The effect of epoch length on estimated EEG functional connectivity and brain network organization

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Running Title

Effect of epoch length on EEG networks

Keywords

EEG; Epoch length; duration; time-window; Functional connectivity; Brain networks; Resting-state; Minimum spanning tree.

Abstract

Objective. Graph theory and network science tools have revealed fundamental mechanisms of functional brain organization in resting-state M/EEG analysis. Nevertheless, it is still not clearly understood how several methodological aspects may bias the topology of the reconstructed functional networks. In this context, the literature shows inconsistency in the chosen length of the selected epochs, impeding a meaningful comparison between results from different studies.
Approach. The aim of this study was to provide a network approach insensitive to the effects that epoch length has on functional connectivity (FC) and network reconstruction. Two different measures, the phase lag index (PLI) and the Amplitude Envelope Correlation (AEC) were applied to EEG resting-state recordings for a group of eighteen healthy volunteers using non-overlapping epochs with variable length (1, 2, 4, 6, 8, 10, 12, 14 and 16 seconds). Weighted clustering coefficient (CC_w), weighted characteristic path length (L_w) and minimum spanning tree (MST) parameters were computed to evaluate the network topology. The analysis was performed on both scalp and source-space data.
Main results. Results from scalp analysis show a decrease in both mean PLI and AEC values with an increase in epoch length, with a tendency to stabilize at a length of 12 seconds for PLI and 6 seconds for AEC. Moreover, CC_w and L_w show very similar behaviour, with metrics based on AEC more reliable in terms of stability. In general, MST parameters stabilize at short epoch lengths, particularly for MSTs based on PLI (1-6 seconds versus 4-8 seconds for AEC). At the source-level the results were even more reliable, with stability already at 1 second duration for PLI-based MSTs.

Significance. The present work suggests that both PLI and AEC depend on epoch length and that this has an impact on the reconstructed network topology, particularly at the scalp-level. Source-level MST topology is less sensitive to differences in epoch length, therefore enabling the comparison of brain network topology between different studies.

Introduction

In the last decade, the use of tools derived from graph theory and network science in resting-state EEG and MEG analyses have revealed fundamental mechanisms of normal and pathological functional brain organization (Stam 2014; Bullmore & Sporns 2009; Sporns 2013). Nevertheless, it is still not clearly understood how several methodological choices may affect the topology of reconstructed functional brain networks, eventually hindering the meaningful comparison of results from different studies. In a recent review, van Diessen and colleagues discussed the methodological choices in EEG and MEG resting-state analysis that affect the reconstruction of functional network topology (Van Diessen et al, 2015), including the duration of the time-window over which functional connectivity is estimated.

Previous studies have shown that estimates of functional connectivity are biased by epoch length and that the severity of this bias varies for different connectivity metrics (Bonita et al. 2014; David et al. 2004; Chu et al. 2012; Honey et al. 2007; Vinck et al. 2011). Together with the observation of inhomogeneity in the length of EEG epochs across resting-state functional connectivity studies, these aspects may severely impede the meaningful comparison of results between studies. Furthermore, these biases may have direct consequence for the estimation of network topology (van Wijk et al. 2010). Approaches that allow for the characterisation of brain networks, whilst avoiding arbitrary choices, are therefore required. Recently, it has been shown that the minimum spanning tree (MST), a backbone of the original weighted network, enables an unbiased comparison between networks (Tewarie et al. 2015; Stam et al. 2014), although it is unknown how epoch length affects the MST.

In this study we aimed to provide a network approach insensitive to the effects that epoch length has on functional connectivity (FC) and network reconstruction. We therefore first demonstrated the effect of different durations (in the range of commonly selected EEG segments for resting-state analysis) on two well-known and widely used connectivity measures: the phase lag index (PLI) (Stam et al. 2007) and the Amplitude Envelope Correlation (AEC) (Brookes et al. 2011;

Hipp et al. 2012). These measures capture two distinct types of intrinsic coupling (one arising from phase coupling, the other from fluctuations of signal envelopes) that seem to play a role in defining the interactions in on-going brain activity (Engel et al. 2013; Guggisberg et al. 2015). Furthermore, we investigated the effect of epoch length on MST topology, as well as on some commonly used network measures: weighted clustering coefficient (CC_w) and weighted characteristic path length (L_w). We hypothesized that traditional approaches to network representation (CC_w and L_w) would be strongly affected by the biases in FC estimates that are due to epoch length, since the strength of connections are taken into account in weighted network analyses. In contrast, the MST was expected to be less affected as it is based on the rank order of the connections rather than the (biased) absolute values.

