Transition dynamics of EEG-based network microstates during mental arithmetic and resting wakefulness reflects task-related modulations and developmental changes

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Received: 18 July 2014/Revised: 7 December 2014/Accepted: 7 January 2015/Published online: 18 January 2015
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Abstract We studied how maturation influences the organization of functional brain networks engaged during mental calculations and in resting state. Surface EEG measurements from 20 children (8–12 years) and 25 students (21–26 years) were analyzed. Interregional synchronization of brain activity was quantified by means of Phase Lag Index and for various frequency bands. Based on these pairwise estimates of functional connectivity, we formed graphs which were then characterized in terms of local structure [local efficiency (LE)] and overall integration (global efficiency). The overall data analytic scheme was applied twice, in a static and time-varying mode. Our results showed a characteristic trend: functional segregation dominates the network organization of younger brains. Moreover, in childhood, the overall functional network possesses more prominent small-world network characteristics than in early adulthood in accordance with the Neural Efficiency Hypothesis. The above trends were intensified by the time-varying approach and identified for the whole set of tested frequency bands (from δ to

low γ). By mapping the time-indexed connectivity patterns to multivariate timeseries of nodal LE measurements, we carried out an elaborate study of the functional segregation dynamics and demonstrated that the underlying network undergoes transitions between a restricted number of stable states, that can be thought of as “*network-level microstates*”. The rate of these transitions provided a robust marker of developmental and task-induced alterations, that was found to be insensitive to reference montage and independent component analysis denoising.

Keywords EEG · Resting state · Numerical cognition · Developmental · Network connectivity microstates · Symbolic dynamics

Introduction

Synchronized oscillatory activity reflects the developmental trends of cortical circuits as it has been demonstrated by changes in the frequency and synchronization strength of neural oscillations during development (Uhlhaas et al. 2009). Neural synchrony can be measured non-invasively with electroencephalography (EEG) and magnetoencephalography (MEG). There is a large body of evidence from such recordings in humans, indicating a close relation between synchronous oscillatory activity and a variety of perceptual and cognitive functions (Herculano-Houzel et al. 1999; Fries et al. 2001; Buzsaki 2005; Womelsdorf et al. 2007; Klimesch et al. 2007; Palva and Palva 2007, 2011).

Alterations in the brain waves at resting-state, regarding frequency content, amplitude and synchronization, were described by various studies during development (Srinivasan 1999; Niedermeyer and Da Silva 2005; Thatcher et al. 2008;

Electronic supplementary material The online version of this article (doi:10.1007/s11571-015-9330-8) contains supplementary material, which is available to authorized users.

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Boersma et al. 2011, 2012; Biswal et al. 2010). Task-related oscillations associated with cognitive and perceptual processes have already been examined during different developmental stages (Yordanova and Kolev 1996; Uhlhaas et al. 2009; Muller et al. 2009). Several studies have shown the influence of maturation on the EEG signals in childhood based on spectral and synchronization analysis (e.g. Clarke et al. 2001; Dustman et al. 1999; Boersma et al. 2011, 2012). In one of them, the developmental changes in four functional networks were scrutinized by means of various network-related metrics and with respect to the modular organization (Fair et al. 2009). That study, based on subjects within the range of (7–31) years, revealed an age-dependent modularity¹ and the stability of network metrics regardless the age. More specifically, the organization into communities was predominantly guided by anatomical proximity in children, whereas it was found reflecting functional relationships in adults. Similar, age-related, changes in modular organization were identified in another fMRI study (Meunier et al. 2009) as well.

Connectivity at rest and during cognitive tasks has been the subject of various researches, based on different methodological approaches (Sporns et al. 2000; Ioannides et al. 2012; Stam et al. 2007a, b; Micheloyannis 2012; Dimitriadis et al. 2009, 2010a, b, 2012a, b, c, d; Turk-Browne 2013). Graph theoretic principles and algorithms are in the heart of all these approaches that are aimed at anatomical (He et al. 2007; Hagmann et al. 2008) and functional networks defined empirically from EEG, MEG and fMRI recordings (Bassett and Bullmore 2006; Stam et al. 2007a, b). In the majority of connectivity-related studies, the segregation and integration tendencies of the underlying network are captured, correspondingly, by the clustering coefficient (and local efficiency) and shortest path length (and global efficiency) descriptors (Stam et al. 2007a, b; Micheloyannis et al. 2006). Locally, the fraction of triangles around an individual node is known as the clustering coefficient and is equivalent to the fraction of the node's neighbors that are also neighbors of each other (Watts and Strogatz 1998). The average shortest path length between all pairs of nodes in the network is known as the characteristic path length of the network (Watts and Strogatz 1998). The average inverse shortest path length is a related measure known as the global efficiency (Latora and Marchiori 2001) while the inverse shortest path length within each nodes' functional neighborhood is related with local efficiency (Latora and Marchiori 2001). These network

metrics are employed so as to characterize the topological organization of functional brain networks, at the level of EEG sensors.

The vast majority of previous studies has been devoted to analyzing the topological properties of static graphs, where nodes correspond to distinct brain regions and links to pair-wise associations among them. The links in these graphs remain fixed over time. Whereas this consideration might be realistic for anatomical connectivity, it implies strict assumptions when functional connectivity patterns are encountered and seems unreasonable in the particular case of fast-recording modalities (EEG/MEG). Previous studies have already strongly supported the need for time-varying functional connectivity analysis (Allen et al. 2012; De Vico Fallani et al. 2008; Dimitriadis et al. 2010b, 2012d; Ioannides et al. 2012; Betzel et al. 2012; Dimitriadis et al. 2013a, b; Jamal et al. 2014). Network metrics computed over different instantiations of the functional connectivity graph (FCG) can provide a quantitative view of the reconfigurable brain. At a more elaborate level, network metric time series (NMTS) can be formed which encapsulate the dynamical changes of functional dependencies computed over time-varying FCGs (TVFCGs) (Dimitriadis et al. 2010b, 2013b).

In line with such a time-varying mode of analysis there are algorithmic procedures for detecting consistent connectivity patterns that are characterized by their regular recurrence. These patterns can be understood as reflecting "connectivity microstates". Microstates literature, so far, has been focused on prototyping (summarizing) amplitude related spatiotemporal dynamics, and in relation with particular cognitive processes (Lehmann 1990). In a recent study (Dimitriadis et al. 2013a), a framework for handling quasi-instantaneous patterns of functional connectivity and deriving a restricted repertoire of *functional connectivity microstates* (FCμstates) was introduced and shown to simplify the complexity of observed brain dynamics [in the sense of (Kelso and Tognoli 2007; Tognoli and Kelso 2009)].

