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Review of advanced techniques for the estimation of brain connectivity measured with EEG/MEG

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ABSTRACT

Brain connectivity can be modeled and quantified with a large number of techniques. The main objective of this paper is to present the most modern and widely established mathematical methods for calculating connectivity that is commonly applied to functional high resolution multichannel neurophysiological signals, including electroencephalographic (EEG) and magnetoencephalographic (MEG) signals. A historical timeline of each technique is outlined along with some illustrative applications. The most crucial underlying assumptions of the presented methodologies are discussed in order to help the reader understand where each technique fits into the bigger picture of measuring brain connectivity. In this endeavor, linear, nonlinear, causality-assessing and information-based techniques are summarized in the framework of measuring functional and effective connectivity. Model based vs. data-driven techniques and bivariate vs. multivariate methods are also discussed. Finally, certain important caveats (i.e. stationarity assumption) pertaining to the applicability of the methods are also illustrated along with some examples of clinical applications.

1. Introduction

There has been a growing interest in studying both normal and pathological brain function with respect to identifying variations in activation within and interactions between brain areas. Understanding and modeling brain function is based not only on the correct identification of the active brain regions, but also on the functional interactions among the neural assemblies distributed across different brain regions. The aforementioned concepts are addressed in theoretical neuroscience, as the *functional segregation* (activation of specialized brain regions/neural assemblies) and *integration* (coordinated activation of very large numbers of neural assemblies distributed across different cortical areas that constitute large-scale distributed systems of the cerebral cortex) principles [1].

Integration of cerebral areas can be measured by assessing brain connectivity. Brain connectivity can be subdivided into *neuroanatomical* (or structural), *functional* and *effective connectivity*. *Neuroanatomical connectivity* is inherently difficult to define given the fact that at the microscopic scale of neurons, new synaptic connections or elimination of existing ones are formed dynamically and are largely dependent on the function executed [2]. But for the sake of simplicity structural connectivity may be considered as fiber pathways tracking over extended regions of the brain, which are in accordance with general anatomical knowledge [3]. Magnetic Resonance Imaging (MRI) and especially Diffusion Tensor Imaging (DTI) can be used to examine structural connectivity and convey information concerning the white matter fiber tracts. Techniques for measuring neuroanatomical connectivity are discussed in other articles within this special issue.

Functional connectivity is defined as the temporal correlation (in terms of statistically significant dependence between distant brain regions) among the activity of different neural assemblies [4]. Many neurophysiologic signals can be assessed with functional connectivity techniques, including signals derived from single unit and local field potential (LFP) recordings, Electroenchaphalography (EEG), Magnetoencephalography (MEG), Positron Emission Tomography (PET) and Functional Magnetic Resonance Imaging (fMRI).

Effective connectivity is a relatively new concept defined as the direct or indirect influence that one neural system exerts over another [5]. It describes the dynamic directional interactions among brain regions. *Effective connectivity* can be estimated from the signals directly (i.e. data-driven) or can be based on a model specifying the causal links (i.e. model-based combination of both structural and functional connectivity).

Several different modalities can be used to assess brain connectivity. fMRI is widely used mostly due to the large availability of MRI scanners. fMRI provides a high spatial resolution (1–10 mm), while EEG/MEG has more limited spatial resolution

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(1–10 cm). On the other hand, fMRI has a limited temporal precision (~1 s), primarily due to the limitations of the hemodynamic response, while EEG/MEG has high temporal precision of the EEG and MEG techniques (<1 ms). Because functional and effective connectivity techniques are largely dependent on calculating the correspondence of neural signals over time, techniques such as EEG and MEG, which have excellent temporal resolution, are optimal for calculating such connectivity.

This review focuses on the most promising methodologies for assessing functional and effective connectivity from EEG or MEG signals. The introductory section provides an overview of brain connectivity, whereas Section 2 provides a historical and methodological perspective of different families of functional and effective connectivity techniques. Section 3 discusses the merits and the limitations of these techniques. The underlying assumptions of each technique are also discussed along with some illustrative clinical paradigms. Finally, the fourth section concludes this review and points out future research directions.

2. Methods

From the early 1960s [6], scientific research focusing on brain connectivity has been increasing. Throughout this time, developing methods to efficiently and accurately quantify brain connectivity has been, and still remains, a challenging problem. In this section we provide an overview of the most widely used techniques and portray some of the most representative measures in each of the following categories:

- Effective connectivity (Section 2.1)
  - o Model-based (Section 2.1.1) & data-driven (Section 2.1.2) techniques
- Functional connectivity (Section 2.2)
  - o Linear (Section 2.1.1), nonlinear methods (Section 2.2.2) and information-based techniques (Section 2.2.3)

In-depth technical details of each method are provided in relevant references.