Furthermore, many resting-state EEG studies still use activity recorded at the scalp to estimate patterns of functional connectivity and brain network organization. However, in this case several factors (e.g. field spread and volume conduction effects) can affect the reliability of the estimated parameters. Although these problems cannot simply be overcome by using source analysis, several methods that project scalp signals to the underlying sources enable a more straightforward interpretation of results (in terms of relation to anatomy) (Michel et al. 2004). In order to assess differences between these two approaches, the analyses were performed on both scalp EEG and sources-reconstructed time-series.

Material and Methods

Participants.

Eighteen healthy volunteers (13 male and 5 female; age = 38.6 ± 14.0 years) were enrolled in the present study. Informed consent was obtained prior to the recordings. The present study was approved by the local ethics committee.

Recordings.

EEG signals were recorded using a 61 channels EEG system (Brain QuickSystem, Micromed, Italy) in eyes-closed resting-state condition. Recordings were acquired in sitting position in a normal daylight room; a dimly lit and sound attenuated room and supine position were avoided to prevent drowsiness (Van Diessen et al, 2015). Signals were digitized with a sampling frequency of 1024 Hz, low-pass filter at 70 Hz, the reference electrode was placed in close approximation of the electrode POz and all signals were digitally offline re-referenced to the common average reference. For each subject three artifact-free segments of 32 seconds (32.768 samples) were selected for the analysis. EEG segments were chosen as the first after the start of the recording (Van Diessen et al, 2015). Since it has been shown that EEG frequencies above 20 Hz mainly reflect myogenic artifacts (Muthukumaraswamy, 2013; Pope et al, 2009; Whitham et al, 2007), EEG signals were off-line band-pass filtered between 1 and 20 Hz using two-way least-squares filtering method as implemented in EEGLAB with *fir1* filter type. Data were converted to EDF format and all analyses were performed using Matlab (MATLAB R2010a, The MathWorks Inc., Natick, MA), EEGLAB (version 13.1.1b) (Delorme et al, 2004) and the Brain Connectivity Toolbox (version 2014_04_05) (Rubinov et al, 2010).

Protocol.

To study the effect of epoch length on functional connectivity and brain network organization, the three segments were sub-divided in non-overlapping epochs with variable length of 1, 2, 4, 6, 8, 10, 12, 14 and 16 seconds. All the results reported in the study refer to the use of 6 epochs. Moreover, in order to investigate the effect of sample frequency, the analyses were also performed on the same dataset after down-sampling to 128 and 256 Hz (see Supplementary material).

Source reconstruction.

In order to explore differences between signal-space and source-space, the analysis was also performed on source-reconstructed time-series. For this, a head model was generated using a symmetric boundary element method in OpenMEEG (Gramfort et al, 2010; Kybic et al, 2005); the head model was based on a default anatomy derived from the MNI/Colin27 brain (Collins et al. 1998). Sources, and their time-series, were reconstructed using weighted Minimum Norm Estimates (wMNE), which allows compensating for the tendency of MNE to favour superficial sources (Eddy et al, 2006; Hämäläinen et al, 1994; Lin et al, 2004). To avoid differences between scalp- and source- analysis due to differences in network size, source-reconstructed time-series were projected onto 64 ROIs (regions of interest) defined by the Desikan-Killiany atlas (Desikan et al, 2006), following which time-series within the same region were averaged (after flipping the sign of sources with opposite directions). See Supplemental Material for a list of the ROIs. All the analyses were performed using the Brainstorm software (version 3.2) (Tadel et al, 2011).

Functional connectivity.

Functional connectivity was estimated using two different measures: the Phase Lag Index (PLI) (Stam et al, 2007) and the Amplitude Envelope Correlation (AEC) (Brookes et al. 2011; Hipp et al. 2012). The PLI quantifies functional connectivity on the basis of phase-relationships, whereas the AEC detects amplitude-based coupling among brain signals. Before estimating the correlation between amplitude envelopes (using the absolute value of the analytical signal) the time-series were orthogonalized by means of linear regression analysis (Hipp et al. 2012; Brookes et al. 2011), in order to remove trivial correlations that are due to field spread or volume conduction (leakagecorrected AEC). For every epoch length, the mean value of PLI and AEC across all channels was estimated. Mean PLI and AEC values were successively averaged over epochs and over subjects. In-house Matlab implementations were used for these analyses.

