안정기 뇌파를 이용한 기능적 연결성 분석

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Resting-State Electroencephalography (EEG) Functional Connectivity Analysis

Advances in network science and computer engineering have enabled brain connectivity analysis using clinical big data such as brain magnetic resonance imaging (MRI), electroencephalography (EEG), or magnetoencephalography (MEG). Resting-state functional connectivity analysis aims to reveal the characteristics of functional brain network in various diseases and normal brain maturation using resting-state EEG. Simplified sequence of resting-state functional connectivity analysis methods will be reviewed in this article. The outcomes from EEG resting-state connectivity analysis are comprised of connectivity itself of the specific condition and the network topology measure which describe the characteristics of specific connectivity. An increasing number of studies report the differences in the functional connection itself, global network measures including segregation (connectedness), integration (efficiency), and importance of specific nodes (centrality or node degree). Several issues that are relevant in the resting-state connectivity analysis are obtaining good quality EEG for analysis, consideration of particular features of EEG signal, understanding different types of association measures, and statistics for comparison of connectivities. Well-designed and carefully analyzed EEG resting-state connectivity analysis can provide useful information for patient care in pediatric neurology.

Key Words: Brain, Connectivity analysis, Network, Resting state

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Introduction

Understanding brain anatomy and function has long been a topic of research. Recent advances in diagnostic technology, such as brain magnetic resonance imaging (MRI), digital electroencephalography (EEG), and magnetoencephalography (MEG), have provided big data regarding brain anatomy and function. Advances in computer engineering have tremendously increased computing power. This increase has enabled scientists to perform very complex calculations handling these huge-size datasets. Network science is an academic field that aims to understand complex networks^{1,2)}. Complex network analysis was first applied to human society in such issues as social relationships or economic findings. Success and advances in network analysis have gained the interest of medical researchers. Researchers began applying network analysis to medicine in order to understand the very complex human body, from gross organs to small molecular

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environment. The number of EEG connectivity studies is increasing rapidly in the hope of understanding the structure and function of the brain and finally utilizing this knowledge for better patient care.

Modes of human brain connectivity can be divided mainly into anatomical and functional connectivity³. The analysis scheme is similar regardless of the different type of connectivity^{4,5}. A simplified scheme in connectivity analysis using the graph theory is: (1) define the node (2) define and calculate the association measure between the nodes (3) create a connectivity matrix and (4) calculate network measures. However, the actual process of performing connectivity analysis is very complicated because many different fields of science are involved. Medical information of disease and pathophysiology is the critical issue of interest. It is difficult for clinicians to understand different types of association (or similarity) measures, especially those of EEG⁶ and the network topology measures⁷. We need a method developed from phase physics or mathematics to extract specific features from EEG or MRI signals. In EEG connectivity analysis these features are the many different types of association measures. Understanding what these measures represent is crucial in explaining the significance of research findings to physiologic systems. Signal processing, which is a fundamental step in quantitative EEG analysis, is a field of electronic engineering. Other fields that also play an important role are network statistics and network science. This mixture of different parts of science is a significant hurdle in understanding network study results for clinicians.

We will briefly summarize resting state EEG functional connectivity analysis and review significant findings revealed in the field of pediatric neurology. The final goal of this review is to familiarize clinicians with connectivity analysis so that they can understand up-to-date research findings and plan one of their own.

EEG resting-state functional connectivity analysis—methods (using graph theory)

We will explain a very simplified sequence of resting-state EEG analysis. The goal of resting-state EEG functional connectivity analysis is to understand the connectivity constructed by EEG association measures during the resting state. A quiet wakefulness recording of a routine EEG is usually used for this purpose. Other studies such as evoked potential studies or stimulation associated studies aim to assess states with stimulation. MRI findings such as an fMRI signal during resting state can also be utilized. Frequently

used materials of EEG connectivity analysis are scalp and intracranial ictal EEGs.

1. Node and edge selection

The key concept in graph theory is representing the complex system as simplified nodes and edges. In most cases the nodes will be sensors (EEG electrodes), and the edges will be an imaginary connection where strength is defined and calculated as association (similarity) measures. Edges can be binary (present or absence of connection) or weighted (varying degree of connectivity.) In a certain study, nodes can be a source of specific activity (brain regions in most cases). A relevant and debatable issue in this situation is the use of inverse problem solving. For EEG source analysis, it is never possible to find the correct source of specific activity. In other words, we can only guess the source with varying accuracy.

2. Epoch selection and frequency band separation

Selecting high-quality epoch is one of the challenging parts in the research using clinical EEG. Researchers should carefully review the EEG and select sufficient length (usually calculated as data points, sampling rate $\times$ duration) of epoch. This length varies widely depending on association measures. Usually, the broadband EEG data are separated into different frequency bands, such as delta, theta, alpha, and beta⁸. Narrower decomposition of frequency bands is possible or required for specific association measures.