2.1. Effective connectivity

Neural assemblies synchronize and interact dynamically in local or distant regions in order to accomplish perceptual, motor or cognitive functions [17]. Such functions reflect complex interactions that include anticipation of the stimulus, attention to the stimulus and preparation for its associated actions [18]. Such an interaction process can be realized through bidirectional or unidirectional coupling. The former case resembles mutual synchronization, where both systems adjust their rhythms to each other, whereas the latter case reflects causal interaction between the driver (initiating external force) and the response (the driven system). Dynamic Causal Modeling (DCM) [10] and *Granger-causality* [19] belong to this family of techniques. These techniques will be discussed within this section.

2.1.1. Model-based effective connectivity techniques

Neurobiologically evidence and plausible theories generated from this evidence can form theoretical models that describe how brain areas interact and influence each other. This idea is the basis for model-based effective connectivity. Using this technique competing neurobiological models and hypotheses can be evaluated. This technique allows proposed causal interactions to be assessed.

Neurobiological data are considered mixtures of independent brain sources that are spatially and temporally correlated within the context of the specific brain state being investigated. Although, this idea dates back to the mid-1980s [7], during the past decade, studies have developed novel approaches for determining the brain sources that underlie the spatial and temporal patterns of EEG and MEG signals [8,9]. In 2003, dynamic causal models were introduced for fMRI [10]. Later, this basic idea was extended to EEG and MEG [11,12]. The key to *Dynamic Causal Modeling* (DCM) technique is that the response of a dynamic system can be modeled by a network of discrete but interacting neuronal sources described in terms of neural-mass [13–15] or conductance-based models [16].

2.1.2. Data-driven effective connectivity techniques

In contrast to model-based technique, data-driven techniques do not assume any specific underlying model or prior knowledge concerning spatial or temporal relationships. *Granger-casuality* (GC) is one of the prototypical data-driven effective connectivity techniques. *GC* is based on the assumption that causes precede their effects in time. If a signal can be predicted by the past information from a second signal better than the past information from its own signal then the second signal can be considered causal to the first signal. GC is a time-domain approach, but in 1982 Geweke [20] applied this concept in the frequency domain. Geweke's work enabled the analysis of coupling between EEG frequency bands that have a well-known biomedical significance. As GC developed, the concept was generalized from bivariate to multivariate signals [21,22]. Recently the *Directed Transfer Function* (DTF) [23] and *Partial Directed Coherence* (PDC) [24] techniques were developed out the GC method. DTF and PDC are equivalent when applied in bivariate cases, but in the multivariate case PDC is able to detect not only direct but also indirect pathways linking interacting brain regions. PDC is briefly described below.

2.1.2.1. Partial directed coherence (PDC). PDC is based on the concept of *partial coherence* [25], a technique that quantifies the relationship between 2 out of n signals while avoiding volume conduction (the most critical issue of traditional coherence) by accounting for the influence of interactions from all other $n-2$ signals. PDC extends the concept for *partial coherence* by measuring directional (i.e. causal) influences. PDC is formulated using MVAR models. Suppose that a set of n simultaneously observed time series $\mathbf{x}(t)=[x_1(t),\ldots,x_n(t)]^T$ is adequately represented by an autoregressive model of order p:

$$\mathbf{x}(t)=\sum_{r=1}^{p}\mathbf{A}_r\mathbf{x}(t-r)+\boldsymbol{\varepsilon}(t) \tag{1}$$

where $\mathbf{A}_r=\begin{bmatrix} a_{11}(r) & \cdots & a_{1n}(r)\\ \vdots & \ddots & \vdots \\ a_{n1}(r) & \cdots & a_{nn}(r)\end{bmatrix}$ is the coefficient matrix at time lag r, and $\boldsymbol{\varepsilon}(t)=[\varepsilon_1(t),\ldots,\varepsilon_n(t)]^T$ is a multivariate Gaussian white process having zero mean and covariance matrix $\boldsymbol{\Sigma}$. The autoregressive coefficients $a_{ij}(r)$, $i,j=1,\ldots,n$ represent the influence of $x_j(t-r)$ on $x_i(t)$. Non-zero coefficient values can be considered as information flow from signal j to signal i. GC is a time-domain approach. PDC provides a frequency-domain description of GC [25–27].

