

## Review

## Opportunities and methodological challenges in EEG and MEG resting state functional brain network research



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## ARTICLE INFO

## Article history:

Accepted 20 November 2014

Available online 28 November 2014

## Keywords:

Resting state

EEG

MEG

Functional connectivity

Functional networks

Graph analysis

Minimum spanning tree

## HIGHLIGHTS

- Resting state EEG and MEG recordings are increasingly used for functional connectivity and functional brain network analysis.
- We highlight advantages and disadvantages of methodological choices throughout the recording and analysis pipeline and how this may affect construction of functional connectivity and networks.
- We give several recommendations for subject instructions and data acquisition for resting state neurophysiological research.

## ABSTRACT

Electroencephalogram (EEG) and magnetoencephalogram (MEG) recordings during resting state are increasingly used to study functional connectivity and network topology. Moreover, the number of different analysis approaches is expanding along with the rising interest in this research area. The comparison between studies can therefore be challenging and discussion is needed to underscore methodological opportunities and pitfalls in functional connectivity and network studies. In this overview we discuss methodological considerations throughout the analysis pipeline of recording and analyzing resting state EEG and MEG data, with a focus on functional connectivity and network analysis. We summarize current common practices with their advantages and disadvantages; provide practical tips, and suggestions for future research. Finally, we discuss how methodological choices in resting state research can affect the construction of functional networks. When taking advantage of current best practices and avoid the most obvious pitfalls, functional connectivity and network studies can be improved and enable a more accurate interpretation and comparison between studies.

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<http://dx.doi.org/10.1016/j.clinph.2014.11.018>

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## 1. Introduction and rationale

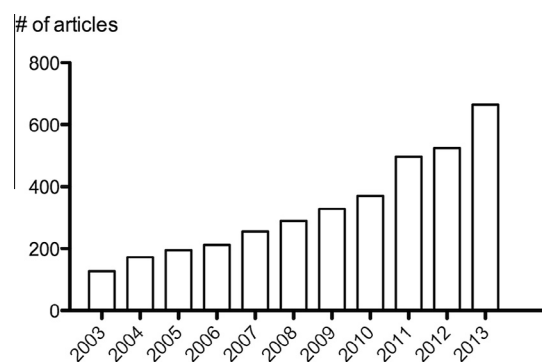
In recent years, there has been a growing interest in characterizing the functional network of the brain ‘at rest’. This so-called ‘resting state’ paradigm is believed to reflect intrinsic activity of the brain, which may reveal valuable information on how different brain areas communicate (Greicius et al., 2003; Deco et al., 2011; Birn, 2012). It has linked spontaneous – task independent – fluctuations in neural activity to diseases, cognitive decline, and disturbances in consciousness (Greicius, 2008; Bassett and Bullmore, 2009; Bullmore and Sporns, 2009; Stam, 2014).

This interest in the ‘resting state’ is associated with several breakthroughs in functional magnetic resonance imaging (fMRI) research (Raichle, 2009). The claim, however, that valuable information on communication between brain areas can be inferred from intrinsic activity – obtained with neurophysiological techniques – is much older (for a comprehensive overview see Pinneo, 1966; Snyder and Raichle, 2012)). The high spatial resolution might be a favourable feature of fMRI; still this technique only provides an indirect measurement of brain activity and has a limited temporal resolution. Information processing in the brain, however, acts on multiple time-scales, depending on the specific cognitive or behavioural function (Lopes da Silva, 2013). A considerable part of the information processed in the brain at rest is encoded on time scales from milliseconds to seconds (Koenig et al., 2005), a time scale that better suits techniques such as electroencephalography (EEG) and magnetoencephalography (MEG).

In the last decade, EEG and MEG connectivity and functional brain network studies have gained considerable interest resulting in a yearly growing number of published studies on this subject (Fig. 1). These studies have provided valuable information on the deviant organisation in the diseased brain, such as in Alzheimer’s disease (Stam et al., 2007a; Dubovik et al., 2013), epilepsy (Bartolomei et al., 2006; Ibrahim et al., 2013), schizophrenia (Hinkley et al., 2010; Siebenhuhner et al., 2013), multiple sclerosis (Schoonheim et al., 2013; Van Schependom et al., 2014), Parkinson’s disease (Fogelson et al., 2013), as well as in the healthy brain on topics as aging (Smit, 2012; Vecchio et al., 2014), gender differences (Boersma et al., 2011) and a healthy lifestyle (Douw et al., 2014). Furthermore, connectivity and functional brain network studies can be used in the clinical setting. For example, in epilepsy it has been shown to prompt early diagnosis (van Diessen et al., 2013) and to improve accuracy of epilepsy surgery by removing aberrant network nodes (Wilke et al., 2011). In Alzheimer’s disease,

EEG connectivity studies were used to monitor the success of novel interventions (de Waal et al., 2014). Similarly, progression of cognitive deficits in Parkinson’s disease was correlated with functional brain network changes (Olde Dubbelink, 2014). Together these examples clearly underline the importance and additional value of connectivity and brain network analyses in EEG and MEG research.

When performing these analyses, one makes several assumptions and choices that may influence the eventual results. Moreover, the literature on functional connectivity and functional network studies is rapidly evolving, with an increasing number of analysis methods becoming available. Discussion is needed to obtain uniformity and comparability between different studies (Duncan and Northoff, 2013; Gross, 2014). The present paper therefore aims to highlight challenges, problems, and opportunities that are encountered when performing this type of research. As there are only few methodological studies that address these issues systematically, our review can be seen as a reflection of the current state of the field. We provide an overview of the methodological issues that should be considered when performing functional connectivity and network studies with EEG or MEG, and highlight the advantages and disadvantages of different approaches. Although we specifically focus on resting state EEG and MEG studies, most of the information provided is also applicable to task-related studies and other imaging techniques such as fMRI.



**Fig. 1.** Number of articles per year from Pubmed search using keywords “(EEG OR MEG) AND (connectivity OR brain networks OR functional networks OR graph theory OR network analysis)” in the period 2003–2013.

We start with subject-related methodological issues that are of interest when conducting a resting state study. What is resting state, and how does the heterogeneous experience of subjects affect resting state studies? Furthermore, we explain how the state of vigilance and an eyes open versus eyes closed condition might influence the resting state recording. We then summarize analysis-related methodological choices that can strongly influence the eventual results of a functional connectivity or network study, namely: choice of EEG reference, source space analysis, artifact handling and filtering, epoch selection, choice of frequency bands, and test–retest reliability. For each methodological choice we introduce current common practice, explain why these choices are important for the eventual data analysis and summarize the advantages and disadvantages of each choice. Furthermore, we discuss issues that are still unresolved or subject of debate and give some general recommendations. Subsequently, a concise overview of currently used functional connectivity measures is provided and how these connectivity measures relate to various methodological choices and assumptions. Finally, we discuss current challenges in functional network analysis based on EEG and MEG recordings.

