In this work, using spectral Granger causality on EEG recordings, we identified characteristic spatio-temporal CC patterns pertaining to the emerged cortical activity of groups of control and epileptic children in the interval that coincides with the time window of stimuli discrimination during a one-back matching visual WM task with GO and NOGO conditions. Using this method, a *quadruple* dissociation between control and epilepsy groups for GO and NOGO tasks was revealed. This clear dissociation emerged at the level of causal connectivity both in time and in space.

Fig. 5 β band. *Top* temporal evolution of the Total-Degree of the CC networks of the CCN whose connections represent statistically significant differences for the 4 group comparisons: CT versus CNT (grey line), ET versus ENT (blue line), CT versus ET (black line) and CNT versus ENT (red line). The post-stimulus period is divided

into five characteristic time intervals of 80 ms duration (1: [35, 115] ms, 2: [135, 215] ms, 3: [235, 315] ms, 4: [335, 415] ms, 5: [435, 515] ms) are marked with grey bars. *Bottom* topographic maps of node degrees which correspond to 1, 2, 3, 4 and 5 time intervals marked with grey bars. (Color figure online)

Our results build up and support hypotheses of previous studies highlighting the distinct important role mainly of θ and α activity in cognitive processes such as visual discrimination involving the mechanism of WM.

At this point we should note that the degree distribution is the first of the statistical measures that one would use for measuring both coarse (global) and detailed/spatial (local) structural differences (and therefore differences) between the reconstructed CC networks. Other well known metrics, such as the average path length, clustering coefficient, small-world index (which belong to the global measures) and centralities (which belong to the local measures), could be also used. These measures are used to reveal differences between networks that maybe are not apparent with the degree distribution. In our case, the degree distribution provides a clear dissociation among the different network topologies. Hence we did not proceed to compute other “higher order” measures. Furthermore, the resulting statistically significant CC networks were rather sparse (with a maximum of 80 connections), which make the use of “higher order” measures such as mean clustering, small-world index and centrality more ambiguous.

In line with many other studies that have employed GC, we have chosen to perform the causal connectivity analysis on the sensor-level EEG signals. Source reconstruction, apart from the inherent ambiguities imposed by the ill-defined inverse problem (Dale et al. 2000; Kitzbichler et al. 2011) does not remove source mixing effects completely (see e.g. Palva and Palva (2012) for a critical review). Furthermore, it has been shown that such reconstruction procedures including Laplace transformation alter the original correlation between signals and the phase relations and for that matter the causality directions are disturbed (Kaminski and Blinowska 2014). Thus, our findings should not be interpreted as actual brain interactions but rather as apparent spatio-temporal patterns emerged at the sensor level, which however provide statistically significant differences in time–space and frequency between normal and epileptic children.

In our study, twelve children were diagnosed with idiopathic generalized epilepsy (IGE). In a recent study, Wei and coauthors found functional connectivity alterations between intrinsic connectivity networks in patients with IGE, with fronto-parietal areas largely involved (Wei et al. 2015). As group differences in our work were

frequently located over the frontal and parietal regions, it is possible that those differences are partly explained by the intranet work connectivity alterations similar to those found in IGE patients in aforementioned study. However, this could not be the solely explanation as the patient cohort as well as methodology differed between our work and this of Wei and his colleagues.

GO task

For the GO task we found that the highest CC network activity is observed mainly in α band for the control group. The epilepsy group exhibits its highest CC activity in β band, while in α band the CC network seems disrupted as reflected by the small number of connections. Consequently, in α band the spatio-temporal differences between the CT and ET were more striking and widespread, compared to other frequency bands. These results come in accordance with other studies underlying the enhanced α band activity during higher level attention tasks and decision processes (Klimesch et al. 2004; Marzetti et al. 2014; Palva et al. 2010). Killory and his colleagues, found that children which suffered from absence epilepsy (subgroup of idiopathic generalized epilepsy) showed decrease connectivity and thus presented disrupted attention networks compared to normal subjects in alpha band (Killory et al. 2011). Hongou and his colleagues reported a decrease of alpha-2 power in children with epilepsy compared to control group (Hongou et al. 1993).