Let the matrix $\bar{\mathbf{A}}(f)=\mathbf{I}-\mathbf{A}(f)=[\bar{\mathbf{a}}_1(f)\bar{\mathbf{a}}_2(f)\cdots\bar{\mathbf{a}}_L(f)]$ with elements $\bar{a}_{ij}(f)$ representing the difference between the n-dimensional identity matrix $\mathbf{I}$ and the matrix $\mathbf{A}(f)$. The elements $a_{ij}(f)$ of $\mathbf{A}(f)$ form the Fourier transform of the elements $a_{ij}(r)$ of the coefficient matrix $\mathbf{A}_r$, i.e. $a_{ij}(f)=\sum_{r=1}^{p}a_{ij}(r)e^{-i(2\pi/p)rf}$ Furthermore, $\bar{\mathbf{a}}_i(f)$, $i=1,2,\ldots,n$ denote the columns of $\bar{\mathbf{A}}(f)$. Then the PDC from channel j to channel i is given by

$$\pi_{ij}(f)=\frac{\bar{a}_{ij}(f)}{\sqrt{\bar{\mathbf{a}}_j^H(f)\bar{\mathbf{a}}_j(f)}} \tag{2}$$

where H denotes the transpose and complex conjugate operation. Thus, PDC ranks the relative strength of causal interaction with

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respect to a given channel while fulfilling the following normalization properties: $0 \le |\pi_{ij}(f)|^2 \le 1$ and $\sum_{i=1}^{L} |\pi_{ij}(f)|^2 = 1$, for all $1 \le j \le n$.

2.2. Functional connectivity

2.2.1. Linear connectivity

In the 1960s, linear brain connectivity began to be measured using *cross-correlation* of pairs of EEG signals [6, 28]. Higher correlations indicate stronger functional relationships between the related brain regions. In order to measure linear connectivity in the frequency domain, the use of *Magnitude Squared Coherence* (MSC) or *coherence* was introduced. Coherence allows the spatial correlations between signals to be measured in different bands [29]. Coherence is sensitive to both change in power and change in phase relationships. In other words, if either power or phase changes in one of the signals, the coherence value is affected. If there is no variation over time in the original relationship between the two signals, the coherence value remains unity [30]. This means that coherence does not give direct information on the true relationship between the two signals, but only on the stability of this relationship with respect to power asymmetry and phase relationship. Correlation, on the other hand, may be calculated over a single epoch or over several epochs and it is sensitive to both phase and polarity, independent of amplitude. However, under normal physiological conditions, no strong and abrupt power asymmetries would be expected to occur. Thus, the influence of power on coherence should be negligible and results similar to those produced by correlation would be expected for the coherence measures.

2.2.1.1. Magnitude squared coherence (MSC). Cross-correlation and MSC are the most commonly used linear synchronization methods and are defined as follows:

Consider two simultaneously measured discrete time series x_n and y_n, $n=1,\ldots,N$. Then the *cross-correlation* function (C_{xy}) is defined as

$$C_{xy}(\tau) = \frac{1}{N-\tau} \sum_{n=1}^{N-\tau} ((x_n - \bar{x})/\sigma_x)((y_{n+\tau} - \bar{y})/\sigma_y) \tag{3}$$

where $\bar{x}$ and σ_x denote mean and variance, respectively, while τ is the time lag. MSC or simply coherence is the cross spectral density function S_{xy}, which is simply derived via the FFT of Eq. (3), normalized by their individual autospectral density functions. However, due to finite size of neural data one is forced to estimate the true spectrum, known as periodogram, using smoothing techniques (e.g. Welch's method [31]). Thus, MSC is calculated as

$$\gamma_{xy}(f) = \frac{|\langle S_{xy}(f) \rangle|^2}{|\langle S_{xx}(f) \rangle| |\langle S_{yy}(f) \rangle|} \tag{4}$$

where $\langle \cdot \rangle$ indicates window averaging. The estimated MSC for a given frequency f ranges between 0 (no coupling) and 1 (maximum linear interdependence).