3. Association measures

Association (similarity) measures represent the degree of functional connection between different nodes⁹. A basic assumption in this analysis is that the value of association between the two different nodes represents strength of connection. These measures are calculated between the two separate nodes and they provide the numeric value of similarity. It is very important to understand which information of the EEG signal the specific association measure represents. Classical measures are correlation and coherence. Correlation is a measure of association in amplitude over time and coherence is a measure of similarity in distribution of frequency (composition of difference frequency bands for the specific segment of EEG signal in the frequency domain). Recently, other measures are used such as phase lag index, phase locking value, and phase slope index. These measures are phase based measures and they are known to better represent synchrony. There are information based measures such as mutual information. Detailed information and source of reference are available in a review article by van Diessen et al⁶.

4. Functional connectivity map

Once all the association measures are calculated for the entire possible nodes, these results (functional connectivity map) can be displayed in a matrix (Fig. 1) or a graph (Fig. 2). If we apply certain thresholds to edge values, we can make a binary (presence or absence of connection) matrix.

5. Network topology measures

We can calculate different network measures that tell specific features of the functional connectivity. Local measures give

information about the node of importance or increased connectivity. Global measures tell us the global efficiency, segregation, and integration⁷.

Findings derived from connectivity analysis

The key features in resting-state functional connectivity analysis are the functional connectivity itself and its network topology measures. We can compare the functional connectivity itself

Fig. 1. Heatmap of resting-state electroencephalography connectivity constructed using the weighted phase lag index. Comparison of alpha frequency band connectivity in patients with benign epilepsy with centrotemporal spikes (A, n=30) and their age- and gender-matched disease-free controls (B, n=30).

Fig. 2. Graph presentation of resting-state electroencephalography connectivity. Nodes are electroencephalography sensors and edges are connections with specific thresholds of patient (A) and its age- and gender-matched control (B).

between individuals and also sequentially in the same individual. Group comparison is also possible between two distinct groups. Since the results are a continuous variable, they can be compared using measures of the mean comparison. If the different edges are concerned for statistical comparison, the Bonferroni correction or a specific statistical method can be used, such as false discovery rate or network-based statistics¹⁰.

Network topology measures describe specific features of the network. Most commonly used topology measures are characteristic path length, mean clustering coefficient, and small-worldness⁵. Shortest path length is the shortest path distance from one node to the other. Characteristic path length is the average of the shortest path lengths of all possible edges, and this represents the degree of network integration. The smaller the characteristic path length, the more integrated the network. Mean clustering coefficient is the average of all clustering coefficient of the nodes, and it is a measure of segregation. If we consider these two measures, regular and random network would be the extreme of the shortest characteristic path length and mean clustering coefficient. A regular network is a network with a very short characteristic path length so that we can tell that it is highly integrated. The random network is a network with the largest mean clustering coefficient telling us that it is very well segregated. Small-worldness is a network topology measure estimating integration and segregated at the same time, and it is commonly observed in a real-world biological network¹¹. Recently, many of the topology measures are calculated from a weighted graph.

Resting state functional connectivity studies (Table 1)

A very influential initial study was a MEG study in Alzheimer's

dementia (AD). Researchers compared resting-state functional connectivity between AD patients and healthy controls. Patients with AD had lower mean connectivity values in lower alpha and beta bands and showed highly connected network hubs were at risk. Connectivity studies of networks in health and diseases have increased, and many of the earlier studies are available in the review by Bassett and Bullmore¹². Review articles for connectivity analysis in epilepsy¹³⁻¹⁵ and other neurological disorders¹⁶ are also available.

Resting state connectivity studies in focal epilepsy consistently revealed increased functional connectivity in the earlier studies¹⁷⁻²⁰. These studies also revealed decreased efficiency at the resting state. There are conflicting results regarding clustering coefficient, which is a measure of local segregation (connectedness)²¹. Theta band connectivity was increased in patients with a first unprovoked seizure, and subsequent epilepsy compared to those without epilepsy¹⁹. This study suggested network difference as a potential marker to predict epilepsy. When researchers looked at the connectivity constructed using the phase locking value from patients with benign epilepsy with centrotemporal spikes, they found higher degrees around interictal spikes²². They also revealed that specific connections were decreased. There was a systematic review and meta-analysis of connectivity in focal epilepsy²³. They included 13 connectivity studies on focal epilepsy using either anatomical or functional study data. In focal epilepsy, characteristic path length and average clustering coefficient were higher in patients showing that resting functional connectivity is less integrated and more segregated. When only the EEG and MEG studies were included (n=7), only the mean clustering coefficient showed a consistent and significant increase. In a study by E van Diessen et al., they used a matrix of different network characteristic measures and compared this between pediatric focal epilepsy and healthy controls²⁴. They showed that this combination increased

Table 1. Details of Resting-State Electroencephalography (EEG) or Magnetoencephalography (MEG) Functional Connectivity Studies