Network measures.

To evaluate the effects of epoch length on network measures, the clustering coefficient (CC_w) and the characteristic path length (L_w), were computed for each weighted connectivity matrix, where EEG electrodes/ROIs and PLI/AEC values were represented as nodes and edges of the network, respectively. CC_w and L_w are two commonly used network measures, which respectively reflect functional segregation and functional integration (Rubinov & Sporns 2010; Watts & Strogatz 1998). Even though graph measures are often normalized via random surrogate data, we decided not to use normalized versions of CC_w and L_w since it has been shown that this procedure may increase the sensitivity to differences in network size and average degree distribution (van Wijk et al. 2010). To avoid these biases altogether the minimum spanning tree (MST) was computed. The MST is an acyclic sub-graph that contains most of the strongest connections[1] of the original graph, which was computed from each weighted connectivity matrix using Kruskal's method (Kruskal 1956). MST topology was characterised using several parameters: leaf fraction (Lf, number of nodes with degree of 1 divided by the total number of nodes), diameter (D, largest distance between any two nodes in the network[2]), tree hierarchy (Th, reflects the balance between diameter reduction and overload prevention), eccentricity (E, the longest distance between a node and any other node) and kappa (K, the broadness of the degree distribution). See (Tewarie et al. 2015; Stam et al. 2014; Boersma et al. 2013; Demuru et al. 2013) for a detailed description of these parameters. Network measures were evaluated for each epoch and then averaged.

[1] For the construction of the MST, the edge weight is defined as 1 – (functional connectivity estimate).

[2] The distance between nodes is expressed as the inverse of the sum of the weights on the shortest path between the nodes.

Statistical analysis.

Non-parametric Friedman tests were used to detect the effect of different epoch lengths on functional connectivity measures and network parameters. In case the Friedman test showed a significant effect, the shortest epoch length that did not show a significant difference (using post-hoc Dunn's multiple comparison tests) with any longer epoch was defined as the onset of a stability zone. Linear regression analysis was used to estimate the relationship between epoch lengths and the standard error of the mean for the different measures. The level of significance was accepted at $p < 0.05$. All statistical analyses were performed using Prism (GraphPad, version 5.0f).

Results

Scalp analysis: effect on functional connectivity.

Both PLI and AEC showed a decrease in mean values for increasing epoch lengths (Figure 1 left panel), with Friedman statistics $\chi^2(8) = 137.7.0$, $p < .0001$ for PLI and $\chi^2(8) = 96.6$, $p < .0001$ for AEC. The effect is slightly more evident for the PLI, where the results stabilize for epochs with lengths of 12 seconds, compared to 6 seconds for the AEC. It is of interest to note that epoch length not only affects the mean FC values, but shorter epochs also show less clear (more blurred) FC patterns than those obtained for longer epochs (Figure 2, upper panel).

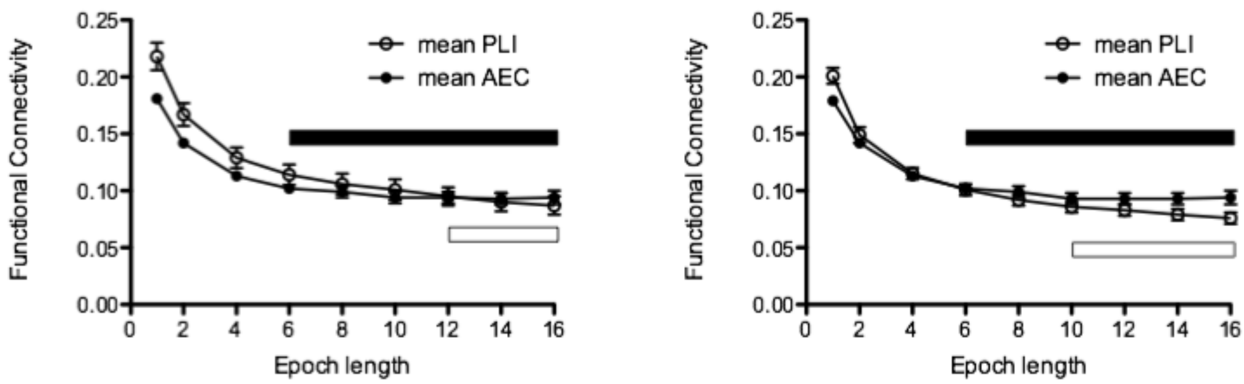

Fig. 1. Mean PLI and AEC values for scalp analysis (left panel) and source analysis (right panel). Error bars refer to standard error of the mean. The white and black boxes indicate the stability zones for PLI and AEC, respectively.