NOGO task

Regarding the NOGO task, the denser CC network among all group types was observed at θ band for the control group. Differences in the spatial topography between the CT and CNT group types were also more widespread in θ band. Studies investigating the synchronization between brain areas under motor inhibition (relevant to NOGO tasks) an enhanced widespread synchronization was found at theta band. It is argued that the NOGO processes involve several sub-processes like discrimination of the stimulus, decision not to move and inhibition of the motor action, thus implying that activation should involve multiple brain areas (Müller and Anokhin 2012; Shibata et al. 1998).

Our results show that the epilepsy group exhibits its highest CC activity in α band but with significantly lesser network connections compared to the control group in θ band. Widespread differences between CNT and ENT were found mainly in θ band bilaterally at left temporal-midline parietal areas. Concluding, our findings may provide a helpful insight on the mechanisms pertaining to the cognitive response of children with well-controlled epilepsy and could potentially serve as “functional” biomarkers (Ponjavic-Conte et al. 2012) for diagnosis and monitoring purposes.

Possible limitations

Studies on cognition in children with epilepsy always have to take into account different confounding factors (Lagae 2006). Here, although we could not completely control for the possible effect of anti-epileptic medication, we did not see any performance differences in the epilepsy group, which is already reassuring in this respect. Furthermore, there are some reports in the literature stating that epilepsy treatment resulting in a seizure-free state, leads to a normalization of functional connectivity between different brain regions (Clemens et al. 2013, 2014).

Motor artifacts are the common problem in the neurophysiological studies. We thoroughly performed an artifact resection procedure during the preprocessing stage thereby receiving an EEG signal clean from (eye) movement artifacts and epileptic activity, which was then used for further analysis. However, it is currently appeared to be a more complicated issue than was previously thought. As shown in the recent study of Zeng and colleagues (Zeng et al. 2014), there is a bidirectional relationship between head motion and brain connectivity. Namely, the connectivity in a distributed set of cortical regions, primarily in the default network, was stronger in subjects with lower head motion than in those with high head motion. One could surmise that these differences can partly explain the between-group differences found in our study. On the other hand, we cannot directly extrapolate the results of the work of Zeng et al. to our study. Firstly, Zeng et al. employed a limited group of the healthy subjects. Furthermore, no research on this issue is done in different pathologic conditions and it is therefore not known whether the disease-specific patterns of head motion exist.

Regarding the computational method that we employed to reconstruct the CC networks, i.e. the spectral GC, this is not a model-free method (Hu and Liang 2012); it requires the use of a linear regression model. This could lead to spurious results if the underlying dynamics are nonlinear and/or generally if they do not comply with AR structures. One could alternative use non-parametric approaches which bypass the problems that are linked with the identification of an explicit model (Wen et al. 2013). The comparison of the efficiency of different approaches in reconstructing the “actual” connectivity networks remains still an open problem (see e.g. Astolfi et al. 2007; Wu et al. 2011; Seth et al. 2015).

References

- Alloway TP, Gathercole SE, Pickering SJ (2006) Verbal and visuospatial short-term and working memory in children: are they separable? *Child Development* 77(6):1698–1716. doi:10.1111/j.1467-8624.2006.00968.x