## 2. Subject-related methodological issues

### 2.1. What is ‘resting state’ and how does it affect the recording?

Resting state is the state in which a subject is awake and not performing an explicit mental or physical task. Traditionally, the ‘resting state’ condition was commonly used in EEG research – besides event-related potential studies – to study patterns of brain activity, whereas fMRI research was mainly focused on alterations in activity during task performance. Early EEG studies, including the first EEG recordings performed by Berger (Berger, 1929), already provided evidence for patterns of brain activity when subjects were not performing a task (Collura, 1993). Ironically, it was not until Biswal and colleagues revealed a distinct fMRI pattern of interacting brain regions when not performing a task that the resting state condition became a research paradigm for the study of interconnectivity of brain regions (Biswal et al., 1995). Since then, many studies have identified sets of brain regions that share a common activation pattern during the resting state (Greicius et al., 2003; Damoiseaux et al., 2006) including the ‘default mode network’ (Shulman et al., 1997; Raichle et al., 2001) and other so-called resting state networks (Rosazza and Minati, 2011). These resting state networks have been replicated and validated both in neuroimaging and neurophysiological studies (Miller et al., 2009; Brookes et al., 2011; Hipp et al., 2012), suggesting that resting state patterns of connectivity are the result of robust and specific intrinsic neural activity.

In contrast to task related activity, it is difficult to control the behaviour of subjects during a resting state experiment. Differences in the specific instructions for the resting state period may at least partly influence the activity of the default mode network (Benjamin et al., 2010). Commonly, subjects are asked to close the eyes and not to fall asleep. As a result, thoughts are drifting and thereby creating stimulus independent thoughts (Andreasen et al., 1995; Teasdale et al., 1995). A recent study investigated what kind of thoughts patients experienced during a resting state recording and found several phenotypes of resting state cognition (Diaz et al., 2013). Even when similar instructions were given to subjects, the subjective experience during a resting state recording varied greatly, thereby potentially confounding the results. In addition, the cognitive state before the recording could also influence resting state dynamics (Lopez Zunini et al., 2013). These findings underline the heterogeneous experience of subjects during the resting state condition. Instructing a resting state condition might

thus not be as straightforward as it seems. Controlling spontaneous thoughts is difficult, however, it might not be necessary as the experienced random episodic spontaneous thoughts seems to activate similar brain regions as resting state networks (Andreasen et al., 1995). Furthermore, consistent activation patterns of resting state networks in healthy controls among studies suggest only a limited influence (Damoiseaux et al., 2006). To reduce the externally induced heterogeneity of the resting state condition, we recommend the use of a priori defined instructions throughout a study, which should be reported in the method section of the eventual manuscript. Furthermore, subjects should have a similar pre-experimental procedure, to avoid introducing variance in cognitive state. Therefore, researchers should consider the order of neuropsychological testing and recording of resting state. We suggest to first record a resting state condition after which an experimental session can be performed to minimize disturbances of the resting state condition. Finally, longer registration increases the stability of resting state networks, as with time it becomes more likely that the complete repertoire of resting state networks has been activated (Honey et al., 2012), but this also increases the risk of drowsiness in subjects when no precautions are taken. The exact relation between duration of recording and stability in EEG and MEG resting state functional connectivity remains complex and is discussed further in Section 3.4.2.

### 2.2. State of vigilance

During the day, the brain is constantly shifting between different levels of activation, also called ‘states of vigilance’. In EEG and MEG research, we distinguish several vigilance states. These different states can be identified by visual inspection or spectral analysis of the EEG (Olbrich et al., 2009; Minkwitz et al., 2011). The three most studied vigilance states are wake, sleep, and sleep deprived. The state ‘drowsiness’ is often avoided in resting state research, because alertness or wakefulness is reduced during a drowsiness state and may vary and influence measurements greatly. However, recognizing drowsiness in resting state recordings can be difficult and requires a systematic approach (Koenis et al., 2013; van Diessen et al., 2014). Each state of vigilance has specific characteristics that contribute to differences in spectral power (Niedermeyer, 1987; Cantero et al., 1999) and functional connectivity (Kuhnert et al., 2010; Piantoni et al., 2013). Several factors have been identified that influence state of vigilance: circadian rhythm (Kuhnert et al., 2010), task performance before the recording (Klimesch et al., 1999), including neuropsychological testing, medication use, or even caffeine intake (Siepmann and Kirch, 2002; Barry et al., 2011; Tal et al., 2013). Body posture and recording environment may also affect vigilance and, consequently, functional connectivity measures. For example, drowsiness is more likely to occur in a dimly lit and sound attenuated room with the subject in supine position, compared to a noisy environment with the subject sitting in daylight. Also, the amplitude of the EEG recording changes as a result of different body postures due to shifts in cerebrospinal fluid layer thickness (Rice et al., 2013). The effect size of these possible confounders in resting state studies is unknown. It is therefore recommended to eliminate or record and correct for these possible confounders as much as possible.

### 2.3. Eyes open versus eyes closed

Whether a recording is performed with eyes open or eyes closed influences the resting state condition greatly. Evidence from fMRI, MEG and EEG studies has revealed differences between eyes open and eyes closed conditions for functional connectivity measures and functional networks (Horstmann et al., 2010; Tan et al., 2013; Jin et al., 2014; Xu et al., 2014). Irrespective of the condition,

eye movements affect neurophysiological recordings, particularly the frontal channels (Davidson, 1988; Allen et al., 2004) and are thus a potential confounder in connectivity analyses. Both eyes open and eyes closed are associated with specific eye movements. For example, eye blinks are more prevalent during eyes open condition, whereas rolling of the eyes might particularly influence the eyes closed condition. Rolling of the eyes during eyes closed condition is often due to drowsiness, which is normally not a state of vigilance where resting state studies are interested in and, as a result, discarded from further analysis (Section 2.2). Furthermore, the eyes closed condition, is more stable over sessions when quantifying EEG parameters than the eyes open condition (Corsi-Cabrera et al., 2007) and standardization of the procedure is relatively straightforward even in subjects who are difficult to instruct such as children, or patients with behavioral or cognitive problems. Together with the robust topographic effect posteriorly in the alpha frequency band when eyes are closed, thereby giving good guidance for selecting resting state epochs, we advocate to use the eyes closed condition during resting state recordings. Methods to automatically remove eye movements from the EEG and MEG recordings are discussed in Section 3.3.