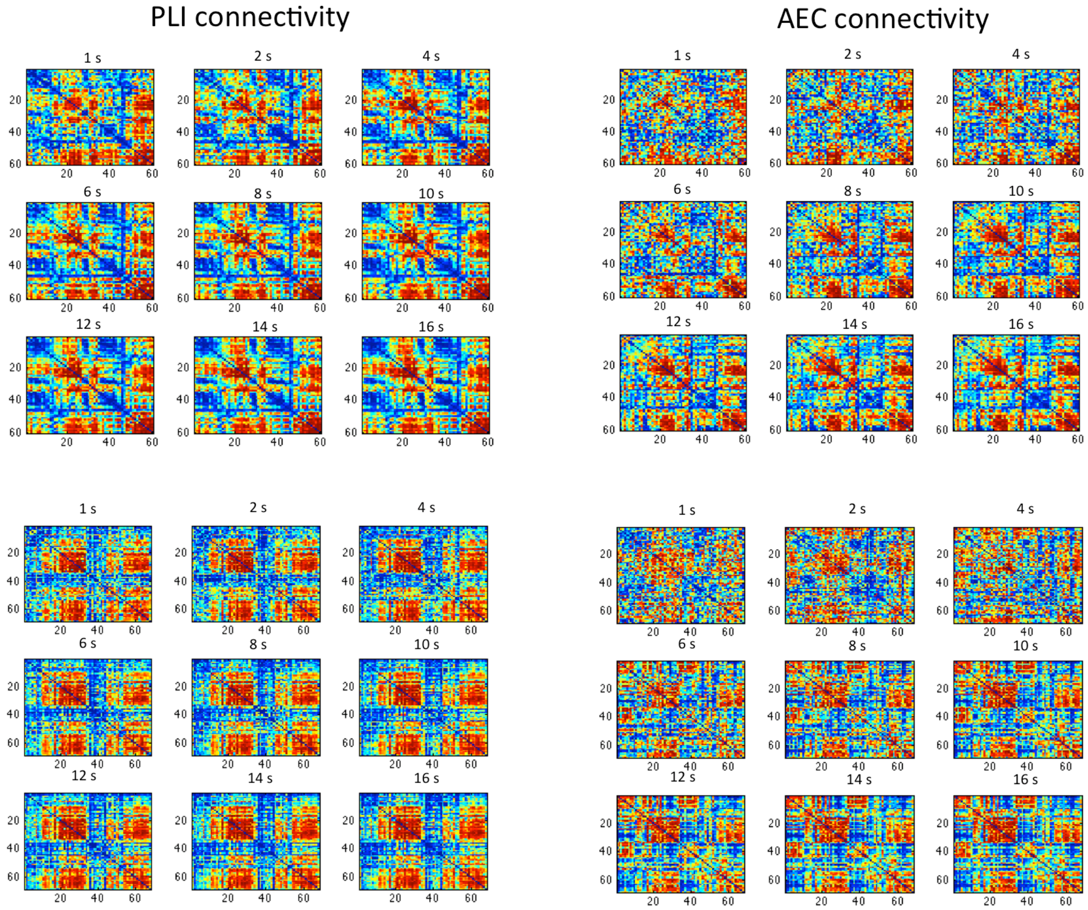

Fig. 2. Representation of FC patterns for different epoch lengths for PLI and AEC for scalp (upper panel) and source (lower panel) EEG analysis. In order to allow comparison between conditions, images represent the rank order of the FC metric (see Supplementary Material for a list of channels/ROIs).

Scalp analysis: effect on network measures.

As for the functional connectivity, the weighted network measures also decreased with increasing epoch lengths. CC_w and L_w stabilized earlier for networks based on AEC than for those based on PLI (4 versus 12 seconds for both metrics). In contrast, MST parameters already stabilized for shorter epochs, namely for epochs between 1 and 6 seconds for PLI-based MSTs and for epochs between 4 and 6 seconds for AEC-based MSTs (depending on the MST parameter). All the results are summarized in Table 1, Figure 3 and Figure 4.