- Astolfi L, Cincotti F, Mattia D, Marciani MG, Baccala LA, Fallani FD, 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* 28:143–157. doi:[10.1109/IEMBS.2005.1615463](https://doi.org/10.1109/IEMBS.2005.1615463)
- Bano S, Yadav SN, Chaudhary V, Garga UC (2011) Neuroimaging in epilepsy. *J Pediatr Neurosci* 6(1):19–26. doi:[10.4103/1817-1745.84401](https://doi.org/10.4103/1817-1745.84401)
- Barnett L, Seth AK (2011) Behaviour of Granger causality under filtering: theoretical invariance and practical application. *J Neurosci Methods* 201(2):404–419. doi:[10.1016/j.jneumeth.2011.08.010](https://doi.org/10.1016/j.jneumeth.2011.08.010)
- Barrett AB, Murphy M, Bruno MA, Noirhomme Q, Boly M, Laureys S, Seth AK (2012) Granger causality analysis of steady-state electroencephalographic signals during propofol-induced anaesthesia. *PLoS One*. doi:[10.1371/journal.pone.0029072](https://doi.org/10.1371/journal.pone.0029072)
- Benjamini Y, Hochberg Y (1995) Controlling the false discovery rate: A practical and powerful approach to multiple testing. *J R Stat Soc Ser B (Methodol)* 57(1):289–300. doi:[10.2307/2346101](https://doi.org/10.2307/2346101)
- Bledowski C, Kaiser J, Wibral M, Yildiz-Erzberger K, Rahm B (2012) Separable neural bases for subprocesses of recognition in working memory. *Cereb Cortex* 22(8):1950–1958. doi:[10.1093/cercor/bhr276](https://doi.org/10.1093/cercor/bhr276)
- Blinowska K, Kuś R, Kamiński M (2004) Granger causality and information flow in multivariate processes. *Phys Rev E* 70:050902. doi:[10.3389/fncom.2014.00061](https://doi.org/10.3389/fncom.2014.00061)
- Bollimunta A, Chen Y, Schroeder CE, Ding M (2008) Neuronal mechanisms of cortical alpha oscillations in awake-behaving macaques. *J Neurosci Off J Soc Neurosci* 28(40):9976–9988. doi:[10.1523/JNEUROSCI.2699-08.2008](https://doi.org/10.1523/JNEUROSCI.2699-08.2008)
- Brovelli A, Ding M, Ledberg A, Chen Y, Nakamura R, Bressler SL (2004) Beta oscillations in a large-scale sensorimotor cortical network: directional influences revealed by Granger causality. *Proc Natl Acad Sci USA* 101(26):9849–9854. doi:[10.1073/pnas.0308538101](https://doi.org/10.1073/pnas.0308538101)
- Campo P, Maestu F, Garcia-Morales I, Gil-Nagel A, Strange B, Morales M et al (2009) Modulation of medial temporal lobe activity in epilepsy patients with hippocampal sclerosis during verbal working memory. *J Int Neuropsychol Soc* 15:536–546. doi:[10.1093/cercor/bhr201](https://doi.org/10.1093/cercor/bhr201)
- Chaix Y, Laguitton V, Lauwers-Cancès V, Daquin G, Cancès C, Démonet JF et al (2006) Reading abilities and cognitive functions of children with epilepsy: influence of epileptic syndrome. *Brain Dev* 28(2):122–130. doi:[10.1016/j.braindev.2005.06.004](https://doi.org/10.1016/j.braindev.2005.06.004)