One of the major assumptions when using coherence is stationarity of signal. But, if the *Short Time Fourier Transform* (STFT) is used instead of the classical Fast Fourier Transform approach to calculate coherence, then the stationarity assumption can be relaxed and coherence may be calculated around a number of time instants. This technique produces the so-called "coherogram", which forms a three dimensional matrix of time and frequency vs. coherence. However, stationarity is still required within each time interval for which coherence is calculated, meaning that in practice one should carefully decide on the optimal section length (window) over which each coherence estimate is measured. Window length and overlapping within each coherence estimate affect the resolution of the measure.

An alternative method for calculating coherence is the *Wavelet Coherence* (WC) [32]. This approach requires a-priori information about the coupling range in time and frequency, in order to allocate the optimal time–frequency resolution.[1] WC is a function of both time and scale that can be mapped to specific frequency bins, broadly referred as pseudo-frequencies. The mapping procedure requires the calculation of the leading dominant frequency of the scaled wavelet basis function. WC is particularly suited to quantifying time varying coherence, since it uses a shorter window for higher frequencies and a longer one for lower frequencies, thus avoiding the constant size windows as in the STFT coherence case. Similarly to the coherogram, WC produces the so-called "scalogram", as depicted in Fig. 1.

An interesting enhancement to the calculation of WC is the definition of a probability distribution of the calculated coherence values that can be used to define the 95% confidence level. In order to apply these ideas on real EEG signals one may set a population specific background spectra (or control-task spectra) defined as the mean time-averaged wavelet power spectrum for each EEG channel and scale averaged over all subjects performing a control task [33]. Having derived this threshold, it is possible to indicate significant regions of increased or decreased coherence over the scalogram and form a single measure per scale that reflects the *Significant Wavelet Coherence* (SWC). Basically, we are able to obtain the coherence values over those time- and frequency band-localized regions where significant coherence is indicated by taking the coherence averages over certain bands and significant time intervals (contours depicted as dashed lines in Fig. 1). An interesting study that successfully utilizes this approach in extracting the variability of neural interconnections in schizophrenia patients, as compared to healthy controls [34], is discussed later in the clinical application section.

2.2.2. Nonlinear coupling techniques

Nonlinear methods are not designed to outperform linear methods but rather provide complementary information under certain and rather strict assumptions. Nonlinear measures for measuring the dynamics of an EEG signal were developed based on deterministic chaos [35]. Nonlinear neural time series analysis was motivated by the fact that many crucial neural processes have nonlinear characteristics (e.g. the regulation of voltage-gated ion channels corresponds to a steep nonlinear step-function relating membrane potential to current flow). In the early 1980s, the concept of synchronization was introduced to measure neural connectivity. Synchronization is based on interacting chaotic oscillators [36,37]. Synchronization may be understood as an adjustment of rhythms of oscillating objects due to their weak interaction [38]. In neuroscience studies, synchronization is mainly represented by the concepts of the *phase-* and *generalized-synchronization* [39]. Phase-synchronization (PS) [40] is most commonly seen in gamma frequency large-scale oscillations that enter into precise phase-locking over a limited period of time when the subject is engaged in cognitive tasks. PS is also considered an important mechanism in certain diseases, such as the genesis of epileptic phenomena [41]. One representative method capable to obtain a statistical measure of the strength of PS in different areas of the brain is the *Phase Locking Value* (PLV) [39, 42].

2.2.2.1. Phase synchronization—PLV. The PLV approach assumes that two dynamic systems may have their phases synchronized

[1] Time-frequency resolution is constrained by the uncertainty principle: the wider the windows, the better the frequency resolution, at the expense of timing information, and vice versa.

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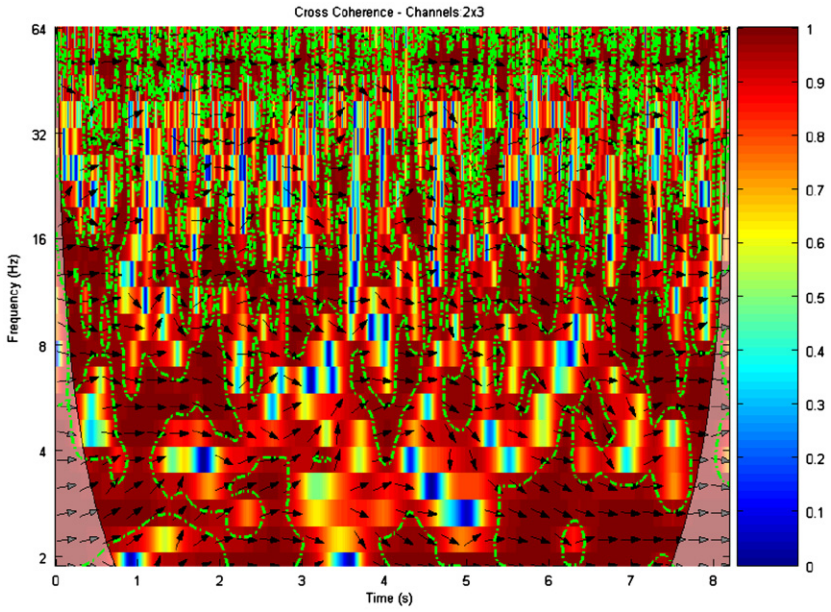

