Advances in EEG-based functional connectivity approaches to the study of the central nervous system in health and disease

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Abstract

Functional brain connectivity is closely linked to the complex interactions between brain networks. In the last two decades, measures of functional connectivity based on electroencephalogram (EEG) data have proved to be an important tool for neurologists and clinical and non-clinical neuroscientists. Indeed, EEG-based functional connectivity may reveal the neurophysiological processes and networks underlying human cognition and the pathophysiology of neuropsychiatric disorders. This editorial discusses recent advances and future prospects in the study of EEG-based functional connectivity, with a focus on the main methodological approaches to studying brain networks in health and disease.

Key words: EEG, brain connectivity, brain oscillations, central nervous system, clinical neuroscience

The "old but gold" electroencephalogram

Ever since the German psychiatrist Hans Berger discovered human brainwaves in 1920, the electroencephalogram (EEG) has remained an essential tool for assessing the pathophysiology and brain functions associated with cognitive processes and behavior, as well as brain disorders. The EEG is one of the most frequently used high-temporal resolution techniques in different but convergent scientific fields, including neuroscience, neurology and psychiatry.[1] Indeed, EEG systems are low-cost, non-invasive, can be implemented at the bedside of patients, and have been shown to have high test–retest reliability, sensitivity and specificity.[2–6] Thus, EEG is considered a valuable method for studying temporal hierarchy and dynamics of neurocognitive processes and the central nervous system in health and disease.[7–11] In particular, EEG-based measurements can capture fast cognitive dynamics and the temporal progression of cognitive events in the time-frame in which cognition occurs.[12–19]

Although the use of the EEG in humans for research and clinical purposes is dated, thousands of studies are now described in the scientific literature, and today we can firmly state that EEG is a valuable tool among the neurotechniques that allow the study of brain functions and cognition, as well as their complex interactions. Indeed, due to technological advancements, EEG still represents a valid technique that constantly presents new theoretical, functional and computational challenges. Therefore, in our opinion, we can define it as the 'old but gold' neuroscientific methodology.

EEG technical and methodological promises and pitfalls

Over the last two decades, a growing interest has emerged in quantitative measures of EEG-based connectivity. These quantitative analyses allow for the evaluation of interdependencies between brain signals recorded from the scalp level (i.e., sensor space) or between neural nodes (i.e., source space). Different methodological procedures can be applied to the study of EEG-based connectivity.[20] Nevertheless, many methodological and theoretical problems may arise. For example, volume conduction represents a primary issue when analyzing sensor–space connectivity.[21–23] In this regard, the low spatial resolution of the EEG makes it challenging to interpret connectivity results in relation to brain areas. In particular, common neural sources can influence contiguous electrode activity, which may increase the risk of false positive connectivity for contiguous electrodes.[4,21,24,25] Thus, it is possible to calculate source-level connectivity to reduce the effect of volume conduction.[4,21] However, source-level methods also have some limitations. While connectivity measures from sensor-level EEG recordings have low spatial precision, source-level analysis requires a large number of electrodes or accurate head models to infer how electrical fields propagate through the head at a reasonable spatial resolution.[26] This process is called the inverse problem.[27] Recent studies propose new methodological advances and recommendations to reduce technical and theoretical issues related to EEG analyses.[3,28] Furthermore, the consensus on using EEG-based measurements may have crucial implications for their application in clinical research.

In a clinical context, the ad hoc visual evaluation of EEG data is still an important criterion for the assessment of epilepsies and disorders of consciousness.[29–33] However, new computational advances would allow for a more objective and quantitative EEG data analysis. Indeed, scalp-level EEG visual analysis does not allow estimates of the interconnections between distant brain areas and quantitative data, which differs from visual evaluation, as the latter can be compared with normative data.[7] Finally, these quantitative analyses of EEG data can be used as biomarkers for classifying neuropsychiatric disorders and identifying the psychophysiological correlates of cognition.[20,34–37]

EEG-based functional connectivity

Empirical research and mathematical models in neuroscience propose oscillatory synchronization between brain nodes and networks as a key mechanism for information sharing within neural networks.[38–40] However, complex neural networks implicated in cognitive functions communicate at multiple spatial and temporal scales.[41] Indeed, EEG-based measures of connectivity may reflect diverse aspects of these spatiotemporal relationships between electrodes at the scalp level or between nodes at the source space.[3] In general, EEG-based connectivity can describe either the statistical linear or non-linear covariation between signals (i.e., functional connectivity) or the causal influence of the activity of one signal over another as effective connectivity.[42–44] These computational models may unveil intrinsic brain networks and functional mechanisms underlying sensorimotor, cognitive and affective processes in healthy participants and patients with neurological and psychiatric disorders.

There are several methods for quantifying and evaluating functional connectivity using EEG-recorded data,[45] and each method has its advantages and limitations. Different measures are better suited for specific purposes or assumptions about underlying neurophysiological processes.[46] In particular, functional connectivity measurements can be based on associations between phases (e.g., phase lag index, phase locking values and phase coherence),[25,47,48] between the amplitude of the oscillations in specific frequency bands (e.g., power-based coherence and cross-frequency coupling),[49–52] and in the complexity of the EEG signal (e.g., mutual information and transfer entropy).[20,53] In the subsequent sections, we will briefly describe some of the EEG functional connectivity analyses and recent advances, in the use of these analyses, for the study of the brain functioning in health and disease.