In the present study, we attempted to reveal developmental changes in functional connectivity using signals from two different recording conditions (a resting state and a mental arithmetic task) and by following both a static and a time-varying mode of analysis. Phase relationships provide a fruitful and convenient way to estimate the synchrony between brain waves recorded over distinct brain regions (Lachaux et al. 1999; Varela et al. 2001; Sauseng et al. 2004; Palva and Palva 2011). On the expectation that functional brain networks are gradually turning from networks dominated by immature local processes to networks operating in a collective fashion (Fair et al. 2009), we studied network metrics that express functional integration and segregation. Based on EEG signals, recorded at resting-state and during a comparison task, we described

¹ **Modularity** is one measure of the structure of networks or graphs. It was designed to measure the strength of division of a network into modules (also called groups, clusters or communities). Networks with high modularity have dense connections between the nodes within modules but sparse connections between nodes in different modules. Modularity is often used in optimization methods for detecting community structure in networks (Newman 2006).

segregation/integration by means of local/global efficiency in the static and dynamic patterns of functional connectivity and assessed the corresponding *small-worldness* of the underlying networks in children and young adults. Finally, we defined network microstates (Netμstates) from the NMTS through an intelligible summarization of the observed variations in network organization. The adopted scheme resulted in a novel format for representing brain's functional reconfiguration and facilitated the comparison between age-groups and recording conditions.

The paper is organized as follows. In Section “**Materials and methods**”, after a short description of the experimental data, we describe the static and time-varying network analysis, and also the procedure to represent NMTS by means of a confined repertoire of Netμstates. Section “**Results**” is devoted to the results. Section “**Discussion**” discusses the importance of our findings and their correlation with recent literature.

Materials and methods

Subjects

Twenty children aged 8–12 years and 25 students of the medical faculty in Crete, aged 21–26 years were evaluated. The children had no medical history. Intellectual and school-achievement abilities and behavior were normal. They were tested using four subscales of the Greek version of the WISC-III test, the auditory association and reception subscales of the Greek version of the Illinois test of psycholinguistic abilities, the ZAREKI test for calculation abilities and the Greek version of the child behavior checklist. The students had no pathological history and no learning difficulties as it was shown by the good degrees in the previous 2 years of their studies at the university.

EEG recordings

The EEG recording was performed, while the individuals were comfortably seated in a declined chair in a dimly illuminated and sound attenuated room. In the first part of the recordings (no task—resting state condition) the subjects were fixating on a small star on the screen of a PC. In the second part, they performed an arithmetic comparison task based on the numbers presented on the PC screen. For children two-digit numbers were used, while for adults, three-digit ones. This was done so as to bring both age groups in a comparable state regarding the required mental effort for the task (i.e. the comparisons were of a similar difficulty level; Micheloyannis et al. 2009). The performance of subjects, in the comparison task was very high (100 %).

The EEG signals were recorded during two different studies. In the first study, the brain activity of children was recorded at a sampling frequency of 400 Hz. In the second one, the brain activity of adults was recorded at a sampling frequency of 500 Hz. In order to “align” both recording sets at equal sampling frequency (400 Hz), we downsampled the recording set of adults using ‘resample’ function in MATLAB. Both types of recording had been performed via “CONTACT Precision Instruments amplifiers” and with the help of a “DATAQ AD Converter”, using 30 electrodes according to the international 10/20 system: FP2, F4, FC4, C4, CP4, P4, O2, F8, FT8, T4, TP8, PO8, Fz, FCz, Cz, CPz, Pz, Oz, FP1, F3, FC3, C3, CP3, P3, O1, F7, FT7, T3, TP7, PO7, and the A1 + A2 as reference. By means of careful visual inspection (carried out offline by an experienced neurophysiologist), one artifact-free epoch of 4,096 samples was selected from both recording conditions and for every subject. An additional variant of the overall dataset was also created, in which average-rereferencing and ICA-denoising had been applied. This step was considered necessary, since in our methodology the emphasis was put on the phase aspects of the recorded signals. Hence, interferences which were shared among sensors (like heart activity signals) could lead to overestimated neural coordination. To exclude the possibility that our results were a mirage of artifactual contributions, we included as supplementary material the corresponding results from working with the “ICA-cleaned”, average-rereferenced counterparts of the data.

By applying 3rd-order Butterworth band-pass (in zero-phase mode), we derived the EEG activity in different narrow frequency bands, as well as in the conventional bands of brainwaves which were defined as follows: δ (1–4 Hz), θ (4–8 Hz), α_1 (8–10 Hz), α_2 (10–13 Hz), β_1 (13–20 Hz), β_2 (20–30 Hz) and γ (30–45 Hz) bands. Hence, in the results presented below, the use of band-limited brain activity is implied.

Brain oscillations within α and β frequency bands had been divided into α_1 – α_2 and β_1 – β_2 subintervals respectively and the subsequent network analysis revealed distinct dynamic behavior (Fig. S.2, 3). Numerous previous studies have shown that such a dichotomy is valid, both for α band (Klimesch 1999; Stam et al. 1999; Fink et al. 2005; Laufs et al. 2006; Micheloyannis et al. 2005; Dimitriadis et al. 2010a, b, 2012a, 2012c, d) and β band (Kramer et al. 2008; Roopun et al. 2008).

Graph theoretic analysis

Constructing functional connectivity graphs (FCG)

To detect and characterize neural synchrony between distinct recording sites, we adopted Phase Lag Index (PLI;

Stam et al. 2007b). PLI is an estimator of the presence of a systematic phase difference between two time series. It quantifies the asymmetry in the distribution of instantaneous phase differences $\Delta\phi(t_k)$, $k = 1 \dots N$

$$PLI = |\langle \text{sign}[\Delta\phi(t_k)] \rangle| \quad (1)$$

The PLI ranges between 0 and 1. A PLI of zero indicates either no coupling or coupling with a phase difference centered around $0 \bmod \pi$. A PLI of 1 indicates perfect phase locking at a value of $\Delta\phi$ different from $0 \bmod \pi$. The stronger this nonzero phase locking is, the larger PLI will be. The PLI estimator was applied, in a pairwise fashion, to the corresponding signals filtered within a particular frequency band. The derived quantities were tabulated in an $[N \times N]$ matrix, in which an entry conveyed the strength of the functional coupling between a particular pair of recording sites. Such a matrix has a natural graph representation, called hereafter the “functional connectivity graph”, with the nodes being the recording sites and edges representing the in-between links weighted by the tabulated value. We adopted an appropriate methodology for estimating, for each frequency band independently, the duration (in number of cycles) of the window employed in the time-varying phase connectivity analysis (Dimitriadis et al. 2010b) (Table 1).