Fig. 1. The squared WC time–frequency transformed scalogram. The 5% significant regions over the time-scale transform are indicated by the contours (green dashed outline). The outer elliptical region at the edges of the second graph indicates the cone of influence in which errors (edge effects) may be apparent due to the transformation of a finite-length series EEG signal [48]. The relative phase relationship is also shown as arrows (with in-phase pointing right, and anti-phase pointing left). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

even if their amplitudes are zero correlated [43]. PS is defined as the locking of the phases associated to each signal, such as

$$|\phi_x(t)-\phi_y(t)| = const \tag{5}$$

In order to estimate the instantaneous phase of a signal, Hilbert transform (HT) may be used to form the analytical signal $H(t)$ as

$$H(t) = x(t)+i\tilde{x}(t) \tag{6}$$

where $\tilde{x}(t)$ is the HT of $x(t)$, defined as

$$\tilde{x}(t) = \frac{1}{\pi} PV \int_{-\infty}^{\infty} \frac{x(t')}{t-t'} dt' \tag{7}$$

where PV denotes the Cauchy principal value. The analytical signal phase is defined as

$$\phi(t) = \arctan\frac{\tilde{x}(t)}{x(t)} \tag{8}$$

Therefore for two signals $x(t)$, $y(t)$ of equal time length with instantaneous phases $\phi_x(t),\phi_y(t)$ the PLV bivariate metric is defined as

$$PLV = \left| \frac{1}{N} \sum_{j=0}^{N-1} e^{i(\phi_X(j\Delta t)-\phi_Y(j\Delta t))} \right| \tag{9}$$

where Δt is the sampling period and N is the sample number of each signal. PLV takes values within [0,1], where 1 indicates perfect phase synchronization and 0 indicates lack of synchronization.

2.2.2.2. Generalized synchronization. After the successful application of PS in EEG analysis, another type of synchronization, namely the *Generalized Synchronization* (GS), was developed. GS represents how well neighborhoods (i.e. recurrences) of one chaotic attractor maps onto the other. Attractor mapping is considered to be a robust way of assessing the extent of GS [39, 44–46], even if it is prone to stationarity shortcomings. To form such attractors from the raw EEG data, delay vectors need to be constructed out of the time series using the following procedure known as time-delay embedding [47]:

$$x_n = (x_n,\ldots,x_{n-(m-1)\tau}) \text{ and } y_n = (y_n,\ldots,y_{n-(m-1)\tau}) \tag{10}$$

where $n=1,\ldots,N$, and m and τ are the embedding dimension and time lag, respectively. Let $r_{n,j}$ and $s_{n,j}$, $j=1,\ldots,k$, denote the time indices of the k nearest neighbors of x_n and y_n, respectively. For each x_n the mean squared Euclidean distance to its k neighbors is defined as

$$R_n^{(k)}(X) = \frac{1}{k}\sum_{j=1}^{k} (x_n - x_{r_{n,j}})^2 \tag{11}$$

and the Y-conditioned squared mean Euclidean distance $R_n^{(k)}(X|Y)$ is defined by replacing the nearest neighbors by the equal time partners of the closest neighbors of y_n. If the set of reconstructed vectors (point cloud x_n) has an average squared radius$R(X) = (1/N)\sum_{n=1}^{N} R_n^{(N-1)}(X)$, then $R_n^{(k)}(X|Y) \approx R_n^{(k)}(X) \ll R(X)$ when the systems are strongly correlated, while $R_n^{(k)}(X|Y) \approx R(X) \gg R_n^{(k)}(X)$ if they are independent. Hence, an interdependence measure is defined as [46]:

$$S^{(k)}(X|Y) = \frac{1}{N}\sum_{n=1}^{N} \frac{R_n^{(k)}(X)}{R_n^{(k)}(X|Y)} \tag{12}$$

Since $R_n^{(k)}(X|Y) \geqslant R_n^{(k)}(X)$ by construction, S ranges between 0 (indicating independence) and 1 (indicating maximum synchronization). Another normalized and more robust version of S is defined as [45]:

$$N^{(k)}(X|Y) = \frac{1}{N}\sum_{n=1}^{N} \frac{R_n(X) - R_n^{(k)}(X|Y)}{R_n(X)} \tag{13}$$

For an in-depth mathematical reasoning and historical overview of the aforementioned techniques the interested reader is referred to [48], while a detailed comparison of the aforementioned synchronization methods applied in epileptic data analysis is presented in [39].