	PLI-based networks		AEC-based networks	
Network measure	$\chi^2(8)$	p	$\chi^2(8)$	p
CC_w	137.0	.0001	89.8	.0001
L_w	126.2	.0001	73.7	.0001
MST Leaf fraction	36.6	.0001	95.2	.0001
MST Diameter	15.2	ns (.059)	61.5	.0001
MST Eccentricity	12.6	ns (.126)	57.6	.0001
MST Hierarchy	22.4	.004	65.6	.0001
MST Kappa	11.0	ns (.204)	59.5	.0001

Table 1. Statistics for PLI and AEC –based network measures at scalp level, reporting the main effect from the Friedman test.

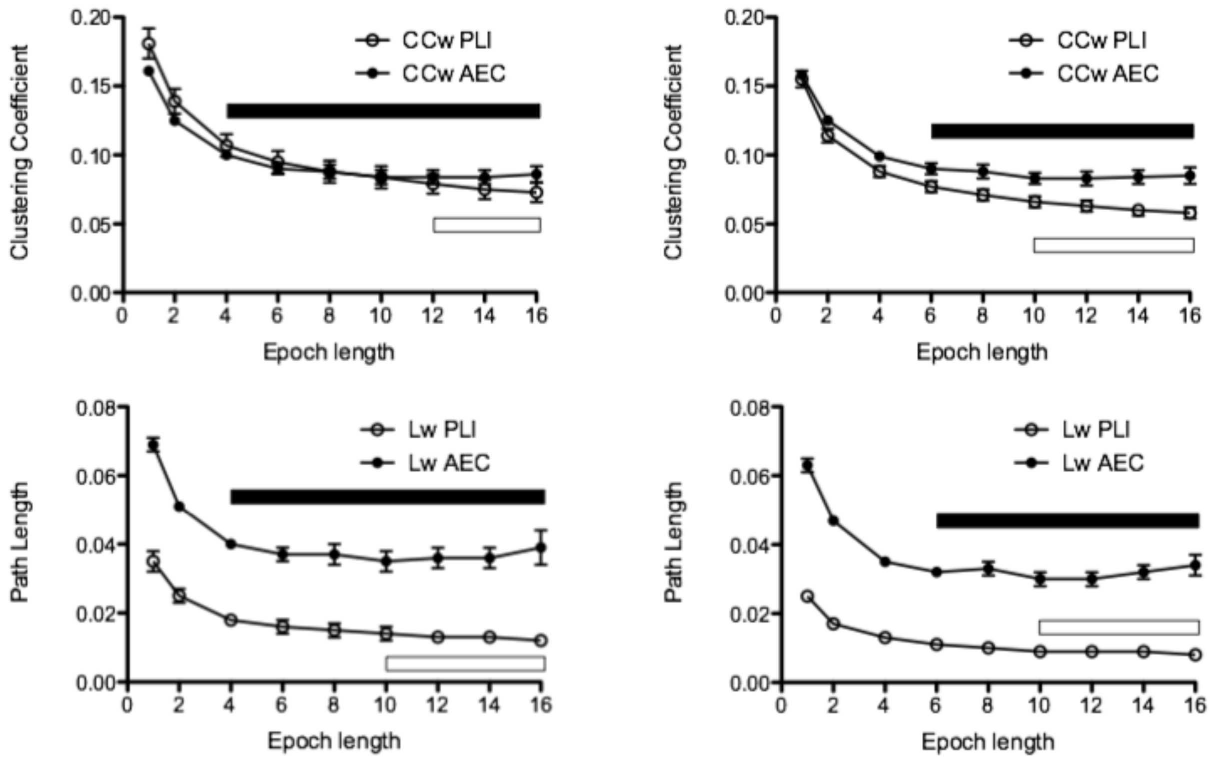

Fig. 3. CC_w (top panel) and L_w (bottom panel) values for scalp analysis (left panel) and source analysis (right panel). Error bars refer to standard error of the mean. The white and black boxes indicate the stability zones for PLI and AEC –based networks, respectively.

Scalp analysis: linear regression.

A significant relation between epoch length and the standard error of the mean was found for PLI, AEC, and the different network metrics (see Table 3).

Source analysis: effect on functional connectivity.

