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Article

Measuring Electromagnetic Oscillatory Brainwaves and Networks: Methodological Considerations

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Abstract: Ever since the first discovery of human brain waves in 1929, brain rhythm has been attracting interest in the field of neuroscience. The integration of distributed brain functions similar to small-scale circuits for the same task in a larger scale network which oscillations facilitate offers a means to study the brain at work. Importantly, changes in synchronized brain oscillations may reveal important aspects of pathophysiology. For example, excess beta rhythms are characteristic of Parkinson's brain. However, various spatial distributions and frequencies of neuronal oscillations and nonlinear and complicated neuronal processes make it difficult to understand neuronal messages, and it is needed to find an appropriate model. Thus, we present a brief review of techniques used in characterizing frequency-related local fluctuations and interactions between neuronal assemblies by measuring electroencephalography (EEG) or MEG. Specifically, we focus on the objectives of these methods, including: (1) inferential versus non-inferential, (2) linear versus nonlinear, (3) uni-versus multi-variate, and (4) power modulation versus phase-synchrony. Three practical issues – that are typically confronted when applying these methods – are also discussed. This article aims to provide readers who are not familiar with current methods an accessible overview – that may help the neuroscientists to interpret the similar findings of this study.

Keywords: Oscillations, Brainwaves, Networks; MEG, EEG, Analytic Method, Connectivity, Synchronization

1. Introduction

Oscillatory brain activities and their functional roles

Frequency contents such as spectrum define electromagnetic waves, which are applied to brain rhythms. Brain rhythms are grouped into θ, α, β, γ, and high γ bands according to the frequency such as 4–8, 8–14, 15–30, 30–80, and 80–150 Hz, respectively. The oscillatory feature has been observed in human brains in different scales from a unit-based process by using a local to a larger scale measures of EEG or MEG [1–4]. According to regions in a brain or an underlying task, brain rhythms have different frequency contents. For example, mu (10– and 20– Hz) rhythms are observed in sensorimotor regions during rest [5], while occipital alpha rhythms (–10 Hz) with closed eyes [6]. As oscillations integrate segregated and engaged brain areas as small-scale circuits and large-scale networks, neuroscientists have been interested in brain rhythms [7–11]. For example, the modulation of oscillations at >10, >20, and >30 Hz are associated with M1 of the primary motor cortex, M2 of the supplementary motor area (SMA), and PM of the premotor cortex, respectively, for the control of movement [12–15]. It reflects moving mechanisms such as speed and movement types [3, 16–23]. In particular, mu rhythms are read during observation of actions by playing a certain role in the 'mirror neuron' system [24–25]. In diseases, oscillatory activity may reveal the pathological modulation of specific frequencies affecting particular neuronal systems. Patients with Parkinson's disease show a simultaneity at 4–6 Hz in the contralateral primary motor cortex and forearm muscles, which contributes to the resting tremors. Their excessive synchronization at 10–35 Hz in the basal ganglia/subthalamic nucleus is related to bradykinesia [26]. Moving face muscles engage multiple oscillations of δ, θ, α, β, γ bands [27]. Face recognition changes in the frequency of 4–45 Hz in the parietal and frontal cortices, and fusiform gyrus [28,29]. Recently, functional asymmetries have been found in the fusiform and occipital face area in face recognition in the connections of a core network [30].

Neuronal oscillations have various spatial distributions and frequencies, which involve brain network functions. The complex and nonlinear neuronal process makes it difficult to understand the nature of passing neuronal messages and functional integration.

Thus, an appropriate modeling method becomes self-evident. In this article, methodological issues in neural networks are reviewed and compared between uni-and multivariate methods for inferential and non-inferential modeling, linear and nonlinear methods, and power fluctuation and phase-synchronization.