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2.2.3. Information-based techniques

Information-based techniques are sensitive to both linear and nonlinear statistical dependencies between two time series. The most representative method is the *Cross Mutual Information* (CMI) that measures the mutual dependence between two signals by quantifying the amount of information gained about one signal from measuring the other, as a function of delay between these two signals. CMI has been used in method for diagnosing Alzheimer's disease and Schizophrenia [49,50], as discussed in Section 4.

Another information-based method for assessing the dependence between time series is based on the degree of predictability of each of the two time series as a function of the other [39]. More specifically, the *Minimum Description Length* (MDL) principle is based on the idea that the best model for representing a signal is the one with the shortest possible code length. According to the MDL principle, the savings in code length of one signal due to the knowledge on the other is a measure of dependence between the two processes [51].

Information-based measures may also assess causality as already discussed in Section 2.1.2.

3. Discussion

This section illustrates the different underlying assumptions and limitations of each family of methods, in order to help the reader decide upon the best candidate method for a particular research study.

3.1. Model-based vs. data-driven techniques

The different underlying assumptions of both model-based and data-driven techniques need to be considered when selecting one of these methods for a specific problem. Model-based approaches (e.g. DCM) are based on well-defined biophysical models of neuronal dynamics. In this case one should choose the best model (or set of interacting models) and predefine or experiment with a large number of different parameters in order to test a preset hypothesis. The uncertainty in predefining these parameters and the large number of possible combinations of parameters is the main drawback of model-based techniques. Established methodologies may assist in determining the best possible model [52]. However, it is very possible that no single model exists but rather multiple models may be equally appropriate for a given data set.

Data-driven methods do not assume any specific underlying spatial or temporal relationship. Such methods can be used in assessing connectivity when no a-priori structural knowledge is available.

3.2. Stationarity considerations

Most of the methods presented assume stationarity. For a process to be stationary, the mean, variance and autocorrelation structure cannot change over time. Generally, an EEG distribution is considered as a multivariate Gaussian process even if the mean and covariance properties change from segment to segment. Therefore, strictly speaking, an EEG signal is quasi-stationary since it is stationary only within short intervals. During mental and physical activities this assumption can easily be violated since the state of the brain can change in alertness and wakefulness. In addition, care must be taken when examining EEG signals from epilepsy patients as transitions between pre-ictal and ictal states often occur in such cases. WC provides a balance between a data segment long enough to provide good frequency resolution and short enough to satisfy the condition of stationarity. In conditions in which the stationarity assumption is violated, a stationarity independent measure such as PLV can be used. In addition, a novel and promising technique capable of decomposing a multivariate time series into its stationary and nonstationary part known as stationary subspace analysis can be utilized to overcome these implicit stationarity constraints [53].

3.3. Multivariate modeling considerations

There is a growing interest in extending interdependence analysis from bivariate to multivariate signals. This is important since pairwise analysis is likely to find spurious correlations in cases where one driver drives two responses. In this case both responses may have a common driver, even if the responses appear to be fully independent. Several of the techniques are multivariate, such as the GC, DTF, PDC and the GS measures. However, all these methods depend on the reliability of the fitted MVAR model and especially the model order and epoch length. If the order is too low, the model misses the dynamic nature of the signal, whereas if it is too high overfitting mainly emphasizes noise. A number of methods such as the Akaike Information Criterion (AIC) [54] can be used to determine the optimal model order.

3.4. Linearity/nonlinearity assumptions

Chaotic systems appear to have noisy behavior, which is actually ruled by deterministic laws. Although the nonlinear measures presented are capable of identifying nonlinear interdependences, they are highly susceptible to noise and, in the case of GS, the embedding parameters. Another crucial issue is the requirement of rather long stationary epochs. However, even though neurons are theoretically highly nonlinear devices, strong evidence of chaos has not been found in EEG data [55]. Hence, at the present time, there is a wide consensus that the EEG signal is not chaotic, at least in low-dimensions. Another classical misconception is that nonlinear tools may replace linear ones. The opposite seems to be more valid; linear measures are more robust and perform well even in nonlinear cases [39]. Nevertheless, nonlinear analysis should be used to complement linear ones in order to capture and provide additional information hidden in linear approaches [39].