As for the scalp analysis, in the source space both PLI and AEC show a decrease of mean values for increasing epoch lengths (Figure 1 right panel), with Friedman statistics $\chi^2(8) = 141.1$, $p < 0.0001$ for PLI and $\chi^2(8) = 99.2$, $p < 0.0001$ for AEC. The onset of the stability zone occurred for epoch length of 6 seconds for AEC and 10 seconds for PLI. Again, shorter epochs show less clear (more blurred) FC patterns than those obtained for longer epochs (Figure 2, lower panel).

	PLI-based networks		AEC-based networks	
Network measure	$\chi^2(8)$	*p*	$\chi^2(8)$	*p*
CC_w	139.3	.0001	94.7	.0001
L_w	130.3	.0001	80.1	.0001
MST Leaf fraction	15.5	ns (.051)	74.4	.0001
MST Diameter	21.0	.007	52.4	.0001
MST Eccentricity	17.7	.024	52.8	.0001
MST Hierarchy	4.0	ns (.85)	35.8	.0001
MST Kappa	19.4	.013	37.6	.0001

Table 2. Statistics for PLI and AEC –based network measures at source level, reporting the main effect from the Friedman test.

	PLI				AEC			
	scalp		source		scalp		source	
	R^2	*p*	R^2	*p*	R^2	*p*	R^2	*p*
FC	*.69*	*.006*		*ns*	*.92*	*.0001*	*.93*	*.0001*
CC_w	*.70*	*.005*		*ns*	*.92*	*.0001*	*.93*	*.0001*
L_w	*.60*	*.01*		*ns*	*.76*	*.002*	*.67*	*.007*
MST Leaf fraction	*.79*	*.001*		*ns*	*.65*	*.009*		*ns*
MST Diameter	*.81*	*.0009*		*ns*		*ns*	*.60*	*.01*
MST Eccentricity	*.71*	*.005*		*ns*		*ns*		*ns*
MST Hierarchy	*.71*	*.004*		*ns*	*.62*	*.012*		*ns*
MST Kappa		*ns*		*ns*	*.73*	*.004*	*.75*	*.003*

Table 3. Linear regression analysis for standard errors and epoch lengths. The significant relations between epoch length and the standard error of the mean was positive for all metrics, except for PLI, CCw and Lw based on PLI.