2. Measuring brain waves and network connectivity: methods

2.1. Inferential and Non-inferential modeling

Numerous time-series data is necessary for neuroscience provides abundant, which requires developing and validating methods for studying the architecture of brain functions. Generally speaking, there are two ways to study neuronal time-series modeling: inferential and non-inferential. Breiman stated that there are two statistical modeling methods: a stochastic data model and an algorithmic model [31]. A stochastic data model is referred to as the inferential method, while an algorithmic model is referred to as the non-inferential method. The inferential method integrates previous learning into deterministic or probabilistic models with data based on Bayes' theorem [32]. The evaluation of the distribution in the posterior and parameters of a model is used to infer the underlying model. Non-inferential methods recognize the variation source without an explicit model to examine the validity of data and detect outliers. Non-inferential methods adopt descriptive methods to investigate correlation and coherence for functional connectivity. Inferential methods are used to measure connectivity. Both methods have different analysis approaches. Inferential methods are based on assumptions of the model to restructure an analysis method. The general linear model (GLM) and dynamic causal model (DCM) belong to the inferential method [33–35]. In the method, the analysis through inference is focused on the model parameters and structure. Non-inferential models explore the data to suggest the most appropriate structure. The principal component analysis (PCA) [36] or ICA [37–39] belong to it. As the non-inferential model does not require model specifications, using the model is easy but interpreting the results is difficult. Figure 1 describes the inferential and non-inferential approaches.

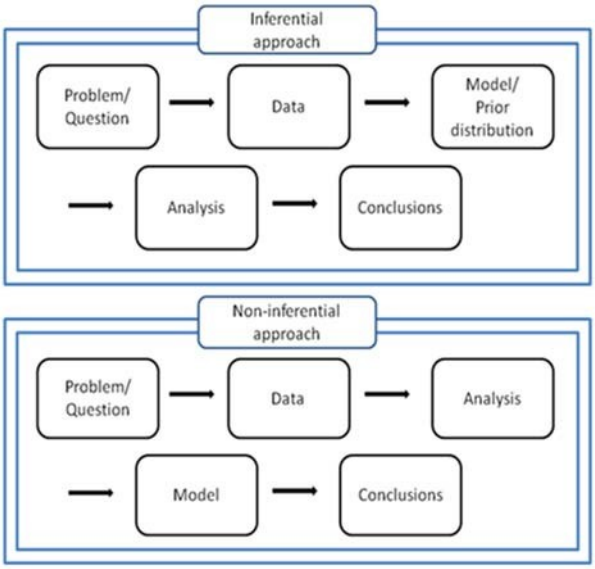

Fig. 1. Data analysis process of inferential and non-inferential models.

2.2. Linear and Nonlinear methods

A function f with independent variables $\boldsymbol{X} = \{x, x \ldots x\} \in \boldsymbol{R}^n$ is linear if $f(X) = AX+B$. A nonlinear function cannot be written as such. $f(X) = AX^2 + BX + C$ is an example with the constants of A, B, and C. A linear function follows the superposition principle: $f(a X_1 + b X_2) = a f(X_1) + b f(X_2)$. In the control theory of signal processing, a system is characterized solely by a fundamental function [32,40]. Here, the system is composed of sets of multiple interconnected components with $X(t)$ (input), $Y(t)$ (output), and the system function $f(t)$. $f(t)$ is an impulse response function in the time domain or transfer function in the frequency domain. It transforms the input to the output and is represented as $Y(t) = f(t) \otimes X(t)$ ($\otimes$: convolution operator). The system is linear only with linear $f(t)$. Then, estimating neuronal architectures (coupled neuronal systems) is allowed with the system function. Linear methods estimate the dependencies of variables, whereas nonlinear methods do not. The linear method only concerns the transfer function of the first order, as the function is easily applied to estimate, while the non-linear method concerns high-order and generalized transfer functions as they are related to brain dynamics that are with linear features in bispectral analysis.

In the frequency domain, cross-frequency interactions are nonlinear as different frequencies are coupled by high-order transfer functions [41]. Linear methods measure the coupled frequencies based on a first-order transfer function. Coherence and correlation as linear approaches are used to study oscillatory neuronal activity and associated networks [42–45]. Linear methods are adopted to extract the significant data features and summarize system characteristics. However, a linear method does not represent all brain signals accurately [46] as nonlinearity is crucial in neuronal dynamics [47]. Nonlinear methods are widely applied in inter-areal communication that uses cross-frequency coupling with time-series properties [14, 33, 47–50]. On a microscopic scale, nonlinear interactions at synaptic connections show a modulatory effect on post-synaptic response generation [51]. However, on a macroscopic scale, the nonlinear coupling has yet to be fully understood in its roles [47, 51–52]. However, the nonlinear coupling is thought to have modulatory effects for top-down processing [53–55], which is important as brain function such as prediction uses both bottom-up and top-down connections in recurrent neuronal message passing. That is, when the area of cortical hierarchy processes sensory information, the prediction is passed to the area as bottom-up processing, which is predictive coding [56,57].