3.5. Source estimation imaging vs. surface electrode connectivity

Another great concern lies in the problem of acquiring mixed activity captured from more than one brain region, when using surface sensors (electrodes) to capture the signals. This can cause spurious connectivity patterns. There are a number of recently proposed source imaging techniques that can account for volume conduction effects and can be applied in some of the techniques reviewed in this paper. Most prominently, linear decomposition techniques such as Principal Component Analysis (PCA) [56] and Independent Component Analysis (ICA) [18,57] [58], which attempt to invert the mixing process, can be utilized prior to further connectivity analysis.[2] On the other hand, there is also the possibility to examine only the imaginary part of the cross-spectrum since only the real part is affected by instantaneous effects when using spectrum-based techniques [59]. In that way there is no need for signal decomposition.

Finally, it should be noted that graph-theoretic concepts can also be used to visualize and quantify brain network topologies using the presented connectivity measures [60,61].

Table 1 summarizes the characteristics of the most widely accepted methods discussed in this review.

[2] ICA can be also used in neuroimaging to study connectivity directly.

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Table 1
Comparison of representative methods for estimating brain connectivity.

	DCM	MSC	STFT COH	WC	PLV	GS	GC Geweke	PDC
Linear	X	X	X	X				
Nonlinear					X	X		
Info-based							X	X
Model-based	X							
Data-driven		X	X	X	X	X	X	X
Causality assessing	X						X	X
Multivariate	X					X		X
Stationarity independent				X	X			
Functional connectivity		X	X	X	X	X	X	X
Effective connectivity	X						X	X

DCM: Dynamic Causal Modeling;
MSC: Magnitude Squared Coherence;
STFT COH: Short Time Fourier Coherence;
WC: Wavelet Coherence;
PLV: Phase Locking Value;
GS: Generalized Synchronization;
GC: Granger Causality;
PDC: Partial Directed Coherence.

3.6. Clinical applications

The continuous advancement of neuroscience methods applied in EEG/MEG has been successful in capturing the underlying processes of several neurological disorders and neurodegenerative diseases [62]. Studies incorporating the various connectivity methods discussed in this paper are presented in this section. As will become evident below, there is no single optimum method for assessing brain connectivity. Efficiency greatly depends on the application and the underlying assumptions of each connectivity method.

Epilepsy is a common neurological disorder that has been extensively studied using both EEG and MEG. One clinically useful application is localization of the epileptogenic brain activity to better define a surgically lesion [63]. In childhood epilepsy, visual inspection of EEG tracings or traditional spectral analysis may not show differences between children with a history of seizures and normal controls. Yet, more sensitive connectivity methods, which are able to identify subtle abnormalities, may be useful in the evaluation of neurophysiological activity and guiding clinical management [39]. Different measures of quantifying synchronous oscillatory activity (MSC, MDL, PLV and GS) were evaluated in [39] using a three-stage assessment framework. Initially, the nonlinear methods were validated on coupled nonlinear oscillators (artificial signals) under increasing noise interference; second, surrogate data testing was performed to assess the possibility of nonlinear channel interdependencies in the acquired EEG data; and finally, synchronization on the actual data was measured. This approach concluded that in a real case scenario, one should use both a PS measure (e.g. PLV) and a GS measure, as well as linear connectivity methods since their underlying assumptions are different. For example, the PLV method performed better when applied to phase-synchronized oscillators but underperformed when examining general synchronized oscillators.

In *Alzheimer's disease* (AD) many studies find that reduced brain signal synchrony can facilitate early diagnosis. CMI was studied in [49] in order to quantify information transmission between different cortical areas in 15 AD patients. Information transmission was found to be lower between distant electrodes in the right hemisphere and between interhemispheric electrodes. This suggests a functional impairment of information transmission in long cortico–cortical connections in AD patients, consistent with previous research. MEG coherence can also be used to monitor the effects of intravenous scopolamine injection [64] in AD. In this latter study, interhemispheric and left intrahemispheric coherences were found to significantly decrease in the theta band frequency band. This suggests that MEG and functional connectivity measures may provide a tool for monitoring neurological disorder progression associated with cholinergic abnormalities. More recently GC, phase synchrony and nonlinear generalized synchronization based measures have also been tested in AD [65]. GC was able to discriminate patients from age-matched control patients achieving 82.9% classification rate (in a leave-one-out classification scheme). In addition, CMI when applied in 15 AD patients and age-matched normal controls was successful in identifying EEG abnormalities in AD patients with functional impairment of information transmission in long cortico–cortical connections [49].

