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Review

Magnetoencephalography as a Clinical Tool: A Brief Review of Current Studies

Magnetoensefalografinin Klinik Araç Olarak Kullanımı: Güncel Araştırmaların Kısa İncelemesi

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Abstract: Magnetoencephalography (MEG) is becoming a very popular functional neuroimaging tool in clinical practice. It is currently used with other imaging methods to aid diagnosis and pre-surgical mapping of many conditions ranging from epilepsy to depression. This paper reviews the most current studies that have utilized MEG for investigating some of these conditions and discusses the benefits of using this method in medical practice.
Keywords: MEG, EEG, epilepsy, presurgical mapping, clinical

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Özet: Magnetoensefalografi(MEG) gün geçtikçe klinik alanda kullanımı popüler olan bir nöro görüntüleme aracı olmaktadır. Şu anda bu araçtan diğer nöro görüntüleme yöntemleriyle birlikte tanı ve cerrahi operasyonlar öncesi haritalama amacıyla epilepsiden depresyona kadar birçok alanda yararlanılmaktadır. Bu kağıt bahsedilen medikal problemleri MEG aracılığıyla inceleyen ve MEG'in kullanımının medikal alanda yararlarını tartışan son araştırmaları incelemektedir.
Anahtar Kelimeler: MEG, EEG, epilepsi, operasyon öncesi haritalama, klinik

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1. Introduction

Magnetoencephalography (MEG) is a non-invasive functional neuroimaging method for studying human brain activity. MEG scanners measure the magnetic fields generated by active neurons in the brain with high temporal and good spatial resolution. The MEG signal was measured by David Cohen for the first time in the late 1960s (Cohen, 1968). Since then, the benefits of employing this technique in research have become quite evident and over the years, its strengths and limitations have been thoroughly discussed by many researchers (e.g. Williamson et al., 1991; Wendel et al., 2009) and some of those qualities will also be touched upon in this review. Since its invention, a large number of studies has utilized these strengths by using this method in conjunction with other neuroimaging techniques and it has been proven to be a highly effective tool for exploring many areas of human cognition including memory (e.g. Van Dijk et al., 2010; Popov et al., 2018), vision (e.g Perry et al., 2013; Wu et al., 2018), and language (e.g. Shtyrov et al., 2012; Wang et al., 2018). However, the applicability of this technique is not limited solely to the cognitive sciences, but its advantages have also been demonstrated by the clinical research that had focused on tackling the issues related to medical diagnosis and surgical planning of several medical conditions. This paper is a review of current clinical MEG studies and it tries to answer the question: is MEG a valuable tool for medical practice?

In this review, I aim to cover the most recent MEG studies in the clinical literature. Therefore, many of the important earlier studies will not be included here. I strongly encourage reading the papers published by Stufflebeam et al. (2009) and Braeutigam (2013) for a good review of those previous studies. Moreover, a detailed description of the engineering and physics of MEG scanners is beyond the scope of this paper, but the main instrumentation will be briefly introduced in the next section along with a very brief description of the electrophysiological basis of MEG signals. For a more comprehensive review of those subjects see the following sources: Hämäläinen et al. (1993), theory, instrumentation, and applications; Hansen et al., (2010), An Introduction to Methods, Oxford University Press.

How Does MEG Work and What Does it Measure?

MEG is a direct measurement of the neuronal activity. Neurons generate electric currents when they fire and according to Maxwell's theory, electric currents create magnetic fields around them. Since the currents in the brain are quite small in magnitude, the magnetic fields associated with them are also quite minuscule. However, a MEG scanner is able to measure these magnetic fields owing to a set of sensors called superconducting quantum interference devices (SQUIDs). Each SQUID contains a superconductive loop separated by two parallel Josephson Junctions and in order to maintain the superconductivity, the sensors are bathed in liquid helium and kept around -269 degrees Celsius. Essentially, a biasing current is maintained in the superconductive loop and the voltage is measured at the two ends. Variations in magnetic flux passing through the loop create phase changes in the two Josephson junctions and that in turn generates oscillations in the output voltage making it possible to measure the fluctuations in the magnetic flux directly. Human brain magnetic field strength is around 0.1 - 1 picotesla, but the Earth's magnetic field is much larger than that (300-600 microtesla). As a result, MEG scanners need to be used in magnetically shielded rooms to attenuate the magnetic interference caused by outside sources. Additionally, since the sensor diameters of SQUID devices are very small, single magnetometers or first-order gradiometers are used to increase the efficiency in signal detection and noise attenuation.