- Clemens B, Puskás S, Besenyei M, Spisák T, Emri M, Fekete I (2013) Remission of benign epilepsy with rolandic spikes: an EEG-based connectivity study at the onset of the disease and at remission. *Epilepsy Res* 106(1–2):128–135. doi:[10.1016/j.eplepsyres.2013.04.006](https://doi.org/10.1016/j.eplepsyres.2013.04.006)
- Clemens B, Puskás S, Besenyei M, Kovács NZ, Spisák T, Kis SA, Emri M, Hollódy K, Fogarasi A, Kondákor I, Fekete I (2014) Valproate treatment normalizes EEG functional connectivity in successfully treated idiopathic generalized epilepsy patients. *Epilepsy Res* 108(10):1896–1903
- Colon AJ, Ossenblok P, Nieuwenhuis L, Stam KJ, Boon P (2009) Use of routine MEG in the primary diagnostic process of epilepsy. *J Clin Neurophysiol Off Publ Am Electroencephalogr Soc* 26(5):326–332. doi:[10.1097/WNP.0b013e3181baabef](https://doi.org/10.1097/WNP.0b013e3181baabef)
- Cross JH (2011) Epilepsy in the WHO European region: fostering epilepsy care in Europe. *Epilepsia* 52(1):187–188. doi:[10.1111/j.1528-1167.2010.02903.x](https://doi.org/10.1111/j.1528-1167.2010.02903.x)
- Dale AM, Liu AK, Fischl BR, Buckner RL, Belliveau JW, Lewine JD, Halgren E (2000) Dynamic statistical parametric mapping. *Neuron* 26:55–67. doi:[10.1016/S0896-6273\(00\)81138-1](https://doi.org/10.1016/S0896-6273(00)81138-1)
- Dauwels J, Dauwels J, Vialatte F, Vialatte F, Musha T, Musha T, Cichocki A (2010) A comparative study of synchrony measures for the early diagnosis of Alzheimer's disease based on EEG. *NeuroImage* 49(1):668–693. doi:[10.1016/j.neuroimage.2009.06.056](https://doi.org/10.1016/j.neuroimage.2009.06.056)
- Dean RB, Dixon WJ (1951) Simplified statistics for small numbers of observations. *Anal Chem* 23(4):636–638. doi:[10.1021/ac60052a025](https://doi.org/10.1021/ac60052a025)
- Dhamala M, Rangarajan G, Ding M (2008) Analyzing information flow in brain networks with nonparametric Granger causality. *NeuroImage* 41(2):354–362. doi:[10.1016/j.neuroimage.2008.02.020](https://doi.org/10.1016/j.neuroimage.2008.02.020)
- Dimitriadis SI, Laskaris NA, Micheloyannis S (2015) Transition dynamics of EEG-based network microstates during mental arithmetic and resting wakefulness reflects task-related modulations and developmental changes. *Cogn Neurodyn* 9(4):371–387. doi:[10.1007/s11571-015-9330-8](https://doi.org/10.1007/s11571-015-9330-8)
- Ding M, Chen Y, Bressler SL (2006) Granger causality: basic theory and application to neuroscience. In *Handbook of time series analysis*. pp 451–474. doi:[10.1002/9783527609970.ch17](https://doi.org/10.1002/9783527609970.ch17)
- Follett PL, Vora N, Cross JH (2012) Paediatric intractable epilepsy syndromes: changing concepts in diagnosis and management. *Child Neurology* 39:45–60. doi:[10.1007/978-3-7091-1360-8_2](https://doi.org/10.1007/978-3-7091-1360-8_2)
- Friston KJ (2011) Functional and effective connectivity: a review. *Brain Connect* 1(1):13–36. doi:[10.1089/brain.2011.0008](https://doi.org/10.1089/brain.2011.0008)