Schizophrenia has been another very promising application domain because connectivity analysis is able to test the disconnection hypothesis of schizophrenia [66]. CMI was used to evaluate the information transmission of different cortical areas in 10 schizophrenic patients and age-matched controls [50]. Interhemispheric and intrahemispheric CMI values in schizophrenics were significantly higher than normal controls suggesting left temporal lobe deficit and inter- and/ or intrahemispheric overconnectivity in schizophrenics. PLV was also able to reflect perceptual binding deficits especially in the 40 Hz frequency range [67,68]. More recently, working memory experiments (from 20 stable patients with schizophrenia and controls) based on WC assessment were able to successfully study and support the "disconnection syndrome" hypothesis when examining the gamma frequency band [34]. In a similar working memory framework, using mutual information applied in MEGs from 28 people with schizophrenia, the importance of beta-band oscillations for long-distance functional connections in brain networks was highlighted [69].

Similarly to schizophrenia, an underconnectivity hypothesis also applies in *autism* [70]. A very recent study [71] achieved an overall performance of 87.5% accuracy of discriminating a group of 8 autistic individuals vs. healthy controls, based on GC connectivity measures. Another work suggests that the usage of nonlinear methods and specifically the coarse-grained entropy synchronization applied in sleep EEG may enable differences in children and infant brain connectivity to be detected. More specifically it was found that synchronization was significantly lower in children with autism than in a group of typically developing children [72], supporting the theory that the autistic brain exhibits low functional connectivity. More recently, the nonlinear complexity of resting EEG computed with modified multiscale entropy was able to distinguish typically developing children from a group of infants at high risk for autism spectrum disorder [73]. The study involved 79 different infants (46 at a risk for ASD and 33 controls) and reached almost 100% classification accuracy for boys at age 9 months and 70–90% at ages 12 and 18 months.

As a final example of an application, *alcoholism* is presented. Impaired cognitive functioning and specifically intrahemispheric, posterior coherences are found to be significantly increased in the alpha and beta frequency bands both in long-term abstinent and non-abstinent alcohol-dependent subjects [74]. Alcoholics experience cognitive deficits while performing complex cognitive tasks as expressed also in generalized synchronization studies [75]. Lastly, both linear and nonlinear interdependence measures (MSC, PLV and the GS presented method) were also investigated in alcoholics during mental rehearsal of pictures [76]. The results were in accordance with previous psychophysiology studies suggesting that an alcoholic has impaired synchronization of brain activity and loss of lateralization during the rehearsal process, most prominently in alpha and lower beta frequency bands.

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4. Conclusion

A variety of advanced brain connectivity methodologies are reviewed in this manuscript. Although the majority of these techniques are currently research-based many may be clinically useful in the near future for evaluating cortical dysfunctions in cases where classical EEG evaluation is inadequate. The use of model-based/data-driven, bivariate/multivariate, causality-assessing, linear/ nonlinear and information-based techniques allows the analysis of complex cortical interactions from different, novel perspectives. However, the accuracy of the results highly depends on the underlying assumptions of each approach, as well as the application under consideration. Although analysis of brain functional has evolved significantly during the last decades and a variety of methods addressing both functional and effective connectivity are currently available, there is no single optimum technique to universally assess brain connectivity.

In the years to come, more sophisticated and powerful methods will be developed which empower our current understanding of functional brain connectivity. Future methods for assessing cortical connectivity patterns with greater spatiotemporal accuracy include multimodal fusion approaches integrating modalities that provide excellent temporal resolution (e.g. EEG and MEG) with modalities that offer better spatial resolution (e.g. PET and fMRI). Further development of neuroconnectivity methodologies would include combining both neuroanatomical information derived from diffusion tensor imaging and high temporal resolution functional connectivity approaches. Such methodologies will be suitable for capturing the dynamic evolution of the time-varying connectivity patterns that reflect certain cognitive tasks or brain pathologies.

Conflict of interest statement

None declared.

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