Trimming insignificant functional interactions

To detect significant connections, we utilized surrogate data to form a distribution of PLI-values for each electrode-pair separately that corresponded to cases in which there was no functional coupling (Lachaux et al. 1999). Only those functional connections that showed significant differences with respect to the distribution of PLI-values generated by a randomization procedure that corresponded to each electrode pair were considered. Because our analysis was based on a single sweep, we shuffled the time series of the second electrode for each pair. Finally, the original PLI values were compared against the emerged

baseline distribution (from surrogate data; Khadem and Hossein-Zadeh 2014) and this comparison was expressed via a P value with the threshold set at $P < 0.001$. Significance probabilities were corrected using the FDR method in order to correct for multiple comparisons (Benjamini and Hochberg 1995; Dimitriadis et al. 2012b). The expected fraction of false positives was restricted to $q \leq 0.01$. Graph edges, where the above criterion was not met, were assigned a zero-weighted link.

Estimating the topological properties of underlying networks

The trimmed FCGs were characterized based on the well known topological metrics of global and local efficiency, established for weighted graphs and defined below, with N representing the total number of nodes in the network, E representing the total number of edges and w_{ij} indicating the weight between nodes.

The global efficiency of the network

$$GE = \frac{1}{N} \sum_{i \in N} \frac{\sum_{j \in N, j \neq i} (d_{ij})^{-1}}{N-1} \quad (2)$$

is the inverse of the harmonic mean of the shortest path length between each pair of nodes and reflects the overall efficiency of parallel information transfer in the network (Achard and Bullmore 2007; Latora and Marchiori 2001). On the other hand, LE is understood as a measure of fault tolerance of the network, since it indicates how well the subgraphs exchange information when a particular node is eliminated (Achard and Bullmore 2007). Specifically, each node is assigned the shortest path length within its subgraph G_i

$$LE = \frac{1}{N} \sum_{i \in N} \text{nodal_}LE_i = \frac{1}{N} \sum_{i \in N} \frac{\sum_{j, h \in G_{i,j,h \neq i}} (d_{jh})^{-1}}{k_i(k_i - 1)} \quad (3)$$

where in k_i corresponded to the total number of spatial (first level neighbors) neighbors of the i -th node, while d denotes shortest path length.

Accessing small-world characteristics

The concept of “Small-World”, originally introduced by Watts and Strogatz in 1998, is strongly related to the clustering coefficient, C , and the characteristic path length L , of a given graph (Watts and Strogatz, 1998). Here, we accessed “Small-Worldness” by means of global and local efficiency. Global efficiency [see Eq. (1)] is inversely related to L (Latora and Marchiori 2001). Thus, a small-world network has a GE value that is lower than in a random network, while LE obtains a higher value. The

Table 1 Estimated number of cycles for each frequency band, condition and group based on the maximization of SW index

	Children		Adults	
	RS	AT	RS	AT
δ	2	2	2.5	2.5
θ	3	3	2.5	2.5
α_1	3	3	2.5	2.5
α_2	3	3	2.5	2.5
β_1	3	3	2.5	2.5
β_2	3	3	2.5	2.5
γ	3	3	2.5	2.5

RS resting state, AT arithmetic task

calculations of GE^{rand} and LE^{rand} were based on a randomization procedure where we permuted the edges of the functional networks (De Vico Fallani et al. 2007, 2008; Dimitriadis et al. 2010b). For each actual FCG, we generated 1,000 random networks (Achard et al. 2006) in which the original connectivity matrix was randomly permuted but without preserving the total strength corresponded to each node. By repeating for each random network the computations of Eqs. (2) and (3) and averaging across all the individual outcomes, the GE^{rand} and LE^{rand} were derived. The small-world indices $\gamma = LE/LE^{\text{rand}}$ and $\lambda = GE/GE^{\text{rand}}$ were then calculated for the FCG under study, and the ratio $SW = \gamma/\lambda$ was defined and served as our small-worldness index. This index exceeds 1 in the case of small-world networks (De Vico Fallani et al. 2008; Dimitriadis et al. 2010b).

Studying static and time-varying connectivity patterns

In the static approach, one single FCG was derived from the whole epoch. Before using signals in the predefined well-known frequency bands, we commenced the analysis by constructing FCGs from signals filtered within very narrow bands (of 1 Hz width) and centered from 1 to 45 Hz. We estimated the above mentioned metrics independently for each frequency bin, so as to provide a wider picture before narrowing down the subsequent analysis within a particular frequency range. Since the trends of developmental change in the results (reported in Section “[Static Network Analysis](#)” and see also S.1,2) were found almost equally-spread over the spectrum, we switched to the use of signals filtered within the standard frequency bands.

In the time-varying approach, a temporal-window of frequency-dependent width was employed in a sliding mode. Using a regular time step, the center of the window was moved forward, and the whole network connectivity was re-estimated based on the new signal segments leading to TVFCGs (Time Varying Functional Connectivity Graphs). We optimized the width of the window (number of cycles of the brain waves within the frequency band under study) independently for each frequency band and recording condition, based on the maximization of small-worldness (Dimitriadis et al. 2010b). That was considered a necessary algorithmic step, since each brain rhythm evolves on a different time scale. The end results of the time varying approach were the three 1D time series of network metrics, i.e. $LE(t)$, $GE(t)$ and $SW(t)$, as well as the 30D time series of local efficiency measurement at the nodal level [i.e. the time-indexed 30-tuples of $\text{nodal_}LE_i(t)$]. These vectorial measurements, reflecting the instantaneous state of network organization, were exploited subsequently so as to describe brain’s spectrum of functional organization and its dependency on task and age.