Such nonlinear coupling plays an important role in selecting bottom-up signals and understanding pathological brain states. Studies on Parkinson's disease suggest that beta rhythms (13–35 Hz) in the subthalamic nucleus are coupled nonlinearly [58] and nonlinear properties of multichannel EEG are manifest [59]. The motor system's cortico-cortical coherence is decreased in a linear relationship under the same pathological conditions (symptomatic) despite related oscillations being synchronized [60]. The linear and nonlinear interactions are complementary to each other in the neuronal network, which involves various brain states to affect health and disease dynamically. The linearity of two different time-series data in the statistical dependency is used to quantify long-term interactions by using EEG [43,61] while the nonlinear method is used to explain couplings among different frequencies. The linear and non-linear approaches assess different interdependencies between signals [62].

2.2. Univariate versus Multivariate approaches

Univariate and multivariate approaches have different numbers of variables. While univariate methods deal with one variable, multivariate methods with multiple variables. Univariate methods are used to estimate controlling parameters of the changes of neuronal activity at a point (a channel of MEG/EEG), while multivariate methods are used to assess the dependencies of multiple signals. In multivariate approaches, a large-scale interaction is considered with distributed network elements. Univariate analyses include task-related power (TRPow), ERD/ERS [63–65], or correlation dimension (D2) [66,67] which are for a single time series to find out a task manipulation and difficulty. In this case, the high task loading produces the greater D2 value. Multivariate approaches such as coherence [44, 63–65], Granger causality [68], cross mutual information [48] and dynamic causal model (DCM) [33,34] are used to analyze multiple time series data. The approaches are adopted to estimate neuronal connectivity of the underlying network functions. Recently, with the advent of high-performance computing, many machine learning methods have been developed, such SVM and deep learning [69]. Machine learning is a data analytics technique that teaches computers to "learn" information directly from data. The learning principles, and underlying machine learning algorithms, build a model based on given data features/attributes, known as "training data", without explicitly relying on a predetermined functional form for the model. After training, the neural network can be used to make predictions, decisions or discover previously unknown structures in the data. MEG and EEG studies that employ machine learning methods can be considered a kind of multivariate approach.

Univariate approaches implement and trace time series data easily. However, multivariate approaches estimate covariances from the fluctuations of different time-series data, which is complex to be carried out without appropriate assumptions. For example, with independent errors that are not correlated with each other, error covariance estimation becomes straightforward with its diagonal matrix [70]. The integration of functionally specialized brain areas controls perceptions, thoughts, and actions. Thus, multivariate approaches are more proper to study brain functions. Univariate and multivariate approaches are used to describe

different distinct features of the neurophysiological systems, so dependent on each other. The neuronal network connectivity with multivariate characteristics increases the system's dimensional complexity by a univariate measurement (D2 values) [71].

2.3. Power modulation versus Phase synchronization

Oscillations (oscillatory activity) are described in a time-frequency space in two dimensions by using Fourier or wavelet transforms. The oscillatory activity in time series is a weighted sum at different frequencies which is calculated by basic functions. With a known basic function, the weight of w (different frequencies) and t (time bin of the time series) is projected by a convolution procedure, that is, a convolution of $x(t)$ with a basic function $\phi(t)$. Thus, $W(\omega,t) = \int x(t)\cdot\phi(\lambda - t)d\lambda$. The basic function is sinusoidal and expressed as a Morlet wavelet with Fourier and Morlet wavelet transform. A complex basic function in transformation makes the accompanying spectra complicated. Thus, the following components are found in a spectrum: the frequency-specific amplitudes, the squared magnitude of the real part of complex numbers, and the instantaneous phase $\theta(\omega,t)$. This is induced from the imaginary part of the complex number as $\theta(\omega,t) = a\tan(im(w(w,t)), re(w(w,t)))$.