### 3. Analysis-related methodological choices

#### 3.1. Choice of reference

In contrast to MEG, the electric potentials measured by EEG electrodes are defined with respect to a reference. Besides bipolar recordings, in which EEG activity is defined by the electric potential difference between two electrodes, EEG recordings often use a single common reference such as auricular, mastoid or central electrode as reference. These conventional reference montages are confounded by brain activity that will eventually affect further analysis. As a result, recordings are often re-referenced offline to compute reference montages that are electrophysiologically more silent (Pivik et al., 1993; Nunez et al., 1997; Hu et al., 2010; Kayser et al., 2010). The common average reference has previously been suggested as a practical compromise to reduce the confounding effect of brain activity that is picked up by the reference (Nunez et al., 1997). The advantage of the common average reference of approximating a zero sum reference is, however, increasingly lost in low-density EEG recordings (Schiff, 2005; Nunez and Srinivasan, 2006). To this end, several other methods have been proposed. These include the infinity reference, which tries to estimate a time-varying constant that is removed from the recorded data (Yao, 2001), and the surface Laplacian, which represents a truly reference-free transformation (Hjorth, 1975; Tenke and Kayser, 2012). Similar to the conventional and average common reference, the infinity reference is reversible to the original reference scheme, whereas the surface Laplacian involves the estimation of radial current flow at the scalp, which cannot be undone (Tenke and Kayser, 2012). Both methods, in particular surface Laplacian, have been used empirically in various basic and applied contexts (Nunez and Srinivasan, 2006). Recently, a statistically robust method has been proposed to adequately mitigate the influence of neural activity in the common average reference (Lepage et al., 2014). More investigations are needed to further explore the performance of this theoretically appealing method.

A related question is to what extent reference choice will affect the computation of connectivity measures. For example, Qin and colleagues demonstrated that infinity reference has a superior performance compared to other reference montages when estimating functional connectivity by means of coherence (Qin et al., 2010). Correlation measures such as coherence, however, are increasingly abandoned in connectivity studies, as they fail to include

information on the intrinsic nonlinearity of brain activity (Section 4) and it is currently unclear whether the superior effect of the infinity reference is maintained when using nonlinear connectivity measures. We await future studies that critically evaluate possible biases due to reference as was illustrated for effective connectivity measures (van Straaten et al., 2015).

In the light of the ongoing discussion on reference choice (Kayser et al., 2010; Nunez, 2010) and its effect on connectivity measures (Qin et al., 2010; van Straaten et al., 2015) we encourage researchers to explore the effects of different types of references when computing connectivity measures.

#### 3.2. Signal versus source space

Many resting state EEG and MEG studies use the activity at the electrode level to infer how brain regions are (functionally) interconnected. This analysis is performed in so-called 'signal space' as neural activity is directly inferred from signals measured at the EEG electrode or MEG sensor. When performing connectivity analysis in signal space, several factors should be considered. Firstly, multiple electrodes pick up activity from a single source due to the nature of the signal, also called 'field spread' (Sarvas, 1987). A second problem is related to volume conduction: the 'blurring' effect due to the electrical conduction properties of the human head (van den Broek et al., 1998). Together, these factors can result in an erroneous estimate of the actual connectivity between brain areas. To obtain more reliable information on the communication between brain areas, studies project the activity measured at the electrode or sensor (signal space) back to the underlying sources, the so-called 'source space'. The mapping from signal space to source space is known as the inverse problem (Niedermeyer, 1987). Unfortunately, no unique solution exists to this problem (Helmholtz, 1853), unless constraints and assumptions are made. These assumptions concern, for example, the number of possible sources or the non-linearity between sources (Hillebrand and Barnes, 2005; Michel and Murray, 2012). Furthermore, analyzing neurophysiological signals in source space does not completely overcome the problems of field spread and volume conduction, and it has therefore been suggested to combine source space analysis with a robust connectivity measure (Hillebrand et al., 2012). These robust measures include, for example, imaginary coherence, phase slope index or phase lag index (Section 4). Secondly, the mixture of signals arising from spatially separated sources at a single electrode also hampers the interpretation of connectivity estimate in signal space (Nunez and Srinivasan, 2006; Schoffelen and Gross, 2009). Source space analysis could be helpful in demixing signals (Michel and Murray, 2012). Various approaches for source space analysis have been offered (Baillet et al., 2001), including low resolution brain electromagnetic tomography (LORETA) in EEG research (Pascual-Marqui et al., 1994) and the beam forming approach for EEG and MEG recordings (van Drongelen et al., 1996; Hillebrand and Barnes, 2005). In general, the accuracy of source localization increases with the number of recording sites (Lantz et al., 2003) if the signal quality remains constant, although a noiseless recording condition may also allow source localization with a standard 10–20 system (Laarne et al., 2000). A high channel density recording might even become a disadvantage for source reconstruction approaches that rely on an accurate description of the lead fields. Lead field is defined as the electrode or sensor signal that is produced by a source of unitary strength. Incorrect source and head models lead to deviations from the 'true' lead fields, and subsequently to source reconstruction errors (Hillebrand and Barnes, 2003, 2011). These errors in the lead fields are more discernible when using good quality data. Counter intuitively, recordings with higher signal-to-noise ratio and higher density may therefore degrade source reconstructions in the

presence of these modeling errors. Finally, increased channel density can result in bridging, the incidental spread of electrolyte gel between adjacent electrodes, thereby negatively influencing the recording and subsequent inverse solutions and/or connectivity estimates (Alschuler et al., 2014).