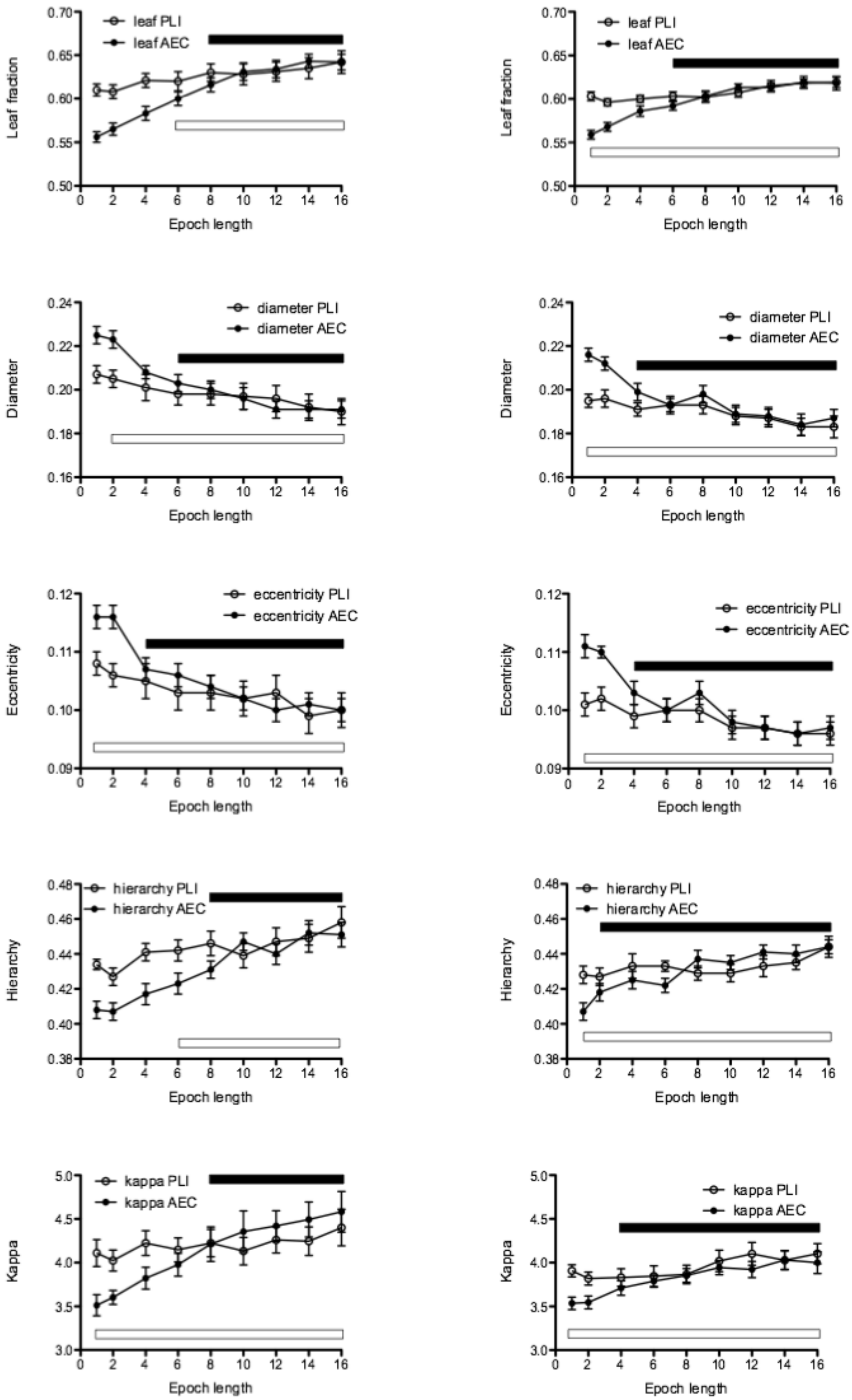

Fig. 4. MST parameters for scalp analysis (left panel) and source analysis (right panel). Error bars refer to standard error of the mean. The white and grey boxes indicate the stability zones for PLI and AEC –based networks respectively.

Source analysis: effect on network measures.

As for the functional connectivity, the weighted network measures also decreased with increasing epoch lengths. CC_w and L_w stabilized earlier for networks based on AEC than for those based on PLI (6 versus 12 seconds for both metrics, respectively). In contrast, as for scalp analysis, MST parameters already stabilized for shorter epochs, namely for epochs of 1 second for PLI-based MSTs (for all MST parameters) and for epochs between 2 and 6 seconds for AEC-based MSTs (depending on MST parameter). All the results are summarized in Table 2, Figure 3 and Figure 4.

Source analysis: linear regression.

As for scalp analysis, for AEC a significant positive relation between epoch length and the standard error of the mean for most of the measures was observed, indicating an increase of the standard error with increasing epoch lengths (see Table 3). For mean PLI and PLI-based networks (as for AEC based MST- leaf fraction, eccentricity and hierarchy) no significant relation with standard error was found.

The effect of sample frequency.

As reported in detail in the Supplemental Material the results show no significant differences when applying different sample frequencies (128, 256 and 1024 Hz), further highlighting the importance of the time-window (epoch length).

Discussion

The present study investigated the effect of epoch length on estimated functional connectivity and brain network organization in resting-state EEG analysis. In summary, we found that i) functional connectivity measures, namely PLI and AEC, are affected by the length of the selected EEG epoch; ii) traditional network measures, namely CC_w and L_w are affected by these biases; and iii) the topology of source-space PLI –based MST is almost unaffected by epoch length.

Functional connectivity is biased by epoch length

Our results confirm previous findings that have reported a similar behaviour for connectivity measures based on linear coupling (Chu et al. 2012; David et al. 2004; Bonita et al. 2014). It should be noted that, as previously reported (Tewarie et al. 2014), AEC and PLI behave similarly at group level analysis. Our results suggest to use epoch lengths of at least of 6 seconds and to keep into consideration the types of coupling captured by the adopted metric. Moreover, even though, compared to PLI, results from AEC stabilize earlier as epoch length increases, this higher stability may be, at least in part, due to the reported increase of variance for AEC with longer epochs, which could be responsible for non-significant post-hoc tests.