Mining network microstates (Netμstates) from nodal NMTS (nNMTS)

By studying the N-dimensional, time-indexed patterns $P(t) = [\text{nodal_}LE_1(t), \dots, \text{nodal_}LE_N(t)]^T$ from the localized efficiency-measurements, we managed to characterize the dynamic behavior of brain’s underpinning networks from the perspective of segregation and express the observed variability in a well-understood topographic format. In particular, we derived prototypical patterns (which corresponded to network microstates or Netμstates) and sketched the temporal evolution of network organization by identifying the dominating microstate for every latency. Below we briefly describe the algorithmic procedure for mining Netμstates, as adapted from a recent article (Dimitriadis et al. 2013a).

In order to summarize the network variations, at the level of group-analysis, we first collected the $P(t)$ patterns from all subjects (but independently for each age group, recording condition and frequency band) and formed the data-matrix P which was of size $[N_{\text{sensors}} \times N_{\text{Total}}]$, where N_{sensors} denotes the number of nodes (here 30) and $N_{\text{Total}} (= N_{\text{segments}} \cdot N_{\text{subjects}})$ is the overall number of signal segments for which a network LE pattern was defined. Then, using *Neural Gas* algorithm (an efficient algorithm that is known about being able to adapt to the complexity of input data manifold and encode it with almost negligible loss of information (Martinez et al. 1993)), we derived a small number k ($k \ll N_{\text{Total}}$) of 30D reference vectors or prototypes $\{\Pi_j\}_{j=1:k}$. These vectors were employed as the finite set of prototypes (or codebook) vectors $\{\Pi_j\}_{j=1:k}$ in a vector quantization scheme that encoded the patterns. Any data vector $P(t) \in P$ was described by the index of best matching among the reference vectors $\{\Pi_j\}_{j=1:k}$. For that assignment, the squared error $\|P(t) - \Pi_j\|^2$ was used as the distortion measure (expressing the error when replacing the $P(t)$ with the assigned codevector). Such a procedure subdivides the manifold in a number of submanifolds

$$R_j = \{P(t) \in P \mid \|P(t) - \Pi_j\| \leq \|P(t) - \Pi_i\| \forall i\}, \quad (4)$$

which are called Voronoi regions. Any data vector $P(t)$ falling in R_j can be coded (i.e. represented) by the corresponding reference vector Π_j . This vector-quantization scheme realizes the “nearest-codevector” rule and is based on (squared) Euclidean distance. The fidelity of the adopted encoding scheme was measured by the normalized distortion error defined as follows

$$n_{\text{Distortion}} = \frac{\sum_{t=1}^{N_{\text{Total}}} \|P(t) - P_{\text{rec}}(t)\|^2}{\sum_{t=1}^{N_{\text{Total}}} \|P(t) - \bar{P}\|^2}, \quad \bar{P} = \frac{1}{N_{\text{Total}}} \sum_{i=1}^{N_{\text{Total}}} P(t) \quad (5)$$

where the matrix P_{rec} contains the approximated timeseries produced by replacing the original patterns with the nearest prototypes. The smaller the $n_{\text{Distortion}}$, the better the encoding. This index gets smaller with the increase of k . Since the vector-quantization step was critical for the subsequent derivation of network microstates, we wanted the mined prototypes to be of equal importance across all groups/conditions/frequency bands. To this end, k was set at the smallest value with which $n_{\text{Distortion}}$ dropped below 4 %. This means that its selection was adapted to the variations in the input data (we repeatedly apply the Neural Gas algorithm with increasing k and identify the first one achieving the desired fidelity).

Results

Network analysis

Static network analysis

The results from the static network analysis based on narrow-band (1-Hz bin) filtered signals are provided as supplementary material (see Fig. S.1). Since this part of analysis did not reveal any additional information with respect to the standard analysis based on conventional frequency bands, we have included here results from the latter approach. Figures 1 and 2 present in direct contrast the network metrics during resting state and mental calculations correspondingly. Apart from indicating the level of the three metrics (global efficiency, local efficiency and small-worldness) for both age-groups, we also indicate the results from their statistical comparison. We assessed the significance of their differences, observed at group-level, by means of Wilcoxon rank-sum test (WRS-test). The adopted statistical procedure revealed systematic and statistically significant inter-group differences ($P < 0.001/7$;

Bonferroni corrected). Functional integration, as captured via GE descriptor, is higher in adulthood within δ , θ , β_1 , γ during resting state and within δ , θ , β_2 , γ bands during the performance of arithmetic comparisons (Figs. 1a, 2a respectively). The opposite holds for functional segregation, since LE descriptor was higher in children within α_1 , α_2 , β_1 , β_2 bands for the resting state (Fig. 1b) and within all bands except δ for the comparison task (Fig. 2b). Small-worldness is significantly higher in children for both recording conditions and for every frequency band (Fig. 1c, 2c). Interestingly, the highest GE and LE values were observed, for both conditions, in δ band.

Repeated-measures ANOVA with factors the network metrics (LE, GE, and SW) estimated from various frequency bands didn't reveal any important developmental factor related with network-metric-frequency bands in both resting-state condition and arithmetic task.

Time-varying network analysis

To accommodate the non-stationarities of EEG signal and further put our work in the perspective of the brain's task-related functional connectivity reconfiguration, we studied the previous three metrics in the setting of time-varying network analysis. Two examples (one from a child and one from a young adult) of how these metrics evolving in time have been included in the rightmost half of Fig. 3.

The traces (NMTS) correspond to connectivity patterns estimated from signals filtered within γ -band and clearly indicate a “jittering” functional connectivity, with fluctuations following the characteristic oscillations of the particular frequency band. In the leftmost half of Fig. 3, we have included Group-averaged NMTS^{GE} – NMTS^{LE} and NMTS^{SW} for γ -band. Due to averaging the within-subject fluctuations have been smoothed out, and hence the most important information carried out by these traces (and the overplotted within-group dispersions) lies in their level.