Category	Study	Target	Association measure	Finding
Tumor	Bartolomei et al. (2006) ¹⁷	Brain tumor (17) vs. healthy control (15)	Synchronization likelihood (SL)	Decreased connectivity in certain frequency bands
Tumor	Bosma et al. (2009) ²⁸	Low grade glioma (LGG) (17) vs. healthy control (17)	Phase lag index (PLI)	Higher short- and long-distance synchronization within the theta band (LGG).
Epilepsy	Douw et al. (2010) ¹⁹	First unprovoked seizure (114) and further focal epilepsy (57)	Synchronization likelihood (SL)	Increased theta band functional connectivity
Epilepsy	Douw et al. (2010) ²⁹	Tumor epilepsy surgery before (17) and after (12) surgery	Phase lag index (PLI)	No change in connectivity before and after surgery. Number of seizures were related to connectivity
Epilepsy	Horstmann et al. (2010) ²¹	Focal epilepsy (21) vs. healthy control (23)	Cross correlation and mean phase coherence	An increased regularity and a diminished modulation capability
Epilepsy	van Diessen et al. (2013) ²⁴	Focal epilepsy (35)	Synchronization likelihood (SL)	Improved diagnostic accuracy using multivariate prediction model
Epilepsy	Chowdhury et al. (2014) ²⁵	IGE (35), relatives of IGE (42) normal control (40)	Phase locking factor (PLF)	Increased theta band degree in patients Increased clustering coefficient in patients and their relatives
Maturation	Boersma et al. (2011) ²⁶	Normal children from 5 to 7 (227)	Synchronization likelihood (SL)	Increased average clustering coefficient and characteristic path length

diagnostic accuracy.

There was an interesting study in patients and relatives of idiopathic generalized epilepsy²⁵⁾. Theta frequency band connectivity was increased in patients. An interesting finding was the increase of average clustering coefficient in the relatives of patients without epilepsy as well as idiopathic generalized epilepsy patients. This study revealed network endophenotype in families with as idiopathic generalized epilepsy.

There are few studies of connectivity in normal development and brain maturation from varying age groups. When synchronization likelihood was used to construct connectivity, average clustering coefficient and characteristic path length increased with brain maturation from age 5 to 7²⁶⁾.

Challenges and limitations

EEG is very prone to various kinds of artifacts, which requires very well-controlled examination environments. Frequently, it is not easy to acquire an ideal resting state during an examination, and this situation is even worse in children. It is challenging to perform an examination well and collect high-quality EEG samples from the pediatric population. Other relevant issues regarding EEG are volume conduction, selection of montage, selection of reference, and handling artifacts²⁷⁾. Volume conduction of EEG is critical in selecting association measures since this will mainly affect the signal and the measurement. Correct interpretation requires an accurate understanding of the association measure that was used. Above all, connecting the results from connectivity analysis to the disease process or pathophysiology is most challenging.

Conclusion

The number of studies using connectivity analysis in neurological diseases is increasing. An increasing number of studies provide interesting and potentially helpful results. The application of most feasible connectivity (association) measures is critical and proper study designs are very important. Even though clinicians alone cannot perform every process of the study, their basic understanding regarding each step of the analysis is required. Well-designed and carefully analyzed EEG resting-state connectivity analysis can provide useful information for patient care in pediatric neurology.

요약

최근 의학의 발전으로 뇌자기 공명 영상, 디지털 뇌파 검사, 뇌자도 검사가 활발하게 이루어지고 이 검사에서 얻어진 방대한 양의 데이터가 모이고 있다. 사회 과학 및 경제학에서 시작된 네트워크 분석이 의학과 생물학 분야에도 적용되었고 최근 비약적인 발전을 보이는 컴퓨터 계산 능력의 도움으로 신경 분야에 대한 네트워크 분석이 가능하게 되었다. 네트워크는 크게 구조적, 기능적 네트워크로 대별되는데, 뇌의 복잡한 구조와 기능을 연구하여 이해하기 위해 네트워크 분석을 하게 되고 본고에서는 안정기의 뇌파를 이용해 네트워크 분석을 하는 연구에 대해 설명하고자 한다. 안정기 뇌파를 이용한 네트워크(연결성) 분석은 양질의 안정기 뇌파를 확보하는 것으로 시작된다. 연관성 지표를 정해서 여러 지점들 간의 연결성의 정도를 계산하여 연결성 지도를 만들고 이 연결성 지도를 기반으로 네트워크 분석을 시행하여 구축된 네트워크의 특성을 파악하는 것이 네트워크 분석이다. 연구에 사용되는 연관성 지표에 대한 이해가 필수적이며 이 지표가 반영하는 정보를 이해하고 지표의 장점과 단점을 정확하게 파악하는 것이 중요하다. 위상 수학, 신호 분석, 데이터 처리, 통계 분석 등 다양한 의학 외의 전문 분야가 함께 관여되기 때문에 다학제 연구에 대한 이해가 중요하다. 이전의 연구에서 밝혀지지 못한 내용을 파악하고 이를 환자 진료에 이용하는데 안정기 뇌파 네트워크 분석이 도움이 될 수 있다.

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