Power and phase are important elements to consider in spectral analysis. A key to understanding neuronal network dynamics is found in fluctuations of the synchronization of power and phase. The power and phase in a spectra $W(w,t)$ are written as $W(w,t) = a_W(t)\exp(i\phi_W(t)t)$ where $a_w(t)$ and $\phi_W(t)$ are the amplitude and phase modulation, respectively [72]. $a_W(t)$ and $\phi_w(t)$ can be correlated but sometimes independent. This characteristic is used in telecommunication such as amplitude modulation (AM) and frequency modulation (FM) [73]. However, the relationship between phase and power remains unclear in neuroscience. Increases of a regional power of event-related synchronization (ERS) increase population activity and phase constancy, while they decrease regional power of event-related desynchronization (ERD) as loss of neuronal activity or phase constancy and phase constancy are suppressed. ERD increases phase constancy through the anti-phase pair formation [72].

Study results in animal neuroscience show that the synchronous discharge in neuronal assemblies interacts in neurons/areas that trigger the brain's organization of functions. Changes in the synchronous discharge cause changes in task-related frequencies in ERS or ERD. This phenomenon changes in the course of an event internally or externally. As the change is dependent on contexts, it occurs over different time scales to alter the connectivity due to attention modulation and somatotopic reorganization due to limb amputation [74]. The change of the spectral densities [75] and partial phase resetting/shifting occurs over multiple frequencies [47,70,76]. For example, the coherence of phase constancy at α and β bands enlarges in the primary motor cortex when movements are prepared and executed of movement, which is followed by ERD [4]. Babiloni et al. reported that β and γ ERS of the hippocampus and θ ERD in the inferior temporal cortex causes the coherence of γ in the middle temporal cortex for repetitive visuomotor events [64]. Phase–power relation is used to explain 'nested rhythms' [77] which occur by the coupled phase of a low rhythm with that of a high rhythm. This is observed in memory tasks that use θ-γ [78] θ-β, θ-β [79], θ-β/γ [80] and in sleep that has infra-slow oscillations of ISOs 0.02/0.2–1 Hz [81] and resting (α-high γ) [82]. A tight coupling may exist in the synchrony of power and phase and even in two different phenomena. Indeed, the coupling is related to common generative mechanisms and has complementary characterizations. Table 1 presents how the above methods are used.

Table 1. Characteristics of the methods in this study

	Linear	Non-linear	Univariate	Multivariate	Inferential	Non-inferential	Power	Phase
Task-related Power/ERD	O		O			O	O	
Correlation Dimension (D2)		O	O			O	O	
Coherence	O			O		O		O
Granger Causality	O	O+		O		O	O	

Principal Component Analysis (PCA) / Independent Component Analysis (ICA)		O		O		O	O	
Phase synchrony	O	O		O		O		O
General Linear Model	O			O	O		O	
Dynamic Causal Modelling for Induced responses	O	O*		O	O		O	
Machine learning methods	●	●		O		O	●	●

+ : Granger causality to measure the nonlinear coupling
* : Dynamic Causal Modelling to measure the nonlinear coupling
● : depending on the nature of input attributes, the features may reflect linear and/or nonlinear properties, phase or power information

3. Three practical questions about measuring the brain dynamics and network connectivity

In this section, we address three practical issues that one could confront when applying these methods to study brain dynamics and network connectivity.

3.1. Functional or effective connectivity?

There are two ways to parameterize the coupling in brain networks: effective and connectivity. Functional connectivity relies upon the statistical dependency among remote neurophysiological time series data. Establishing a connection needs measuring mutual information in the general formulation. Usually, one assesses the degree of frontal connectivity or mutual information in terms of its statistical significance; i.e., how likely is a correlation under the null hypothesis of statistical independence [48, 66]. The most common approaches for functional connectivity analyses are correlation/coherence (linear) and mutual information (nonlinear) methods. Numerous studies have successfully applied these methods to quantify the long-range interactions using M/EEG. The basic criterion for detecting functional connectivity rests on statistical significance and does not consider the factors that affect underlying the dependency. Effective connectivity influences one neural system to exert it over another [53]. In other words, a causal mechanism has a dependency. One typical example is Dynamic Causal Modelling [35, 53]. The idea of DCM is proposed to understand responses in a perturbed dynamic system by exogenous inputs. A set of differential equations are formulated with hypotheses about putative electromagnetic sources. Their connectivity describes the development of the system states. Several competing models are compared to investigate the mechanisms and architectures of the functions related to the responses. The findings by using DCM are conditional for the compared models and one must have adequate prior knowledge before initiating a DCM study. Therefore, if the study goal is to reveal new or unknown relations, functional connectivity may be a more appropriate approach. For studying the effect of experimental manipulation in a well-established task, effective connectivity would normally be a better starting point.