- Gathercole SE, Pickering SJ, Knight C, Stegmann Z (2004) Working memory skills and educational attainment: evidence from national curriculum assessments at 7 and 14 years of age. *Appl Cogn Psychol* 18(1):1–16. doi:[10.1002/acp.934](https://doi.org/10.1002/acp.934)
- Gathercole SE, Alloway TP, Kirkwood HJ, Elliott JG, Holmes J, Hilton KA (2008) Attentional and executive function behaviours of children with poor working memory. *Learn Individ Differ* 18:214–223. doi:[10.1016/j.lindif.2007.10.003](https://doi.org/10.1016/j.lindif.2007.10.003)
- Goodin DS, Aminoff MJ, Laxer KD (1990) Detection of epileptiform activity by different noninvasive EEG methods in complex partial epilepsy. *Annals Neurol* 27(3):330–334. doi:[10.1002/ana.410270317](https://doi.org/10.1002/ana.410270317)
- Gotman J, Grova C, Bagshaw A, Kobayashi E, Aghakhani Y, Dubeau F (2005) Generalized epileptic discharges show thalamocortical activation and suspension of the default state of the brain. *Proc Natl Acad Sci USA* 102(42):15236–15240. doi:[10.1073/pnas.0504935102](https://doi.org/10.1073/pnas.0504935102)
- Grouiller F, Thornton RC, Groening K, Spinelli L, Duncan JS, Schaller K, Vulliemoz S (2011) With or without spikes: localization of focal epileptic activity by simultaneous electroencephalography and functional magnetic resonance imaging. *Brain* 134(10):2867–2886. doi:[10.1093/brain/awr156](https://doi.org/10.1093/brain/awr156)
- Guerrini R (2006) Epilepsy in children. *Lancet* 367(9509):499–524. doi:[10.1016/s0140-6736\(06\)68182-8](https://doi.org/10.1016/s0140-6736(06)68182-8)
- Gülgönen S, Demirbilek V, Korkmaz B, Dervent A, Townes BD (2000) Neuropsychological functions in idiopathic occipital lobe epilepsy. *Epilepsia* 41:405–411. doi:[10.1111/j.1528-1157.2000.tb00181.x](https://doi.org/10.1111/j.1528-1157.2000.tb00181.x)
- Henriksen O (1990) Education and epilepsy: assessment and remediation. *Epilepsia* 31–4(4):S21–S25. doi:[10.1111/j.1528-1157.1990.tb05865.x](https://doi.org/10.1111/j.1528-1157.1990.tb05865.x)
- Hernandez MT, Sauerwein HC, Jambaque I, de Guise E, Lussier F, Lortie A, Lassonde M (2003) Attention, memory, and behavioral adjustment in children with frontal lobe epilepsy. *Epilepsy Behav* 4(5):522–536. doi:[10.1016/j.yebeh.2003.07.014](https://doi.org/10.1016/j.yebeh.2003.07.014)
- Hongou K, Konishi T, Naganuma Y, Murakami M, Yamatani M, Okada T (1993) Development of the background activity of EEG in children with epilepsy; comparison with normal children. *No To Hattatsu* 25(3):207–214
- Hu S, Liang H (2012) Causality analysis of neural connectivity: new tool and limitations of spectral Granger causality. *Neurocomputing* 76(1):44–47. doi:[10.1016/j.neucom.2010.10.017](https://doi.org/10.1016/j.neucom.2010.10.017)
- Hu S, Cao Y, Zhang J (2012) More discussions for granger causality and new causality measures. *Cogn Neurodyn* 6(1):33. doi:[10.1007/s11571-011-9175-8](https://doi.org/10.1007/s11571-011-9175-8)