(a) The functional connectivity measures based on the phase of brain oscillatory activity rely on the phase angle distribution between 2 signals. For instance, the phase lag index (PLI and the similar evolutions, namely weighted PLI and squared weighted PLI) evaluates the consistency of the phase differences between 2 EEG signals recorded over specific electrodes or neural nodes.[47] The PLI has been shown to be less influenced by spurious correlations than power coherence measures because of common sources.[47]

(b) Power-based connectivity analyses involve the correlation between 2 signals over time and across frequency amplitudes. These correlations can be computed between activity in the same or different frequency bands (i.e., power coherence (PC)) and between different events (i.e., inter-trial coherence).[49,50] For instance, PC calculates the absolute correlation between amplitudes in specific frequency bands over time.

(c) Mutual information (MI) and related measures such as transfer entropy and joint entropy are based on the concept of entropy, which can be defined as the amount of information within a variable.[24] Mutual information is a functional connectivity index that estimates the level of information shared between 2 variables or time series, and is calculated by adding the individual entropies of the time series and subtracting the joint entropy.

Therefore, EEG functional connectivity measures can provide multidimensional data and largely independent information. However, the cross-validation of results using more than 1 technique is rare in the literature.[3] These evidence-based approaches highlight neural mechanisms of brain plasticity and connectivity in healthy individuals,[54,55] but more importantly, they could also lead to adequate prediction and evaluation of clinical symptoms or treatment improvements.[10,20,30,36,56–60] In particular, a recent study compared different measures to predict clinical outcomes in patients with traumatic or non-traumatic acquired brain injuries.[20] While the PLI connectivity may reflect the typical diffuse axonal damage in trauma patients, the MI and PC predicted long-term clinical outcomes in all patients. Moreover, a larger PC within the fronto-parietal motor network in the first weeks after stroke correlated positively with subsequent motor and cognitive improvements, while connectivity increases were associated with poorer clinical outcomes.[61]

Impaired PLI connectivity within the fronto-parieto-occipital areas can be an accurate biomarker for predicting the future development of psychiatric disorders in subclinical populations.[60,62,63] In addition, large-scale connectivity impairments within the alpha range have been directly associated with the severity of the positive symptoms of schizophrenia.[64] Furthermore, several studies report a decrease in long-range connectivity among the autism spectrum disorder population using different measures,[65–68] while results regarding short-range connectivity are not as clear.[64] Moreover, abnormal lateralization and inter-hemispheric connectivity in autism spectrum disorders have been consistently reported across studies.[64]

Conclusions and future insights

As discussed, EEG-based connectivity is a multifaceted world comprising various methodological approaches with different advantages and limitations.[69,70] There is no optimal brain connectivity measurement, and using one measure should be based on the study hypotheses and the neurophysiological and/or neurological mechanisms behind the specific connectivity. Many recent studies have focused on modeling and estimating EEG-based connectivity, and increasing evidence shows that it can be helpful in investigating and understanding human cognition as well as psychiatric and neurological conditions.[3,45]

After decades of intensive use, there is no doubt that EEG-based research has a great potential, and the study of EEG functional connectivity can have a massive impact with decisive repercussions in research and clinical practice. However, to use connectivity measures in a clinical context, one of the major advances should be the ability to collect normative data to reduce biases and better understand the link between functional networks and cognition.[3] Moreover, although algorithms were implemented to compute functional connectivity measures, technical advances are needed to make those measures reliable and easy to implement in a clinical context. In this view, international cooperation and open data repositories with strict methodological standards should be encouraged among scientists.[71]

In recent years, quantitative EEG measurements, brain connectivity data and clinical data were combined using machine learning algorithms in multicenter studies to improve accuracy in the clinical classification of neuropsychiatric diseases and brain diseases as well as to study complex cognitive functions.[20,57,72] Advances in the application of machine learning algorithms in a clinical context may help with clinical decision-making and the implementation of brain–computer interfaces in neurorehabilitation. Moreover, integrating psychophysiological, structural and functional imaging data with behavioral data using causative statistics can create models of cognitive functions[73] and neuropsychiatric diseases,[10,74–76] and advance our understanding of human cognition.

In the near future, EEG-based connectivity could provide crucial information about neural network functioning in health and disease with high temporal resolution and precision. These EEG measurements may help characterize the psychophysiological correlates of brain diseases and cognitive functions as well as monitor the psychophysiological effects of neurorehabilitative treatments over time. However, current international guidelines do not endorse the use of EEG biomarkers in clinical trials performed in patients, for example, in Alzheimer's disease,[77] autism spectrum disorders,[78] depression,[79] and other neuropsychiatric disorders, despite increasing evidence.[80] Thus, it is currently reasonable, timely and relevant to make a concerted effort to translate scientific advances into clinical practice.

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