Fig. 1 Group-averaged results from static network analysis carried out using signals within particular frequency bands. **a** Global efficiency (GE), **b** local efficiency (LE) and **c** small-world (SW)

metrics for resting state. With ‘asterisk’ are denoted comparisons resulted in significant differences ($P < 0.0001/7$ based on Wilcoxon test, Bonferroni corrected)

Fig. 2 Group-averaged results from static network analysis carried out using signals within particular frequency bands. **a** Global efficiency (GE), **b** local efficiency (LE) and **c** small-world (SW)

metrics for comparison task. With ‘asterisk’ are denoted comparisons resulted in significant differences ($P < 0.0001/7$ based on Wilcoxon test, Bonferroni corrected)

Fig. 3 Network metrics (GE, LE and SW) from time-varying network analysis applied to signals filtered within γ -band. Group—averaged results are shown in the two leftmost columns, while single-subject data in the two rightmost columns. Each row corresponds to a particular metric, while columns are associated with recording

conditions. In the case of group-averaged results, we are indicating the $m \pm std$ (mean value $\pm$ standard deviation) range of values for the metric as computed for the static counterparts (asterisk denotes $P < 0.0001/7$ based on Wilcoxon test, Bonferroni corrected). (Blue—children, red—adults)

There is a noticeable difference not only between age groups (children vs. adults), but also between tasks (rest vs. mental arithmetic). This observation is common to all frequency bands. We have included, as supplementary material (see supplementary Fig. S.2–4) the group-averaged traces for every frequency band and network metric.

An important observation of this part of our study was that by adopting a dynamic network analysis the important trends of functional organization (segregation, integration and small-worldness), in both age groups, and all frequency bands were intensified with respect to the static analysis mode (see Figs. 1, 2 and Fig. S.1–4). Moreover, the higher small-world character of functional networks in childhood

was reconfirmed with the dynamic network analysis (Fig. S.4). Finally, we need to mention here that no significant inter-frequency and inter-task differences were detected based on the level of $NMTS^{SW}$ (Fig. S.4) (or the SW index from static network analysis Figs. 1, 2c).

To detect task-related and age-related changes and examine the role of frequency-bands, we adopted Wilcoxon rank sum test. Its non-parametric nature is an advantage over more conventional tests (like t test). The application of Wilcoxon rank sum-test (WRS-test) to $NMTS^{GE}$ & LE measurements, from resting state and mental arithmetic task, revealed a significant ($P < 0.0001$) task-related increase in the value of both metrics in all

frequency bands with the exception of δ band. Frequencies can be ranked according to the mean level of $\text{NMTS}^{\text{GE\&LE}}$ distribution. In adults, the ordering of NMTS^{GE} -related level indicated that in both conditions the frequency bands can be ranked according to the global organization (NMTS^{GE}) as follows: $\alpha_1 > \alpha_2 > \theta \approx \gamma > \beta_1 > \beta_2 > \delta$. On the other hand the ranking of frequency bands, based on NMTS^{LE} (i.e. local organization), was: $\alpha_1 > \alpha_2 > \gamma > \theta > \beta_1 > \beta_2 > \delta$ for resting state and $\alpha_1 > \alpha_2 \approx \theta > \beta_1 \approx \gamma > \beta_2 > \delta$ during the comparison task. In both groups, the difference between resting-state and arithmetic task was an increment in the level (i.e. group-means) of GE and LE on each frequency band.

Netstates: a local organization repertoire and its timecourse

The timeseries of network metrics revealed a very active, functionally re-configurable brain. In the last step of our analysis, we attempted to provide a synopsis of the network organization dynamics and its (task-related and frequency-dependent) variations, in a format that would facilitate inter-group comparisons. To this end, we mined prototypical patterns defined at the level of nodal organization (based on local efficiency descriptor), independently for each frequency band, recording condition and age group. We then studied the timecourse of their appearance and quantified their proportionality.

Figure 4 exemplifies these data-analytic steps using network organization patterns associated with brain activity, in γ -band, from adults performing the comparison task. A few examples of nodal LE timeseries are shown in Fig. 4a as images, in which columns correspond to time-dependent patterns of network organization. After forming the ensemble of these patterns (across subjects), we derived three prototypical patterns [i.e. Netstates; see Section “Mining network microstates (Netstates) from nodal NMTS (nNMTS)”] which are shown in the topographic format at the center of Fig. 4. In Fig. 4b we have visualized the comparisons between all the possible pairs of patterns in the ensemble. Figure 4c resulted from the reorganization of the previous image based on the groups formed by assigning the patterns to the nearest Netstate. It was of great interest to examine the time evolution of these microstates. Some indicative examples are provided in Fig. 4d. Using the color associated with each microstate we draw the time-dependent measurements of the index (Global Local Efficiency Power)

$$\text{GLEP} = \sqrt{\frac{\sum_{i=1}^N (\text{LE}_i - \overline{\text{LE}})^2}{N}}, \quad \overline{\text{LE}} = \frac{1}{N} \sum_{i=1}^N \text{LE}_i \quad (6)$$

defined in analogy to Global Field Power (GFP), which is used in conventional microstate analysis (Lehmann 1990). The shown time courses are indicative of the metastability nature of functional organization patterns. Short-lived organization patterns are formed and give their place to others randomly. It must be noticed here that despite the seemingly random character regarding the switching from one organization pattern to the next, only 3 Netstates were enough to summarize the observed variability at a negligible loss of information ($n_{\text{Distortion}} < 0.04$; see Section “Mining network microstates (Netstates) from nodal NMTS (nNMTS)”). We can consider each Netstate as a discrete Markov stable state and the whole symbolic sequence that summarize the evolution of these Network Microstates as Markov Chain (Fig. 4d).

The mined Netstates are all presented in Fig. 5. They constitute a discrete spectrum, or a repertoire, of network organization that characterizes each age-group during a recording condition. Assigned to each microstate is a percentage value expressing its relative frequency of appearance. To objectively compare Netstates between age-groups and conditions for each frequency band, we expressed the dissimilarity in a scale regardless the condition or the group. In this way, the Netstates for both groups and conditions were presented in a common space the geometry of which could be provided using a dimensionality reduction technique (details can be found in (Laskaris and Ioannides 2002; Laskaris et al. 2004)). The CS (Cosine Similarity) metric for all possible comparisons between the Netstates were tabulated in a distance matrix DCS. Hence, a single entry of this matrix quantified the difference between two different Netstates (as 1-cosine similarity). The lower its value, the more alike are the two Netstates. Based on the tabulated measures, by means of classical Multi-Dimensional Scaling (MDS)² techniques, we embedded the different Netstates as distinct points in a reduced 2D space. In this space, the emerging inter-point distances approximated well (as indicated by the computed stress-index that quantifies the discrepancy between the original and approximated distances) all the tabulated comparisons. The purpose of MDS is to provide a visual representation of the pattern of proximities (i.e., similarities) among Netstates across conditions/age-groups/frequency-bands. MDS configures the Netstates as points on a 2D map, such that Netstates that are perceived to be very similar to each other are placed near each other on that map (and, conversely, Netstates that are perceived to be very different from each other are placed far away from each other on the 2D map). This, in turn, enabled the direct visual comparison of groups and conditions. Interestingly, the $\text{Netstates}_{\text{LE}}^{\delta, \beta_2, \gamma}$ of the two age-groups were found to occupy different regions in the 2D

² MDS was implemented via “cmdscale” function in Matlab.