An important difference between effective and functional connectivity lies in the undirected versus directed nature of the coupling, respectively. In other words, the mutual information between neuronal sources A and B is the same as the mutual information between B and A. Conversely, in the effective connectivity, the coupling is directed – usually expressed in terms of differential equations, where the influence of A on B differs from the reciprocal influence. The implicit asymmetry may be important when trying to understand hierarchal message passing of the sort described above in predictive coding and, more generally, in systems like the brain that show turbulent or solenoidal dynamics. Indeed, oscillations are generated by, and only by, asymmetric coupling.

3.2. Can we measure Causality?

Neuroscience has causality in directional connection and temporal precedence. The importance of temporal order from the past to the present is referred to as temporal precedence, while the directional connection to the connection in which A causes B. The most common method to measure temporal and directed relationships are Granger causality [68], structural equation modeling (SEM) [83], and DCM. In general, DCM, Granger causality, and SEM have common characteristics [83,84] in fMRI. They are used for multivariate analyses to estimate the directed coupling and make inferences on models by using temporal causality. At the same time, differences are found among them. In determining coupling directions, Granger causality recognizes the causal influences concerning the temporal precedence. Thus, the directed connections are found, while SEM and DCM specify the directed relationship a priori [53]. Therefore, SEM and DCM tend to infer based on model parameters. In stationary assumptions, Granger causality and SEM assume the systems to be at a steady state when measuring the data. However, DCM assumes that the state of a model proceeds with time, so it does not make the process stationary, except a DCM for steady-state responses [85]. In the exogenous input, DCM and SEM are deterministic and stochastic, respectively. However, Granger causality considers no input. A difference between Granger causality and DCM is that the former is usually applied to data without reference to unobserved or latent states generating the data. Conversely, in DCM (and some applications of SEM) the data are explained by an underlying generative model: either a state-state model based upon differential equations (for DCM) or a general linear model for instantaneous dependencies (SEM). A deterministic input (stimulus onset) is important in a generative model as it allows experimental manipulations in models [83]. In short, causality can be established through temporal precedence and directed connections, and different methods may probe different aspects of causality and be complementary to each other.

3.3. Question of inter-subject variability in frequencies of interest

For studies on oscillatory brain activity, it is challenging to determine the frequencies of interest. This is particularly prescient with large inter-individual variability, especially in α band [63]. That is, each individual has a preferred frequency band in a task. Thus, all frequencies can be explored, which is computationally complex and time-consuming. The other approach is to apply PCA to the entire spectrum to extract the subject-specific frequencies of interest, which has been proposed in dynamic causal modeling of induced responses [33]. Specifically, the spectral density considering frequency, source, condition, and time is reflected in the principal orthonormal frequency. In selecting the number of modes, a modified Kaiser criterion is usually adopted when the explained variance exceeds 90% of the total variance. After projection, each mode pertains to all frequencies in different proportions. Therefore, subject-specific frequencies are preserved without pre-specifying certain frequencies of interest. The price to pay – in PCA – is we discarded certain data. Therefore, the pre-selected frequency band is a good approach if we are confident about the induced frequencies. For tasks that elicit significant inter-subject variability in terms of frequencies, methods like PCA may be more appropriate.

4. Summary

Distributed neuronal dynamics are difficult to solve the problems in message passing and information processing of neuronal networks. Up to date, there is no single best method to analyze neurobiological time series. An appropriate method can be chosen according to the characteristics and quality of the data. Interpreting the analysis results depends on the adopted method sensitively.

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