- Jambaqué I, Dellatolas G, Dulac O, Ponsot G, Signoret JL (1993) Verbal and visual memory impairment in children with epilepsy. *Neuropsychologia* 31(12):1321–1337. doi:[10.1016/0028-3932\(93\)90101-5](https://doi.org/10.1016/0028-3932(93)90101-5)
- Jan MMS, Sadler M, Rahey SR (2001) Lateralized postictal EEG delta predicts the side of seizure surgery in temporal lobe epilepsy. *Epilepsia* 42(3):402–405. doi:[10.1046/j.1528-1157.2001.45999.x](https://doi.org/10.1046/j.1528-1157.2001.45999.x)
- Jiruska P, de Curtis M, Jefferys JGR, Schevon CA, Schiff SJ, Schindler K (2013) Synchronization and desynchronization in epilepsy: controversies and hypotheses. *The Journal of Physiology* 591(4):787–797. doi:[10.1113/jphysiol.2012.239590](https://doi.org/10.1113/jphysiol.2012.239590)
- Kaminski M, Blinowska M (2014) Directed Transfer Function is not influenced by volume conduction—inexpedient pre-processing should be avoided. *Front Comput Neurosci* 8:61. doi:[10.3389/fncom.2014.00061](https://doi.org/10.3389/fncom.2014.00061)
- Keil A, Sabatinelli D, Ding M, Lang PJ, Ihssen N, Heim S (2009) Re-entrant projections modulate visual cortex in affective perception: evidence from Granger causality analysis. *Hum Brain Mapp* 30:532–540. doi:[10.1002/hbm.20521](https://doi.org/10.1002/hbm.20521)
- Keller JM, Gray MR, Givens JA Jr (1985) A fuzzy k-nearest neighbor algorithm. *IEEE Trans Syst Man Cybern* 15(4):580–585. doi:[10.1109/TSMC.1985.6313426](https://doi.org/10.1109/TSMC.1985.6313426)
- Killory BD, Bai X, Negishi M, Vega C, Spann MN, Vestal M, Blumenfeld H (2011) Impaired attention and network connectivity in childhood absence epilepsy. *NeuroImage* 56(4):2209–2217. doi:[10.1016/j.neuroimage.2011.03.036](https://doi.org/10.1016/j.neuroimage.2011.03.036)
- Kitzbichler MG, Henson RNA, Smith ML, Nathan PJ, Bullmore ET (2011) Cognitive effort drives workspace configuration of human brain functional networks. *J Neurosci* 31:8259–8270. doi:[10.1523/JNEUROSCI.0440-11.2011](https://doi.org/10.1523/JNEUROSCI.0440-11.2011)
- Klimesch W (1999) EEG alpha and theta oscillations reflect cognitive and memory performance: a review and analysis. *Brain Res Rev* 29(2–3):169–195. doi:[10.1016/S0165-0173\(98\)00056-3](https://doi.org/10.1016/S0165-0173(98)00056-3)
- Klimesch W, Schack B, Schabus M, Doppelmayr M, Gruber W, Sauseng P (2004) Phase-locked alpha and theta oscillations generate the P1-N1 complex and are related to memory performance. *Cogn Brain Res* 19(3):302–316. doi:[10.1016/j.cogbrainres.2003.11.016](https://doi.org/10.1016/j.cogbrainres.2003.11.016)
- Krause CM, Boman PA, Sillanmäki L, Varho T, Holopainen IE (2008) Brain oscillatory EEG event-related desynchronization (ERD) and -synchronization (ERS) responses during an auditory memory task are altered in children with epilepsy. *Seizure* 17(1):1–10. doi:[10.1016/j.seizure.2007.05.015](https://doi.org/10.1016/j.seizure.2007.05.015)
- Kuzniecky R, Palmer C, Hugg J, Martin R, Sawrie S, Morawetz R, Knowlton R (2001) Magnetic resonance spectroscopic imaging in temporal lobe epilepsy: neuronal dysfunction or cell loss? *Arch Neurol* 58(12):2048–2053. doi:[10.1001/archneur.58.12.2048](https://doi.org/10.1001/archneur.58.12.2048)
- Kwiatkowski D, Phillips PCB, Schmidt P, Shin Y (1992) Testing the null hypothesis of stationarity against the alternative of a unit root. *J Econom* 54:159–178. doi:[10.1016/0304-4076\(92\)90104-Y](https://doi.org/10.1016/0304-4076(92)90104-Y)
- Lagae L (2006) Cognitive side effects of anti-epileptic drugs. The relevance in childhood epilepsy. *Seizure* 15:235–241. doi:[10.1016/j.seizure.2006.02.013](https://doi.org/10.1016/j.seizure.2006.02.013)
- Luton LM, Burns TG, DeFilippis N (2010) Frontal lobe epilepsy in children and adolescents: a preliminary neuropsychological assessment of executive function. *Arch Clin Neuropsychol* 25(8):762–770. doi:[10.1093/arclin/acq066](https://doi.org/10.1093/arclin/acq066)
- 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](https://doi.org/10.1016/j.jneumeth.2007.03.024)
- Marzetti L, Di Lanzo C, Zappasodi F, Chella F, Raffone A, Pizzella V (2014) Magnetoencephalographic alpha band connectivity reveals differential default mode network interactions during focused attention and open monitoring meditation. *Front Hum Neurosci* 8:832. doi:[10.3389/fnhum.2014.00832](https://doi.org/10.3389/fnhum.2014.00832)