Fig. 4 Encoding the time-indexed network states as a sequence of network microstates: an example using signals from adults, recorded during the performance of arithmetic comparisons and filtered within the γ -band. **a** Vectorial Time Series of Local Efficiency measurements (nNMTS^{LE}) for three subjects. **b** Image representation of the grand matrix (GM) containing all the pairwise comparisons (via cosine similarity) among the N_{Total} vectors $P(t)$ representing all possible network states (for all subjects and signal segments).

c Reordered version of the GM derived based on the vector-quantization step and with respect to the three prototypes seen below. **d** The time-evolution of network microstates: the instantaneous “variance” of nodal LE measurements has been drawn using the microstate-specific colors so as time-intervals of constant microstate to be readily recognized. (GLEP global local efficiency power, CS cosine similarity, LE local efficiency, Netustates network microstates)

display (Fig. 6). In contrary, the $Netustates_{LE}^0$ were found intermingled.

In an attempt to describe the temporal behaviour associated with the Netustates (seen in the fluctuations of Fig. 4d), we adopted a Markov chain (MC) modeling of the dynamical system giving rise to the observed network-organization patterns and counted the transitions between the different states (Netustates). More specifically, we introduced the simple measure of Transition Probability (TP):

$$TP = \frac{\#transitions}{length(ST) - 1} \quad (7)$$

where ST refers to the symbolic time series with symbols denoting the Netustates. TP served as an index that reflects brain’s “mobility” tendency in terms of network-reorganization and enabled as to characterize age-groups and recording-conditions across the frequency bands.

The corresponding results, included in Fig. 7, show a clear tendency common in both conditions and groups. TP steadily increases with frequency. Based on WRS-test, we detected statistical differences of TP values between

conditions for each of the frequency band ($P < 0.001$, Bonferroni corrected $P^* = p/7$). TP values were statistically higher from δ to γ for CH^{AT} compared to the rest of conditions. Additionally, TP values were statistically higher from δ to γ for CH^{RS} compared to AD^{RS} and AD^{AT}, while AD^{AT} and AD^{RS} were statistically differed from δ to γ (AD^{AT} > AD^{RS}) (CH stands for children, AD for adults, AT for arithmetic task and RS for resting state).

Discussion

Using surface EEG signals and related functional connectivity estimates, we examined developmental changes in the network organization as these were reflected in brain activity at rest and during a comparison task. We compared the outcomes from static and time-varying network analysis using standard metrics that quantify functional segregation (local efficiency—LE) and integration (global efficiency—GE) in complex networks. Apart from inter-group comparisons, we were interested in identifying task-related changes in network organization and also

Fig. 5 A topographic representations of network microstates (netustates) in different frequency bands and for each group and task based on NMTS^{LE}. The *percentage* attached to each microstate expresses the fraction of network organization patterns associated with it (in the ensemble formed from all subjects and signal segments)

characterizing the role of frequency. Based on activity filtered within standard frequency bands and adopting the static approach, we detected significant inter-group differences in both conditions, but not task-induced differences. On the other hand, time-varying network analysis not only improved inter-group discrimination, but also enabled the detection of task-related differences by enhancing the functional segregation/integration trends in children/adults respectively. Moreover, the small-world network (SWN) character was found higher in children (based on both static and time-varying approach) and this can be suggestive of immaturity in their functional networks. Finally, it was the rate of transitions among network states that mostly reflected the developmental and, in particular, task-induced differences in functional connectivity dynamics. Regarding the detection of differences between resting state and mental arithmetic, it has to be mentioned that the delivered

arithmetic task was considered by all subjects as one easy to perform.

Scrutinizing functional connectivity based on phase interactions was a key concept in our work. A high number of studies have already showed that phase synchronization in the human EEG bears important information regarding cognitive processes. Phase coupling, across brain regions, during resting and cognitive processes reflects highly specific functions (Varela et al. 2001; Sauseng et al. 2004, 2005a,b, 2006; Dimitriadis et al. 2010a, b, 2012a, b, c, d; for a review see Sauseng and Klimesch 2008). Often phase coupling is much more meaningful and informative than other parameters, such as power estimates, traditionally employed in EEG studies. Amplitude-related measures simply reflect the level of general (rather unspecific) brain activation. In the present study, signal power showed important developmental changes, for both recording

Fig. 6 Visual comparison within the “approximate” space of all network microstates (from every age-group/condition/frequency band). In this scatter-plot, the similarity between two Netstates is reflected by their proximity. The size of each coloured triangle/circle

reflects the proportion of network organization patterns associated with it (see Fig. 5). (*SI* stress index, *CH* children, *AD* adults, *AT* arithmetic task, *RS* resting state)

conditions (see Supp. Material S.13), in the slow frequency bands (δ , θ and α_1) only.

In functional connectivity studies, it is important to address the degree of connectivity that can also be explained by volume conduction. Regarding the justification of our approach, the choice of phase-lag index (PLI; Stam et al. 2007b) has to be explained. PLI is an estimator of functional coupling that has been employed in many studies and simulated explorations. It is only sensitive to phase synchronization at nonzero phase lags, and its robustness against volume conduction effects has been demonstrated (Stam et al. 2007b).

Since the quantification of phase interactions is prone to the presence of artifactual signals of biological origin when they are corrupting simultaneously multiple recordings sites, we repeated the functional connectivity measurements using average-referenced, ICA-cleaned data. As a

part of this study, we compared the estimates of brain’s network (re)organization as these were realized using two distinct versions of the same EEG-dataset (see supp. material). The interest in such an investigation has been recently raised, based on a simulation study that questioned the impact of ICA-denoising in subsequent phase-related measurements (Montefusco-Siegmund et al. 2013). A possible quantification of both volume conduction and ICA effects on M/EEG connectivity estimates could be by producing surrogates based on “ICA-free” multichannel recordings and applying to “ICA-corrected” data (Khadem and Hossein-Zadeh 2014).