### 3.3. Artifact handling and filtering

To minimize the influence of artifacts on the results, visual inspection and automatic detection of artifacts are often used to remove artifacts or to select artifact-free data segments. Many attempts have been made to reject or mitigate eye movement artifacts, to reduce interobserver variability, and to improve efficiency in visible inspection of the data (Croft and Barry, 2000; Cassani et al., 2014). Blind source separation, such as independent component analysis, is increasingly used for the detection and removal of ocular artifacts (LeVan et al., 2006; Gao et al., 2010), although it is unknown to what extent these artifact reduction methods influence functional connectivity and network metrics. Furthermore, a number of techniques is available for automatic removal of muscle artifacts; however, none of them guarantees muscle artifact free data (Muthukumaraswamy, 2013). Improvement of software-based muscle artifact recognition is therefore needed (Delorme et al., 2007; Whitham et al., 2007). Currently, most studies use visual inspection to eliminate epochs with myogenic or eye-movement artifacts, although the precise procedure is often not described. Some studies mention the removal of frontopolar and auricular channels to reduce the influence of artifacts (de Haan et al., 2009; van Dellen et al., 2014b). Although these artifacts will also affect other channels due to volume conduction, this influence is reduced when excluding frontopolar and auricular channels prior to offline re-referencing. It is, however, preferable to select artifact free epochs. In addition, visual recognition of any EEG artifact depends on the chosen reference montage. This means that a possible artifact on the reference channel could influence all other recording sites and could lead to the undesirable rejection of an epoch. Although this problem is relatively easy resolved by replacing (e.g. interpolating) the original reference, it underlines the importance that visual inspection should be done by a well-trained researcher.

In EEG and MEG recordings analogue filtering is needed to prevent from aliasing and eliminate the direct current (DC) component. Besides the analogue filtering, software programs have digital filtering options that can be useful to improve inspection and selection of epochs. It is important to realize, however, that this digital filtering may affect amplitude and phase of EEG and MEG recordings. It is essential to know how the data is exported from the recording device and whether a digital filter is contaminating the signal. To avoid any possible influences of the digital filters on the recorded signal, it is therefore important to consider elimination of software based filtering or to use zero-phase filtering, for example by a forward and reversed filtering approach.

### 3.4. Epoch selection

#### 3.4.1. Standardization and interobserver variability in epoch selection

Selection of epochs based on visual inspection is a subjective approach, which may result in inter-observer variability. The effect of epoch selection on functional connectivity has never been investigated systematically. A few studies, however, assessed the stability of their outcome measures by repeating the analysis with a different number and selection of epochs, showing minimal changes between conditions (Douw et al., 2013; Olde Dubbelink, 2014; van Dellen et al., 2014b). This may indicate a modest subjective influence on epoch selection when sufficient epochs are selected. Still, automated analysis could be helpful for researchers

and clinicians in evaluating and improving epoch selection in EEG and MEG recordings (Lodder et al., 2014). The current complexity and limited transparency of automated detection systems demotivate researchers to use it on a larger scale (Anderson and Doolittle, 2010) although recent advances are promising (Shibasaki et al., 2014). Also, it is recommended to define the selection criteria prior to the epoch selection. Selection by two or more experienced researchers or clinicians could improve the reliability of the epoch selection. For example, when a researcher selects epochs according to predefined criteria, a second researcher can be asked to independently evaluate the selected epochs. When both researchers agree on the quality, the epoch can be included. Epochs without consensus can be replaced by new epochs. Another option is the use of an automatic software-based rejection procedure (Section 3.3) or a random selection among all selected artifact-free epochs (Shibasaki et al., 2014). Beside the elimination of artifacts in the included data, it is important to define the time segments in the recording from which epochs are selected. As the variance of vigilance increases with the length of the EEG recording (Maltez et al., 2004), we recommend selecting the first artifact free epochs of sufficient quality after the start of the resting state recording. In this way, selection bias of EEG epochs will be minimized.

#### 3.4.2. Number and length of epochs and sample frequency

Different epoch lengths and number of epochs are currently used in resting state functional connectivity studies, ranging from one second (Knyazeva et al., 2010; Chu et al., 2012) to a few minutes (Tahaei et al., 2012) or even a day (Kuhnert et al., 2010) for epoch length; and from one epoch (Ahmadlou and Adeli, 2011) to over 100 epochs containing the entire EEG recording (Knyazeva et al., 2010). Previous studies have investigated epoch length in relation to connectivity stability (David et al., 2004; Honey et al., 2007; Chu et al., 2012) and showed that the length of epochs to obtain stable connectivity measures is highly dependent on the type of connectivity measure. Recent studies have used a more pragmatic approach and extended the original analysis to investigate connectivity stability for the included subjects, for example, by determining the minimum number of epochs that are needed using a leave-one-out analysis (Douw et al., 2013). Similarly, varying the epoch length revealed that a longer epoch length does not automatically imply a more stable connectivity value. For phase synchronization measures, longer epochs could result in lower connectivity values based on the asymmetrical distribution of the phase difference (van Dellen et al., 2014b). From this perspective, we recommend to use epochs of an identical length within a study, as epoch length can influence the connectivity measure (van Dellen et al., 2014b), and to choose an epoch length in accordance with the connectivity measure of choice. Furthermore, we recommend computing connectivity values per epoch and consequently an average value (over epochs) per subject to increase the stability of connectivity values. In some studies, it might be particularly interesting to investigate temporal dynamics of functional connectivity and networks. The use of sequential short epochs might be useful to study these dynamical properties (Singer, 2013).

An often neglected issue when choosing epoch length and number is the sample frequency. Increasing sample frequency will result in a higher temporal resolution and, consequently, a higher number of samples in one epoch. It is unclear how sample frequency influences connectivity measures exactly, although it is reasonable to assume that a lower sample frequency leads to a reduced sensitivity and a larger variability over epochs for detection of coupling between signals. Sample frequencies commonly used in functional connectivity EEG and MEG studies range between 250 and 512 Hz. Analysis of connectivity measures in higher frequency bands requires higher sample frequencies to ful-

fill the Nyquist-Shannon sampling theorem (Candès, 2006). Otherwise, the spectral resolution is only dependent on the length of the epochs. We recommend comparing epochs with a similar sample rate even if this would mean down sampling for some epochs.