- McCarthy AM, Richman LC, Yarbrough D (1995) Memory, attention, and school problems in children with seizure disorders. *Dev Neuropsychol* 11(1):71–86. doi:[10.1080/87565649509540604](https://doi.org/10.1080/87565649509540604)
- Mirsky AF, Duncan CC, Levav M, Bures J, Kopin I, McEwen B, Weiskrantz L (2001) Neuropsychological studies in idiopathic generalized epilepsy. In: Jambaque O, Lassonde I, Dulac M (eds) *Neuropsychology of childhood epilepsy*, vol 50. Kluwer Academic, New York, pp 141–150. doi:[10.1007/0-306-47612-6_15](https://doi.org/10.1007/0-306-47612-6_15)
- Müller V, Anokhin AP (2012) Neural synchrony during response production and inhibition. *PLoS ONE*. doi:[10.1371/journal.pone.0038931](https://doi.org/10.1371/journal.pone.0038931)
- Myatchin I, Lagae L (2011) Impaired spatial working memory in children with well-controlled epilepsy: an event-related potentials study. *Seizure. J Br Epilepsy Assoc* 20(2):143–150. doi:[10.1016/j.seizure.2010.11.005](https://doi.org/10.1016/j.seizure.2010.11.005)
- Myatchin I, Mennes M, Wouters H, Stiers P, Lagae L (2009) Working memory in children with epilepsy: an event-related potentials study. *Epilepsy Res* 86(2–3):183–190. doi:[10.1016/j.eplepsyres.2009.06.004](https://doi.org/10.1016/j.eplepsyres.2009.06.004)
- Nicolaou N, Hourris S, Alexandrou P, Georgiou J (2012) EEG-based automatic classification of “awake” versus “anesthetized” state in general anesthesia using granger causality. *PLoS One*. doi:[10.1371/journal.pone.0033869](https://doi.org/10.1371/journal.pone.0033869)
- Oostenveld R, Fries P, Maris E, Schoffelen JM (2011) FieldTrip: open source software for advanced analysis of MEG, EEG, and invasive electrophysiological data. *Comput Intell Neurosci*. doi:[10.1155/2011/156869](https://doi.org/10.1155/2011/156869)
- Palva S, Palva JM (2012) Discovering oscillatory interaction networks with M/EEG: challenges and breakthroughs. *Trends Cogn Sci* 16:219–230. doi:[10.1016/j.tics.2012.02.004](https://doi.org/10.1016/j.tics.2012.02.004)
- Palva JM, Monto S, Kulashekhar S, Palva S (2010) Neuronal synchrony reveals working memory networks and predicts individual memory capacity. *Proc Natl Acad Sci USA* 107(16):7580–7585. doi:[10.1073/pnas.0913113107](https://doi.org/10.1073/pnas.0913113107)
- Pavlou E, Gkampeta A (2011) Learning disorders in children with epilepsy. *Child’s Nerv Syst ChNS Off J Intl Soc Pediatr Neurosurg* 27(3):373–379. doi:[10.1007/s00381-010-1321-9](https://doi.org/10.1007/s00381-010-1321-9)
- Ponjavic-Conte KD, Dowdall JR, Hambrook DA, Luczak A, Tata MS (2012) Neural correlates of auditory distraction revealed in theta-band EEG. *NeuroReport* 23(4):240–245. doi:[10.1097/WNR.0b013e3283505ac6](https://doi.org/10.1097/WNR.0b013e3283505ac6)
- Protopapa F, Siettos CI, Evdokimidis I, Smyrnis N (2014) Granger causality analysis reveals distinct spatio-temporal connectivity patterns in motor and perceptual visuo-spatial working memory. *Front Comput Neurosci* 8:146. doi:[10.3389/fncom.2014.00146](https://doi.org/10.3389/fncom.2014.00146)
- Ruff CC, Knauff M, Fangmeier T, Spreer J (2003) Reasoning and working memory: common and distinct neuronal processes. *Neuropsychologia* 41(9):1241–1253. doi:[10.1016/S0028-3932\(03\)00016-2](https://doi.org/10.1016/S0028-3932(03)00016-2)
- Sargolzaei S, Cabrerizo M, Goryawala M, Eddin AS, Adjouadi M (2015a) Scalp EEG brain functional connectivity networks in pediatric epilepsy. *Comput Biol Med* 56:158–166. doi:[10.1016/j.combiomed.2014.10.018](https://doi.org/10.1016/j.combiomed.2014.10.018)
- Sargolzaei S, Cabrerizo M, Sargolzaei A, Noei S, Eddin A, Rajaei H, Pinzon-Ardila A, Gonzalez-Arias SM, Jayakar P, Adjouadi M (2015b) A probabilistic approach for pediatric epilepsy diagnosis using brain functional connectivity networks. *BMC Bioinform* 7:s9. doi:[10.1186/1471-2105-16-S7-S9](https://doi.org/10.1186/1471-2105-16-S7-S9)
- Schwarz G (1978) Estimating the dimension of a model. *Ann Stat* 6(2):461–464. doi:[10.1214/aos/1176344136](https://doi.org/10.1214/aos/1176344136)
- Seth AK (2008) Causal networks in simulated neural systems. *Cogn Neurodyn* 2(1):49. doi:[10.1007/s11571-007-9031-z](https://doi.org/10.1007/s11571-007-9031-z)