It is of interest to note that epoch length not only affects the mean FC values but also it is evident (especially for AEC metric) that shorter epochs also show less clear (more blurred) FC patterns than those obtained for longer epochs (Figure 2). The less clear FC patterns for shorter epochs may be explained as in increase of inter-epoch variability, which would suggest to use shorter epochs to examine the network dynamics.

Traditional network measures are biased by epoch length

As expected, biases in estimates of FC affect the estimated topology of functional networks, at least for the common and widely used metrics that allow estimating global network integration (L_w) and segregation (CC_w). These results suggest that caution should be taken when comparing results from studies on network organization when the analysis is performed with different epoch length, especially for short epochs. The use of epoch length shorter than 4 seconds should be avoided (Figure 3).

MST is almost unaffected by epoch length

Importantly, the use of the MST, which has been shown to be as sensitive to alterations in network topology as conventional network measures (Tewarie et al. 2015), provides stable results also for very short epochs. This can be explained observing that even though mean FC values are affected by epoch length, the rank order is less influenced (Figure 2), especially for PLI based FC. This result implies that results from different studies can be meaningfully compared using the MST. In particular, by the combination of PLI (as functional connectivity index) and MST (for network characterization) in source space it is possible to obtain results that are already stable for time-windows of 1 second. This latter result is also of importance in the context of time-varying (dynamic) network analysis, which is currently a hot topic in (EEG) resting-state analysis (Khanna et al. 2015; Betzel et al. 2012; Hutchison et al. 2013; Mehrkanoon et al. 2014). Indeed, our study, which shows how results depend on the specific approach, can strengthen the idea that time-varying approaches can generate spurious signs of non-stationary dynamics (induced by the procedure itself) even when applied to a stationary process (Hlinka & Hadrava 2015). In this context, the stability of parameters extracted from the MST would give the opportunity to study topology changes (at least at time-scale of 1 second) and to investigate how this topology may correspond to intrinsic resting-state networks (Mantini et al. 2007; Greicius et al. 2003).

Effect of epoch length is reduced in source-space

Better behaviour (in terms of stability) was observed for measures extracted from source analysis as compared with results from scalp analysis. This finding suggests that the use of techniques to reconstruct the time-series at the level of the sources reduces the dependency on epoch length, possibly due to demixing of signals, consequent reduction of volume conduction effects and increased signal to noise ratio. This phenomenon is particularly evident for PLI and PLI–based network parameters, where, differently from other metrics, no relationship between epoch length and the standard error was observed. It should be noted though that many approaches exist to reconstruct source time-series (Baillet et al. 2001; Hillebrand & Barnes 2005; Hillebrand et al. 2005). However, the main focus of this work was not to investigate details, advantages, and/or limitations of these different techniques, but to understand the effect of epoch length in source-space. We therefore decided to use a method (wMNE) that is widely used in EEG analysis and easy to implement with available tools. Furthermore, it has been recently suggested that the combination of wMNE and phase synchronization measures represent a reliable solution to characterize EEG networks (Hassan et al. 2014). Nevertheless, we expect that the general conclusions would hold for other techniques (Hillebrand et al. 2012), where the spatial filtering characteristics of e.g. beamforming may aid to reduce the effects of epoch length even further.

Limitations

Even though the reported results show some clear patterns with respect to epoch length, it should be noted that in real EEG analysis, the real functional connectivity patterns are unknown. Thus it may still be difficult to know whether the PLI and AEC (and network measures) converge, for long epochs, to something that is closer to realistic neurophysiological processes or represent simply some stable statistical estimates unrelated to underlying biological mechanism. It would be of relevance for future works trying to elucidate these mechanisms using simulated data from neural mass modelling approaches, where the ground truth is known (Deco et al. 2008). Furthermore, it should be noted that the present study shows results with a lower limit of 1-second epoch length. However, to study dynamics at millisecond resolution different FC metrics (which avoid the introduction of a time-window) should be investigated, as recently proposed by (Shine et al. 2015).

Sampling frequency seems to play a less important role in the estimation of both functional connectivity and network topology, confirming that our results strongly depend on the definition of the epoch length itself (see Supplemental Material).

Conclusion

Our results show that epoch length has an important impact on both functional connectivity and estimated network topology. Furthermore, the topology of the MST, which has been shown to represent a valid alternative to traditional network analyses, can be reliably estimated for a range of epoch lengths, and may thus facilitate the comparison between results from different studies.

Conflict of interest statement

None of the authors has any conflict of interest to disclose in relation to this work.

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