The main methodological innovation of the present study was the treatment of NMTS as time-indexed multivariate observations. Using an appropriate pattern-analytic framework Dimitriadis et al. 2013a), we estimated that network-organization dynamics can be described by means

Fig. 7 Averaged across subjects TP estimates, regarding the $Net\mu states_{LE}^{\delta, \beta 2, \gamma}$ derived independently for each frequency bands. The size of circles and triangles indicates the corresponding standard deviations (std) within each age-group and condition. (CH children, AD adults, AT arithmetic task, RS resting state)

of small number of recurrent states ($Net\mu states_{LE}$) defined according to segregation characteristics. The comparison of these (group-based, task-related and frequency-dependent) network microstates revealed important developmental trends (Fig. 6), while their transitivity estimated with TP_{LE}^{LE} (Fig. 7) proved to be a novel sensitive developmental biomarker in the case of both tasks. Interestingly, the corresponding transitivity based on global-efficiency (TP_{GE}^{GE} ; see S.5) did not appear as an index of similar sensitivity.

The ordering of brain rhythms based on averaged values of $NMTS_{LE}^{LE}$ and $NMTS_{GE}^{GE}$ (S.2-S.3) for children and adults respectively revealed an important behavior for α sub-bands. $\alpha 1$ and $\alpha 2$ sub-bands showed the highest values in both tasks and in both groups. Moreover, GE and LE estimated in α -subbands captured and highlighted brain networks in children as more functionally segregated compared to adults while brain networks of adults are more functional integrated compared to children. The above tendency was prominent at both resting-state and during the arithmetic task. A previous study, based on the spatial structure of α rhythm, had showed a similar trend of global correlation in adults and local correlation in children (Srinivasan 1999). Another significant trend was the increment of $NMTS_{LE}^{LE}$ level in children and of the $NMTS_{GE}^{GE}$ level in adults, during the comparison task compared to the resting-state. The above findings were also identified in the case of average-rereferenced, ICA-cleaned version of the data (see supp. material).

Brainwaves within standard EEG-bands have been extensively used so as to derive the “electrophysiological signature” of various cognitive functions. The distinct oscillatory rhythms are usually studied in isolation, and it is only recently that cross-frequency phenomena are put under examination. The embedding of all prototypical $Net\mu states$ (originally shown in Fig. 5) in a common 2D display (Fig. 6), it was a step towards the study of the frequency bands in parallel and enabled multiple visual

comparisons. Interestingly, the $Net\mu states_{LE}^{\delta, \beta 2, \gamma}$ of the two age-groups were found to occupy different regions in the 2D display (Fig. 6). On the contrary, the $Net\mu states_{LE}^{\theta}$ were found intermixed. Based on the topographical representation of nodal LE for each prototypical $Net\mu state$ (Fig. 5), we observed a δ -related frontal activation in children during both recording conditions, and a central activation in adults. Brain activity in δ -band has been linked to math tasks (Dimitriadis et al. 2010a) and also to memory encoding and retrieval (Ekstrom and Watrous 2013). Moreover, a $\beta 2$ -related frontal activation was observed in children for both conditions, while a parieto-occipital activation was observed in adults. In general, the role of β -band brainwaves is less clear. In a comprehensive review, Engel and Fries suggested that β -band activity might be associated to maintenance of motor actions and cognition (Engel et al. 2001). Regarding γ -band, the activation was located centrally in children for both conditions, while a frontal/parietal increment in functional segregation was revealed in adults during rest/comparison-task correspondingly. In general, γ -band oscillations have been related to attention, stimulus selection memory formation and conscious awareness (Engel et al. 2001; Fries 2009; Mantini and Vanduffel 2013). Finally, the θ -activity has been linked to various cognitive tasks requiring working memory and attention brain resources (Klimesch et al. 2005; Knyazev 2007; Tesche and Karhu 2000). In the present study, the arithmetic task was such that the demands for working memory were not high and for that reason $Net\mu states_{LE}^{\theta}$ were found to be similar across groups. Despite the topographic similarity, θ -related TP index revealed significant task and group related differences (see Fig. 7).

According to Neural Efficiency Hypothesis (NEH), a subtler activation is needed for responding to a task when the brain networks are more mature. NEH was supported by many experimental studies. Lower local activations were detected under WM load in high performing individuals with fMRI (Rypna et al. 2002). Limited changes in local activation were detected using EEG signals and ERD (Event Related Desynchronization) in the alpha band (Graber et al. 2004). Reduced trends towards SWN organization were found in individuals with higher education (with respect to lower educated individuals) during a WM task (Micheloyannis et al. 2006) it was considered easier for them to respond and hence there was reduced network reactivity. The reported results are in accordance with our findings about higher SWN in children and increased transitivity during the arithmetic task (which was actually not a highly demanding one).

By adopting a static functional connectivity approach based on brain activity filtered within standard frequency bands, we detected significant inter-group differences in

both conditions, but not task-induced differences (Figs. 1, 2). The application of repeated-measures ANOVA, with factors the network metrics (LE, GE, and SW) estimated within the defined frequency bands, did not result to any suggestion about the importance of the “developmental factors” in either task.

In complex systems like the human brain, space and time are interwoven. Only partial information can be gained by treating them separately. Any static approach to functional connectivity analysis focuses on the spatial network organization and collapses the variations in the time domain. To incorporate the spatiotemporal nature of brain activity, especially from EEG/MEG recordings, a novel analytical framework should be adopted. Here, we carried out an elaborate study of the dynamics of functional segregation patterns and demonstrated that the underlying network undergoes transitions with frequency-task-age dependent rate between (a restricted number of—Markov States) microstates (Netjstates). The proposed TP measure is a valuable tool for characterizing and comparing the symbolic (brain) dynamics between conditions and groups (Fig. 7). The network transitions between a restricted number of stable segregation patterns (Fig. 7), but integration pattern (GE; S.5), considered as distinct states (network-level microstates) provided a valuable developmental biomarker in both resting-state and mental task (Fig. 7). The finding of higher TP index for children, in all frequency bands, can be interpreted as an indication for higher effort. The proposed TP developmental biomarker is insensitive to the selection of the number k of prototypical microstates. The TP-indices estimated for $k = 4$ can be found as supplementary material (S.6). While differences (no statistical significant) can be detected compared to TP index based on optimized $k = 3$, there are no major qualitative changes regarding the characterization of transition dynamics. Finally, we need to stress here that the potential of TP-index as marker of developmental and task-induced changes was found unaffected by the change of reference-montage and ICA-denoising (see Fig. S.11 and supp. Section 4). For further comparison of both static and time-varying network analysis between the two approaches an interested reader can see the supplementary material.