- Seth AK (2010) A MATLAB toolbox for Granger causal connectivity analysis. *J Neurosci Methods* 186:262–273. doi:[10.1016/j.jneumeth.2009.11.020](https://doi.org/10.1016/j.jneumeth.2009.11.020)
- Seth AK, Barrett AB, Barnett L (2015) Granger causality analysis in neuroscience and neuroimaging. *J Neurosci* 35(8):3293–3297. doi:[10.1523/JNEUROSCI.4399-14.2015](https://doi.org/10.1523/JNEUROSCI.4399-14.2015)
- Shibata T, Shimoyama I, Ito T, Abila D, Iwasa H, Koseki K, Nakajima Y (1998) The synchronization between brain areas under motor inhibition process in humans estimated by event-related EEG coherence. *Neurosci Res* 31(4):265–271. doi:[10.1016/S0168-0102\(98\)00046-7](https://doi.org/10.1016/S0168-0102(98)00046-7)
- Smith SJM (2005) EEG in the diagnosis, classification, and management of patients with epilepsy. *J Neurol Neurosurg Psychiatry* 76–2(2):2–7. doi:[10.1136/jnnp.2005.069245](https://doi.org/10.1136/jnnp.2005.069245)
- Smith SM, Vidaurre D, Beckmann CF, Glasser MF, Jenkinson M, Miller KL, Nichols TE, Robinson EC, Salimi-Khorshidi G, Woolrich MW, Barch DM, Uğurbil K, Van Essen DC (2013) Functional connectomics from resting-state fMRI. *Trends Cogn Sci* 17:666–682. doi:[10.1016/j.tics.2013.09.016](https://doi.org/10.1016/j.tics.2013.09.016)
- Stam CJ, Nolte G, Daffertshofer A (2007) Phase lag index: assessment of functional connectivity from multi channel EEG and MEG with diminished bias from common sources. *Hum Brain Mapp* 28:1178–1193. doi:[10.1002/hbm.20346](https://doi.org/10.1002/hbm.20346)
- Stores G (1978) School-children with epilepsy at risk for learning and behaviour problems. *Dev Med Child Neurol* 20(4):502–508. doi:[10.1111/j.1469-8749.1978.tb15256.x](https://doi.org/10.1111/j.1469-8749.1978.tb15256.x)
- Swanson HL (2006) Cross-sectional and incremental changes in working memory and mathematical problem solving. *J Educ Psychol* 98(2):265–281. doi:[10.1037/0022-0663.98.2.265](https://doi.org/10.1037/0022-0663.98.2.265)
- Toth J, Lewis C (1997) The role of working memory and external representation in individual decision making. AAAI technical report: 109–115. <http://www.aaai.org/Papers/Symposia/Fall/1997/FS-97-03/FS97-03-014.pdf>
- Van Diessen E, Otte WM, Braun KPJ, Stam CJ, Jansen FE (2013) Improved diagnosis in children with partial epilepsy using a multivariable prediction model based on EEG network characteristics. *PLoS One*. doi:[10.1371/journal.pone.0059764](https://doi.org/10.1371/journal.pone.0059764)
- Wagner DD, Sziklas V, Garver KE, Jones-Gotman M (2009) Material-specific lateralization of working memory in the medial temporal lobe. *Neuropsychologia* 47:112–122. doi:[10.1016/j.neuropsychologia.2008.08.010](https://doi.org/10.1016/j.neuropsychologia.2008.08.010)
- Wei HL, An J, Zeng LL, Shen H, Qiu SJ, Hu DW (2015) Altered functional connectivity among default, attention, and control networks in idiopathic generalized epilepsy. *Epilepsy Behav* 46:118–125. doi:[10.1016/j.yebeh.2015.03.031](https://doi.org/10.1016/j.yebeh.2015.03.031)
- Wen X, Rangarajan G, Ding M (2013) Multivariate Granger causality: an estimation framework based on factorization of the spectral density matrix. *Philos Trans Ser A Math Phys Eng Sci* 371(1997):20110610. doi:[10.1098/rsta.2011.0610](https://doi.org/10.1098/rsta.2011.0610)
- Williams J (2003) Learning and behavior in children with epilepsy. *Epilepsy Behav* 4(2):107–111. doi:[10.1016/S1525-5050\(03\)00024-6](https://doi.org/10.1016/S1525-5050(03)00024-6)
- Wu MH, Frye RE, Zouridakis G (2011) A comparison of multivariate causality based measures of effective connectivity. *Comput Biol Med* 41(12):1132–1141. doi:[10.1016/j.combiomed.2011.06.007](https://doi.org/10.1016/j.combiomed.2011.06.007)
- Yang L, Worrell GA, Nelson C, Brinkmann B, He B (2012) Spectral and spatial shifts of post-ictal slow waves in temporal lobe seizures. *Brain* 135(10):3134–3143. doi:[10.1093/brain/aww221](https://doi.org/10.1093/brain/aww221)
- Zeng LL, Shen H, Liu L, Wang L, Li B, Fang P et al (2012) Identifying major depression using whole-brain functional connectivity: a multivariate pattern analysis. *Brain* 135:1498–1507. doi:[10.1093/brain/aww059](https://doi.org/10.1093/brain/aww059)
- Zeng LL, Wang D, Fox MD, Sabuncu M, Hu D, Ge M, Buckner RL, Liu H (2014) Neurobiological basis of head motion in brain imaging. *Proc Natl Acad Sci USA* 111(16):6058–6062. doi:[10.1073/pnas.1317424111](https://doi.org/10.1073/pnas.1317424111)
- Zhang X, Lei X, Wu T (2013) A review of EEG and MEG for brainnetome research. *Cogn Neurodyn* 8(2):87–98. doi:[10.1007/s11571-013-9274-9](https://doi.org/10.1007/s11571-013-9274-9)