### 3.5. Choice of frequency bands

Factor analysis revealed that the classification of EEG recordings into distinct frequency bands, namely delta (0.5–4 Hz), theta (4–8 Hz), alpha (8–13 Hz), beta (13–30 Hz) and gamma (30–90 Hz), is statistically sound (Lopes da Silva, 1998). Furthermore, each frequency band is associated with distinct cognitive functions (Basar et al., 2001). Nevertheless, considerable disagreement exists whether traditional frequency bands are indeed fixed entities. For example, spectral band limits seems to depend on factors such as age (Aurlen et al., 2004; Boersma et al., 2011). In addition, it has been argued that the lower (8–10 Hz) and higher (10–13 Hz) alpha frequency band are involved in different cognitive processes (Klimesch, 1999). The reliability of the gamma frequency band is under debate as it remains questionable whether gamma oscillations can be reliably inferred from surface recordings (Lopes da Silva, 2013). Although various research fields have consistently identified gamma activity being related to tasks (e.g., visual attention, perception and memory (Lopes da Silva, 2013)) or diseases (e.g., epilepsy, autism, ADHD and schizophrenia (Herrmann and Demiralp, 2005)), studies have suggested that EEG oscillations >20 Hz from surface recordings reflect myogenic artifact (Whitham et al., 2007; Pope et al., 2009). These artifacts can, however, be removed using surface transformations of the EEG (Fitzgibbon et al., 2013). Besides myogenic artifacts, saccadic spike potentials are also known to affect the gamma frequency band (Yuval-Greenberg et al., 2008; Yuval-Greenberg and Deouell, 2009). Finally, various diseases of the brain have been associated with abnormal slowing in specific frequency bands and thereby acting as disease specific modifiers, for review see (Kaplan and Rossetti, 2011). These disease specific spectral changes might become a problem when evaluating connectivity measures in these patients, particularly when connectivity measures are strongly dependent on amplitude. Connectivity measures based on phase differences are therefore recommended, as they are not or less sensitive to amplitude differences (Section 4). In addition, we suggest performing a power spectral analysis along with connectivity and functional network analyses to disentangle disease specific spectral changes from disease related connectivity and network changes in the frequency bands (de Haan et al., 2009; van Diessen et al., 2013). To overcome previously described frequency band-related problems, some studies have used a broadband approach. This could be an option when exploring an undirected hypothesis and to avoid inflated type I error rates due to multiple comparisons across frequency bands, but it will probably fail to disentangle simultaneous (opposing) changes in different frequency bands.

### 3.6. Test re-test reliability

To evaluate changes in resting state EEG recordings over time or the effects of an intervention, it is important to understand the effects of multiple recordings over time on the outcome measures. Previous literature showed a moderate to high intra-individual correlation in EEG spectral analysis, with correlation coefficients ranging between 0.4 and 0.9 (Gasser et al., 1985; Kondacs and Szabo, 1999; Fingelkurts et al., 2006; Gudmundsson et al., 2007; Napflin et al., 2007). These correlations do not seem to depend on the time interval between the recordings (Salinsky et al., 1991; Olde Dubbelink, 2014). When the interval between two tests are separated by a few months or years, one should also be aware

of the effects of aging, especially in pediatric studies (Boersma et al., 2011; Smit, 2012).

## 4. Connectivity measures

To investigate functional interactions between brain regions, EEG and MEG studies have used different connectivity measures, for an overview see (Pereda et al., 2005; Stam, 2005; Bonita et al., 2014). The quantification of interacting brain regions can be subdivided into functional and effective connectivity measures (Friston, 1994, 2011). Connectivity measures are based on statistical interdependencies between signals (Aertsen et al., 1989). The extent to which brain regions are connected is defined by the strength or consistency of this statistical interdependency (Varela et al., 2001), also called synchronization. In dynamical systems the term synchronization generally refers to (phase) coupling of two or more harmonic oscillators (Boccaletti, 2002), but it is currently used in a more liberal way in brain connectivity analyses (Daffertshofer and van Wijk, 2011). Thus, a stronger synchronization, often reflected by a high coupling or consistency of oscillating systems, leads to a stronger connection. In contrast to functional connectivity measures, which only give information about the temporal correlation, effective connectivity measures also provide information on causal and therefore directed information flow between brain regions (Friston, 2011). Increasing evidence suggests that information processing in the brain follows a complex, directional pattern between brain regions (Stephan and Roebroeck, 2012). Besides effective connectivity, directed functional connectivity measures can reveal disturbances in the normal directionality of information flow in the diseased brain, for example, in dementia (van Straaten et al., 2015), epilepsy (Korzeniewska et al., 2014), or when consciousness is disturbed (Lee et al., 2013). These directed functional measures do not provide information about the causal relation between brain areas.

Deciding on the most appropriate connectivity measure can be arduous, as several issues should be considered. This includes the consideration of linear or nonlinear relations, analysis in time or frequency domain, using an amplitude or phase-based measure, obtaining directed or undirected information, and whether to include indirect relations or not (i.e., multivariate or bivariate). Linear correlations to investigate connectivity of the brain have been used for several decades and are relatively straightforward in terms of computation and interpretation, for a review see (Shaw, 1984). Since these linear methods are not able to take into account the intrinsic nonlinearity of neuronal activity, various nonlinear connectivity measures have been introduced (Pereda et al., 2005; Wendling et al., 2009; van Mierlo et al., 2014; Vindiola et al., 2014), including several phase-based connectivity measures, such as the phase locking value (Lachaux et al., 1999) and phase lag index (Stam et al., 2007b). Besides considering nonlinearity, novel multivariate connectivity measures are aiming to differentiate between direct and indirect interrelations (Friston, 2011). Whereas bivariate measures disregard the influence of other signals when computing the interaction between two signals of interest, multivariate measures try to disentangle this information in a meaningful manner. Obviously, all these different connectivity measures have their unique advantages and disadvantages. In Table 1 we provided an overview of the currently most often used measures, including their main advantages and disadvantages.

In addition to computational differences between connectivity measures, it is important to consider related methodological issues that could be encountered when choosing, and interpreting the results of, a connectivity measure. This includes, for example, the problem of field spread, volume conduction (Section 3.2) and specific reference montages (Section 3.1), which for many measures

**Table 1**  
Overview of different connectivity measures used in EEG and MEG research, with their advantages and disadvantages.