Action potentials are not detectable with MEG and EEG. Rather the measured magnetic flux is mainly generated by the postsynaptic currents in the cerebral pyramidal neurons. Around 10.000 to 50.000 of these neurons need to fire simultaneously to be able to create a magnetic field detectable by a MEG scanner. Additionally, these currents should be oriented tangentially to the skull in the brain fissures since the magnetic fields associated with radial currents mostly do not reach out of the head and therefore cannot be picked up (Ahlfors et al., 2010).

EEG and MEG

Although the source of the signals measured by both MEG and EEG are the same and the signal processing methods used to analyze the data are similar to some extent for these two methods, they measure the different aspects of the neuronal activity. EEG measures the electric fields created by neurons via the electrodes placed on the skull, whereas MEG measures the magnetic flux. Electric fields are smeared by the tissues and bone structure, therefore, source localization of EEG signals requires advanced modeling of the human head. Because of the high magnetic permeability of the brain tissues, MEG does not suffer from the same limitation and consequently, a more accurate source localization can be achieved (Grynszpan and Geselowitz, 1973). Although EEG can be performed with more than 100 channels to increase the quality of signal localization, patient preparation can take a significant amount of time since the EEG electrodes need to be applied individually to the subject's head, while a 300-channel MEG scan can be performed with minimal preparation. However, compared to EEG, MEG is less sensitive to deeper sources (Cuffin and Cohen, 1979) and the signal is more affected by the head motion since the electrodes are not directly in contact with the scalp and the subject's head can move freely in the dewar. Additionally, the initial set up and maintenance of MEG facilities are significantly more costly than EEG since MEG scanners require more electronic instrumentation and the liquid helium inside the dewar boils off with time. Both MEG and EEG hold some advantages and disadvantages, but the properties of these methods have been shown to complement each other. Several studies have reached the conclusion that using these methods together immensely increases the source localization and general quality of the measurements (Cohen and Cuffin et al., 1990; Sharon et al., 2007; Liu et al., 2002). Localizing the signals in the brain accurately is of paramount importance to diagnosis and surgical planning hence using a multimodal neuroimaging approach is extremely crucial in clinical research.

Clinical Meg

Considering the strengths of MEG, there are many reasons to use it in clinical practice. However, currently, this technique is not as commonly used as other neuroimaging tools for clinical applications. Hillebrand et al., 2018 suggest that the main reason for this lack of use could be historical. EEG was invented by a psychiatrist and an electrophysiologist and the medical community has been using it for a long time. Therefore, it was adapted as a practical clinical tool over the years and many analysis methods and guidelines were established for clinical use. On the other hand, MEG is mainly dominated by engineers and physicists and most of the analysis pipelines were developed for general neuroscientific research rather than medical practice. Additionally, since MEG is a relatively recent method and the data obtained from the MEG scanners are more complex compared to the other neuroimaging methods, analysis techniques are still evolving rapidly and there are no common practical guidelines for medical practice. Despite these limitations, MEG started to emerge as a very desirable tool for clinics throughout Europe and the United States over the years. In an attempt to study the prevalence of MEG in medical research, a survey was sent to forty-four MEG centers in Europe in 2017. According to the survey results, among the 57% of responders (12 centers from 10 different countries) reported using MEG for clinical applications (Tiège et al., 2017). The same survey also discovered that MEG was mostly used for pre-surgical evaluation of epilepsy and functional localization of the brain regions in disease which will also be the main areas of focus for this review.

1. *Epilepsy Detection and Surgery*

In focal epilepsy, removal of the epileptogenic area in the brain is used as a treatment option. However, triangulating the part of the brain that generates the seizures involves strict planning and monitoring. Currently, there are no established direct measurements of the epileptogenic area in the brain. Instead, clinicians use a variety of different tests to estimate the epileptic sources indirectly. These tests include MRI scans, computed tomography, and conventional or high-density EEG measurements (Rosenow and Luders, 2001). Recent studies have shown that 306-channel MEG detects the distribution of epileptic spikes (irritative zone) more accurately than conventional (21 channels) and high-density (72 channels) EEG (Tamilia et al., 2019). However, other studies have reported that EEG detects more epileptic spikes in the mesialtemporal regions since MEG is less sensitive to deep areas of the brain (de Jong et al., 2005). MEG, on the other hand, was found to be more accurate with neocortical sources (Heers et al., 2010). Apart from the spikes, 80-1000Hz high-frequency ripples are another common electrophysiological biomarkers of epilepsy (Meng L., 2019). Localization of these ripples also can provide valuable information about the epileptogenic zones. These ripples are caught more frequently with EEG compared to MEG, but the location of the ripples can be better reconstructed with MEG (van Klink et al., 2019). As it can be clearly seen from the aforementioned examples, the strengths of EEG and MEG are quite complimentary for the detection and localization of epilepsy. Therefore, a multimodal approach utilizing these two methods can make the confidence of the localization much higher. Unfortunately, even after epileptic surgery approximately 30% of patients still have seizures and re-evaluation of these patients is often required (Spencer and Huh, 2008). A study conducted with patients who had unsuccessful epilepsy surgeries showed a significant association between the resection of the brain areas identified by MEG and seizure freedom (El Tahry et al., 2018). The same study has also evaluated SPECT along with MEG for identifying the epileptogenic areas and the resection of the overlapping brain regions identified by these methods presented an even higher probability of seizure freedom proving the importance of multimodal approach in epilepsy treatment.