The electrophysiological signature of a brain function can include one or more EEG frequencies at resting-state (Mantini et al. 2007; Palva and Palva 2012) and during arithmetic tasks (Dehaene 1996, 1997; Micheloyannis et al. 2005, 2009; Dimitriadis et al. 2010a). Our findings about TP index may be related to the deactivation of the default mode network (δ -band—Dimitriadis et al. 2010a), the manipulation of the information in memory (θ -band—Klimesch 1999; Jensen and Tesche 2002), attentional processes (α_1 -band; Klimesch 1999), the mental representation of number quantities (α_2 -band—Klimesch 1999; Klimesch et al. 2005;

Dehaene 1996, 1997; Dehaene and Cohen 1997), higher cognitive functions (β -band—Wrobel et al. 2007) and encoding/retention of information independent of sensory modality (γ -band—Tallon-Baudry and Bertrand 1999; Herrmann et al. 2004).

Brain complex networks have a small-world topology characterized by dense local connections (high cliquishness) between neighboring nodes and short path lengths between any pair of nodes due to the existence of only a few long-range connections (Basset and Bullmore 2006; Micheloyannis et al. 2005, 2006, 2009; Stam et al. 2007a, b; Dimitriadis et al. 2010a, b). Small-world is an attractive model for characterizing anatomical and functional networks, since it encapsulates both segregation and integration tendencies (Basset and Bullmore 2006). Recently, rich-club architecture has gained great attention among the neuroscience community as a potential alternative model, which complies with current empirical findings and theoretical expectations (according to which high-degree nodes tend to connect densely among themselves (van den Heuvel et al. 2012). In a recent developmental study (Grayson et al. 2014), based on structural and functional diffusion-weighted MRI, the authors demonstrated a significantly greater tendency for a rich-club architecture in adults. As a part of this study, we examined our data, also, from the perspective of rich-club architecture, but we did not succeed in detecting such a network-organization tendency in both static and time-varying networks. This failure could be attributed to the low number of EEG sensors in our recordings.

Small-world network level (SWN) was higher in children in both static and time-varying approach (Figs. 2, 3c and S.4) and across frequency bands. This finding during the comparison task can be supported by the NEH which suggests that in adults the connections between brain areas engaged in working memory tasks are not as well-organized (in a SWN sense) as in children (Micheloyannis et al. 2006). The development of functional networks appears to progress from a localized mode of organization (segregation) to a more distributed mode (integration) (Fair et al. 2009; Sporns 2010). Additionally, the higher values of TP for children compared to adults can be supported from NEH (Fig. 7).

A recent study based on EEG resting-state recordings through the lifespan uncovered the transition from children randomness brain network to a more mature organization of young brains via network analysis based on graph parameters C (local clustering) and L (global path length) (Smit et al. 2012). Our findings in this study are indicative of easier and less SWN organization needed in adults in both resting-state (Boersma et al. 2011, 2012; Smit et al. 2012) and during the comparison task. In addition, the development of functional networks appears to progress from a local or segregated to a more distributed or

integrated mode of organization (Fair et al. 2009; Sporns 2010). The above tendencies were illustrated in the current study with higher functional segregation (local efficiency—LE) in children and higher integration (global efficiency—GE) in adult complex networks across tasks and frequency bands.

Number comparison is an easy automatic response, which does not need to be retrieved but to calculate (Grabner et al. 2009). A mental representation of number magnitude emerges without explicit teaching in young children. Hence, the brain does not need to convert digits to a verbal format in order to compare them (Dehaene 1996, 1997; Dehaene and Cohen 1997). Functional brain imaging confirms that the comparison of numerical magnitudes is a nonlinguistic activity that relies on the right hemisphere as much as on the left. Both hemispheres can recognize digits and translate them into a mental representation of quantities to be compared (Dehaene 1996, 1997; Dehaene and Cohen 1997). It has been suggested that number comparison depends largely upon a core system responsible for numerical representations (Feigenson et al. 2004). Our study demonstrated age-related differences, which are clearly reflected in the rate of functional reorganization (see Fig. 7).

The substrate of neural dynamics includes rhythms within a wide range of frequencies, which are transiently coupled so as to subserve the successful completion of a particular task. This coupling is by far no trivial and influenced by many internal factors like attention. The theory of Coordination Dynamics proposes a mechanism, called metastability, which is a mix of segregation and integration. Brain regions' tendencies express their individual autonomy via a specialized function (segregation) and simultaneously participate in global coordination (integration). The study of metastability must be treated within a spatiotemporal perspective (Fingelkurts and Fingelkurts 2001, 2004; Tognoli and Kelso 2014). In a recent study, we defined *functional connectivity microstates* (FC μ states) in an attempt to describe spatiotemporal connectivity dynamics (Dimitriadis et al. 2013a). In this study, we went a step further by studying metastability via Net μ states based on LE (segregation) and GE (integration). Our analysis illustrated that the transitivity between (a restricted repertoire of) Net μ states^{LE} is a valuable developmental biomarker across frequency bands and in both tasks. Finally, a pool of descriptors can emerge from the evolution of “network-level microstates” that can potentially serve as reliable biomarkers of diseases related with brain dynamics and/or may be used for monitoring medical treatment/brain stimulation/neurofeedback.

The *Dynome* is an emerging research field (Kopell et al. 2014) that is expected to complement the intensively active area of brain connectomics, by incorporating time in the analysis. Among the most recent characteristic examples of

this trend are the two following works (Jamal et al. 2014; Zoltowski et al. 2014), which also build over the concept of time-varying functional connectivity patterns and, hence, bear some methodological similarities with the presented work. Additionally, the *Dynome* project should pay attention to the “electrophysiological and anatomical signature” of a cognitive function (e.g. working memory is located over frontal brain areas and is expressed mainly within θ frequency; Dimitriadis et al. 2014) and also to the understanding of brain dynamics in both spatial and temporal scales through dynamics (dynamic + connectomics) which will drive new understanding of brain function and dysfunction in cognition. Many have hypothesized that autism and schizophrenia are associated with pathological patterns of neural connectivity, or “connectopathies”. The application of dynamic complex network analysis can reveal functional connectivity dynamics, and may contribute to the detection of abnormalities, associated with dynopathies (dynamic + connectopathies) in network (re)organization.

Acknowledgments This research was partially funded by AUTH research committee (Grant 50141).

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