Connectivity measure	Property measured	Advantage(s)	Disadvantage(s)	Key reference(s)
Correlation	The linear relation between the amplitude of two signals in the time domain	Commonly used and straightforward method	Nonlinearity not considered Not possible to make a distinction between direct and indirect relations Sensitive to volume conduction	Brazier and Barlow (1956)
Coherence	The linear relation between the amplitude of two signals in the frequency domain	Commonly used and straightforward method	Nonlinearity not considered Not possible to make a distinction between direct and indirect relations Sensitive to volume conduction	Adey et al. (1967)
Granger causality	The future of signal X can be predicted more precisely when the past of signal Y is included and vice versa	Estimates causal interaction, and therefore directionality is assessed Well established and widely used in many fields of research	Nonlinearity not considered Methodological choices (e.g., choice of reference in EEG), as well as other confounders (e.g., volume conduction) could interfere with the actual causality	Granger (1969), Hesse et al. (2003), Bressler and Seth (2011)
Directed coherence	The directed linear relation between two signal in the frequency domain based on the Granger causality principle	Directionality of information flow	Nonlinearity not considered Not possible to make a distinction between direct and indirect relations Sensitive to volume conduction	Wang and Takigawa (1992)
Directed transfer function	Gives the causal relation between the outflow of node X towards node Y in the frequency domain based on Granger causality principle, normalized by all inflows towards node Y	Directionality of information flow Distinction between common source and interconnectedness Insensitive to volume conduction	Nonlinearity not considered Not possible to make a distinction between direct and indirect relations Noisy channels affect the directionality Difficult to estimate an optimal order for the multivariate model	Kaminski and Blinowska (1991)
Partial directed coherence	Gives the causal relation between the outflow of node X towards node Y in the frequency domain based on Granger causality principle, normalized by all outflows from node X	Directionality of information flow Insensitive to volume conduction	Nonlinearity not considered Not possible to make a distinction between direct and indirect relations No conclusion about the strength of coupling, due to normalization Difficult to estimate an optimal order for the multivariate model	Baccala and Sameshima (2001)
Imaginary part of coherence	Based on coherency <sup>*</sup> , but excluded the influence of volume conduction by including only the imaginary part of the coherency	Less sensitive to volume conduction	Nonlinearity not considered Imaginary part is mostly small, thereby risking to miss meaningful interactions Not possible to make a distinction between direct and indirect relations	Nolte et al. (2004)
Mutual information	Gives the amount of information in signal X that can be explained by signal Y and vice versa, based on the probability distribution of X and Y, and the joint probability distribution of X and Y	Mutual information is sensitive in narrow-frequency band analysis	No directionality of the interaction Weak coupling could be missed Complicated computational measure to obtain from experimental time series Not possible to make a distinction between direct and indirect relations	Fraser and Swinney (1986)
Synchronization likelihood	Describes the normalized strength of the mutual information between signal X with signal Y in state space	Adequately deals with complexity caused by interacting systems Sensitive to nonlinear relations	Sensitive to volume conduction Not possible to make a distinction between direct and indirect relations	Stam and Van Dijk (2002)
Phase locking value	Gives the modulus of the averaged instantaneous phase differences between two time series	Nonlinearity is taken into account	No directionality of interaction Sensitive to volume conduction The size of the instantaneous phase difference is included, however, there is no evidence that the size of the phase difference is important for the coupling strength Not possible to make a distinction between direct and indirect relations	Lachaux et al. (1999)
Phase slope index	Estimates the direction of information flow, based on the slope of the phase difference of the cross spectral density between signal X and Y	Directionality of information flow Weights the contribution of different time series Not affected by mixture of independent sources (e.g., background activity)	Not possible to make a distinction between direct and indirect relations Complicated computational method Not possible to make a distinction between direct and indirect relations	Nolte et al. (2008)

**Table 1** (continued)

Connectivity measure	Property measured	Advantage(s)	Disadvantage(s)	Key reference(s)
Phase lag index	The asymmetry of the distribution of phase differences between two signals	Less sensitive to volume conduction, common sources, and montage	The risk to miss linear but functionally meaningful interactions The instantaneous phase differences are binarized, therefore, small phase differences may also be missed under noisy conditions Not possible to make a distinction between direct and indirect relations	Stam et al. (2007b)
Weighted phase lag index	The contribution of the observed phase leads and lags is weighted by the magnitude of the imaginary part of the coherency	Reduced sensitivity to noise ( <i>cf.</i> PLI) Improved detection of phase synchronization changes ( <i>cf.</i> PLI)	The size of the instantaneous phase difference is included, however, there is no evidence that the size of the phase difference is important for the coupling strength Relative insensitive to phase differences around 0 and 180 degrees Mixes information about consistency and magnitude of phase differences, hampering interpretation Not possible to make a distinction between direct and indirect relations	Vinck et al. (2011)
Directed phase lag index	The probability that the instantaneous phase of signal X was smaller than the phase of signal Y (modulo $\pi$ ) over time	Directionality of information flow Less sensitive to volume conduction and common sources ( <i>cf.</i> PLI)	Directionality can be ambiguous as leading with a small differences is similar to lagging with a large phase difference Not possible to make a distinction between direct and indirect relations	Stam and van Straaten (2012a)

\* Coherency between two time signals is the linear relation at a specific frequency, an imaginary-valued measure containing information about the magnitude and phase between the signals. Coherence is the absolute value of coherency, containing only information about the magnitude.

leads to an erroneously high estimate of connectivity between two recording sites (Nunez et al., 1997; Stam et al., 2007b; Schoffelen and Gross, 2009). It is possible, however, to remove these biases prior to computing connectivity measures (Brookes et al., 2012; Hipp et al., 2012) or to estimate the influence of the bias on the connectivity measure through simulations (Brookes et al., 2011). A more straightforward approach is to use phase-based connectivity measures that are less sensitive to these spurious interactions. Typically, these phase-based measures, such as the imaginary part of coherence (Nolte et al., 2004), phase-slope index (Nolte et al., 2008) and phase lag index (Stam et al., 2007b) ignore the zero phase interaction that are the result of volume conduction/field spread (at the expense of ignoring true zero phase interactions). The phase lag index has the additional advantage that it does not depend directly on the amplitude of the signal (Muthukumaraswamy and Singh, 2011).

## 5. Functional networks

Resting state EEG and MEG data can be used to construct connectivity matrices and, consequently, functional networks by using network analysis (Sporns et al., 2004; Bullmore and Sporns, 2009; Stam, 2010). In contrast to connectivity measures, which only provide information on how pairs of different brain regions are (functionally) connected, network analysis characterizes the organization of networks (Stam and van Straaten, 2012b). Complex network analysis, a branch of graph theory, reduces the brain into a collection of 'nodes' and 'edges' and allows quantitative characterization of these networks. In EEG and MEG research, nodes correspond to the recording sites (electrodes or sensors), or specific brain regions when using a source space analysis. Edges are connections between nodes and represent (functional) connectivity values. Together, nodes and edges form the basic elements of a network, and from these elements various global and local network measures can be inferred, for an overview see (Rubinov and Sporns, 2010) and Section 5.4. Providing an overview on the vast literature on functional networks and its statistical challenges (Zalesky et al., 2010) is beyond the scope of this paper; rather,

we discuss relevant issues that need to be considered when preparing and analyzing a resting state EEG or MEG study.

### 5.1. Network construction

Functional networks are based on the strength or consistency of functional interactions between the network nodes. In a weighted network, the strength of this interaction is taken into account, whereas in an unweighted network only the existence or absence of an interaction is taken into account. Such a binary network is obtained by setting a threshold for the functional connectivity, above which a functional connection is considered to be present. A motivation to use a binary network could be to discard spurious connections that are potentially influenced by, for example, noise (Bullmore and Sporns, 2009). Selecting the value for the threshold is, however, arbitrary and may vary between individuals and groups (van Wijk et al., 2010). Although a weighted network overcomes the problem of this subjective factor and provides a more realistic representation of functional networks, spurious weak connections are also taken into account, potentially influencing network metrics. Besides weighted or unweighted, a network can be directed or undirected. In order to construct a directed network, one should use an effective connectivity measure to infer information on the directionality of communication. Although this could potentially provide useful additional information on network functioning, most studies use undirected networks (van Wijk et al., 2010).

### 5.2. Network density

Network density refers to the number of connections in a network and is influenced by the size of the network. When comparing networks between subjects, the number of nodes should therefore be equal, as it will directly influence network density and various network metrics (van Wijk et al., 2010). A straightforward approach to correct for network density is by using a binary network. This, however, will lead to a data reduction wherein valuable information of the network is not taken into account (van



Wijk et al., 2010). Other ways to reduce the effect of network density on network metrics is by using weighted networks in combination with normalization procedures that use network metrics based on surrogate data for comparison (Rubinov and Sporns, 2010; Stam and van Straaten, 2012b). Although these steps reduce the influence of network density on the eventual network metrics, it is still difficult to make an unbiased comparison between networks (van Wijk et al., 2010; Stam et al., 2014). Furthermore, each of these steps can potentially influence the computation of network metrics and should therefore be included in the methodological section of the study.

### 5.3. Minimum spanning tree

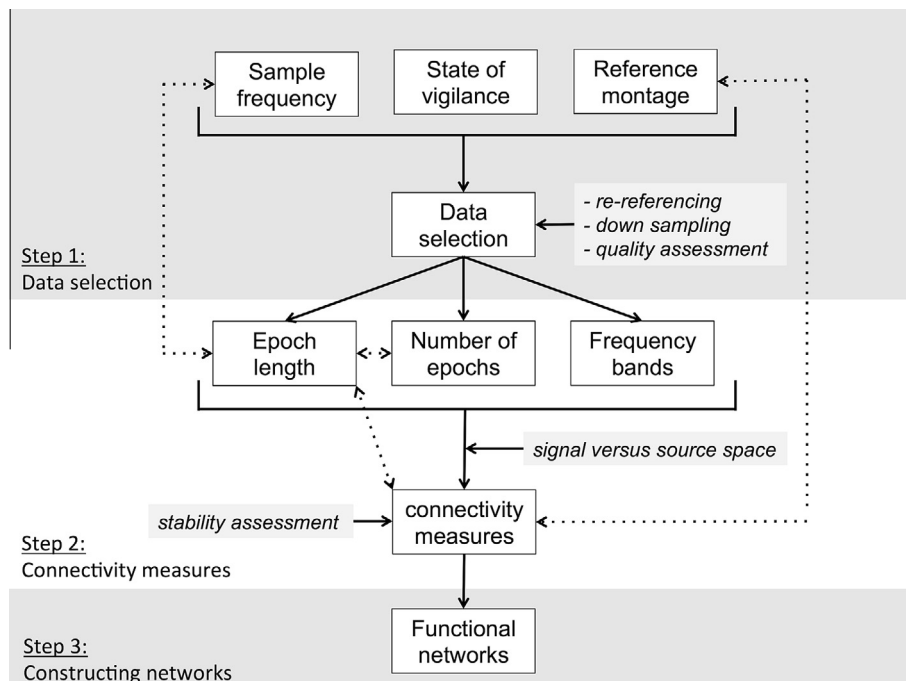
We have briefly mentioned several strategies to improve comparison between networks. Some of these strategies involve specific methodological choices, such as epoch selection, artifact handling, specific frequency bands, and connectivity measures (Section 3). Other solutions include normalization procedures and the use of weighted networks (van Wijk et al., 2010). Despite these efforts, traditional network metrics will remain sensitive to the effect of network density. A new approach to overcome the problem of network density in network analytical studies involves computation of the minimum spanning tree (MST). The MST is a unique acyclic sub graph that contains most of the strongest connections of the original undirected, weighted graph, for review see (Stam et al., 2014). As the communication in the original graph follows the most efficient paths (Van Mieghem and van Langen, 2005), the MST can be considered the backbone of the functional brain network (Van Mieghem and Magdalena, 2005; Wang et al., 2008). During the process of constructing the MST graph, connections that will lead to loops in the network will be excluded from the eventual network. By doing so, the number of connections in an MST graph will always correspond to the number of nodes minus one. As a result, MST networks with the same number of nodes will automatically have the same number of connections,

thereby facilitating the comparison of networks. Moreover, normalization procedures with surrogate networks are not necessary anymore. A possible disadvantage of the MST approach is that it may miss information about the network topology that is contained in the weaker connections of the network. An increasing number of studies have evaluated the practical utility of the MST approach for network analysis in resting state EEG (Ortega et al., 2008; Lee et al., 2010; Schoen et al., 2011; Boersma et al., 2013; van Diessen et al., 2014) and MEG (Olde Dubbelink, 2014; Tewarie et al., 2014; van Dellen et al., 2014a) recordings.

### 5.4. Global and local network metrics

Several metrics exist to characterize the organization of networks (Rubinov and Sporns, 2010). The two most commonly used network metrics are the average path length, a measure of global integration of the network, and the average clustering coefficient that defines local segregation of a network. Both average path length and average clustering coefficient are considered to be global network metrics as they provide global information of the network and are commonly used to describe the network topology. An optimal network organization is characterized by a short average shortest path length and a high average clustering coefficient, also called a 'small-world' configuration (Watts and Strogatz, 1998). Although these global network metrics are appealing to use, as they have been widely used in network analytical studies, they fail to explain the diversity found at node level (Bullmore and Sporns, 2009; Stam and van Straaten, 2012b).

To explain this diversity at node level, local network metrics are used. Network metrics like degree, betweenness centrality, and eigenvector centrality are used to specify the level of importance of a specific node in a network (Rubinov and Sporns, 2010). Nodes with many connections and a central position within the network are considered 'hubs'. Removal of a hub-node will have a considerable impact on the network (Bullmore and Sporns, 2009; Stam and van Straaten, 2012b). Often, a network is built out of smaller



**Fig. 2.** Schematic illustration how various methodological choices will influence resting state data and, consequently, the construction of functional networks. Note that choice of connectivity measures is highly depended on methodological choices. Furthermore, several methodological options exist during step 3. These options are discussed in Section 5.

**Table 2**

General recommendations for methodology of functional connectivity resting state EEG and MEG research.

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Subject-related methodological issues
<i>Heterogeneity of resting state condition</i>
- Use a priori defined instructions throughout a study to reduce the external induced heterogeneity
- Eliminate or control for possible confounders such as time of the day, intake of caffeine or medication, task or physical performance prior to recording and state of vigilance
Measurement-related methodological issues
<i>Choice of reference</i>
- Conventional reference montages will influence EEG measures, both a reference-free and (robust) common average reference are reasonable choices
- Various reference montages will influence the estimated strength and directionality of information flow and thereby the outcome of functional and effective connectivity
<i>Epoch selection</i>
- Select the first artifact free epochs after the start of the resting state recording to minimize any potential selection bias
- Re-inspect selected epochs by an independent researcher to avoid any selection or systematic bias
- Include extra epochs to perform a leave-one-out analysis to investigate stability of connectivity and network measures
- Length and sample frequency of epochs should be equal and appropriate for the connectivity measure that is used
<i>Filtering and artifact handling</i>
- Select epochs without eye-movement or muscle artifacts. If not possible, use an automatic artifact reduction approach and describe these procedures or exclude affected channels (but maintain an equal number of channels per subject)
- Use zero-phase filtering to eliminate the phase shift of digital filters on the signal
<i>Frequency bands</i>
- Differentiate neurophysiological signals in separate frequency bands when an effect is expected in specific bands. Broadband analysis could be used when testing an undirected hypothesis
- Avoid gamma band when impossible to control for myogenic influences
- Perform a spectral power analysis along with your connectivity analysis
Connectivity measures
<i>Volume conduction</i>
- Avoid connectivity measures that are susceptible for volume conduction
- Compute connectivity values per epoch and consequently an average value per subject to increase the stability of connectivity values
Functional networks
<i>Network construction</i>
- Use weighted networks to avoid subjectivity in unweighted network analysis or approaches not influenced by network density (e.g., minimum spanning tree)
- Use directed networks in combination with effective connectivity measures when information is needed on the directionality within the network
<i>Network density</i>
- When using traditional network metrics use a combination of weighted networks and normalization procedures with surrogate data to correct for the influence of density or use the minimum spanning tree approach

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subnetworks, also called ‘modules’. These modules are formed by groups of nodes that are highly connected to each other (Newman, 2006), but much less so to other nodes in the network. Provincial hubs are the most highly connected nodes within a module. Connector hubs are the important nodes connecting one module with other modules in the network (van den Heuvel and Sporns, 2013). Each local network metric captures specific information about the network topology, making it appropriate for certain analysis, depending on the specific research question. For example, the eigenvector centrality gives a more accurate estimation of the centrality of a specific node in the network than degree (Batoool and Niazi, 2014), and has lower computational costs than betweenness centrality (Lohmann et al., 2010), it is less sensitive for the detection of hubs in modules (Joyce et al., 2010) and has specific normalization problems (Ruhnau, 2000).

When making choices for specific network metrics, it is recommendable to take into account the chosen connectivity measure. Connectivity measures that depend on linear correlations or the level of synchronization are more susceptible to volume conduction (Table 1). As a result, particularly the interaction between two nearby network nodes will be overestimated (Stam et al., 2007b), which might result in an overestimation of (local) clustering. Another important issue to consider when choosing network metrics, is the influence of network density (van Wijk et al., 2010). Although it is possible to reduce the effect of network density, the MST approach offers an elegant manner to control for differences in network density. Like in conventional networks, MST metrics are inferred from MST graphs. For example, MST diameter and leaf number are global metrics that provide information on network integration and segregation, similarly to average path length and average clustering coefficient. Furthermore, various other local MST metrics can be computed (Boersma et al., 2013; Stam et al., 2014; Tewarie et al., 2014). Finally, it is important to

realize that some network metrics are highly correlated (Li et al., 2011; van Diessen et al., 2013), which means that some combinations of network metrics are redundant. It is difficult to recommend specific network metrics, as this will eventually depend on the specific research question.

## 6. Conclusions and suggestions for future research

We have summarized several problems and challenges by reviewing current practice in resting state functional connectivity EEG and MEG research. First, performing a resting state recording might not be as straightforward as it seems; behavior during, and perception of, a stimulus independent condition may vary greatly between subjects despite similar instructions (Diaz et al., 2013). In our overview, we differentiated subject-related from measurement-related methodological issues. For future research we suggest to explicitly mention the instructions given to the subject and to control for factors that might influence the state of vigilance of subjects. Second, we mentioned technical issues that are important to consider when collecting data from resting state EEG and MEG recordings (Fig. 2 for summary). Since the current literature is too diverse to provide a uniform methodological guideline, we suggest including different methodological approaches in resting state studies to better understand the influence of these approaches on study results. Some recommendations are, however, useful irrespective of the chosen approach (Gross et al., 2013). We summarized these recommendations in Table 2.

Since resting state EEG and MEG recordings are increasingly used for a network analytical approach (Bullmore and Sporns, 2009; Stam and van Straaten, 2012b), we briefly introduced some relevant topics. It is recommendable to decide on the connectivity measure and network metrics simultaneously as they are mutually

dependent. We provided suggestions to overcome some limitations that are inherent to conventional network analysis (van Wijk et al., 2010) and offered a new approach to overcome the influence of network density on network metrics: the minimum spanning tree (Stam et al., 2014).

Finally, methodological studies are needed to systematically investigate the influence of various choices that researchers have to make when conducting a functional connectivity resting state experiment. Particularly the process of selecting data and artifact handling needs a more evidence-based approach. Regarding the choice of an appropriate connectivity measure, more information on the advantages and disadvantage is available (Pereda et al., 2005; Wendling et al., 2009; van Mierlo et al., 2014; Vindiola et al., 2014). Increasing evidence exist that some connectivity measures are more vulnerable to volume conduction (see Table 1), leading to unreliable connectivity values, and consequently, unreliable network estimations. Future studies should use this knowledge to make appropriate decisions. We await methodological studies wherein different methodological issues are investigated systematically. This would be invaluable to the field of functional connectivity and network studies.

## Acknowledgments

Eric van Diessen was financially supported by the Dutch National Epilepsy Fund (NEF 09-93). We are thankful for the constructive comments of the anonymous reviewers.

*Conflict of interest:* None.

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