MEG is not used for the detection and localization of focal epilepsy only, but its high temporal resolution and good spatial resolution makes it a valuable tool for the diagnosis and treatment of generalized epilepsy as well. Subpolar, limbic and frontal lobes are found to be the most frequent locations of sources for the epileptic discharges in juvenile absence epilepsy (Gadad et al., 2018) and the connectivity studies have discovered that increased temporal connections could be observed in absence epilepsy (Youssofzadeh et al., 2018). Another issue that clinicians commonly face is the false negative MRI results in epilepsy. Approximately, 30% of the epileptic cases can get normal (negative) MRI results (Muhlhofer et al., 2017). In those cases, MEG can be used as a guidance tool for functional MRI in order to decrease the occurrences of these false negative tests (Colon et al., 2018). Yu et al., 2018, for instance, identified MEG spike sources in operculo-insular regions in 11 of 13 of their patients with negative fMRI results. Other studies have reported a relative increase in theta and delta band powers that can also be considered as an indicator of temporal lobe epilepsy in MRI-negative patients (Li et al., 2019). Lastly, the network studies reported that an increase in the frontal and parietal network connectivities in resting state MEG can distinguish healthy patients from the epileptic patients who had negative fMRI results (Li Hegner et al., 2018).

2. *Meg As a Diagnosis Tool*

Spikes, ripples, and disrupted network connections are the biomarkers of epilepsy and those abnormalities can be detected with MEG. However, epilepsy is not the only condition that can be diagnosed with this imaging method. Many clinical studies have been focusing on developing an efficient method for accurately diagnosing several conditions when they occur and even long before the initial symptoms appear. One of these conditions which has been commonly researched with MEG is Alzheimer's disease. The earliest symptoms of Alzheimer's includes disruptions of learning new information and subtle amnesia. However, pathological changes that lead to Alzheimer's disease start earlier in the brain, usually long before these clinical symptoms appear. Therefore, designing a method that would detect those changes is very important for early intervention. Resting state network studies have found vulnerabilities in the left hippocampus, posterior default and occipital networks in the brains of the subjects suffering from Alzheimer's (Yu et al., 2017). One MEG study that used an auditory oddball experiment to investigate the correlation between the disease risk and medial prefrontal cortex response to standard and deviant sounds has reported a decrease in the cortex response to standard sounds in subjects who were at risk of developing Alzheimer's and complete loss of cortex response to both sounds in Alzheimer's disease (Golubic et al., 2017). Also, a reduction in the event related synchronization of the alpha band has been detected in patients with Lewy body dementia following an eye-closing procedure compared to patients with Alzheimer's and healthy subjects showing the potential of MEG for aiding differential diagnosis (Hata et al., 2018).

Another neurodegenerative disease commonly investigated with MEG is Parkinson's disease. Many network studies have reported a relationship between beta band modulations and Parkinson's (see review Boon et al., 2019) and a power increase in theta along with a power decrease in beta and gamma bands have been observed in patients who suffer from visual hallucinations caused by Parkinson's (Dauwan et al., 2019). MEG has also been used to evaluate the effects of deep brain stimulation for Parkinson's treatment (Oswal et al., 2016: Harmsen et al., 2018).

3. Psychiatric Disorders

MEG has played an important part in psychiatric research. There are so many new papers published every year that a whole separate review can be written based only on the most current psychiatric studies. It has been used to investigate the electrophysiological biomarkers of many conditions including depression, schizophrenia, and autism spectrum disorder. Numerous reviews have been written on these studies (e.g. Uhlhaas et al., 2017) and for all of these conditions, changes in brain oscillatory patterns and disturbances in several network hubs have been reported. For instance, in depression, some of those changes include decreases in theta and alpha band powers in frontal and parietal areas (Jiang et al., 2016) and lower alpha to gamma amplitude coupling in right caudate and left thalamus (Chattun et al., 2018). In schizophrenia, low-frequency encoding disruptions have been identified in the auditory cortex and these measurements have been reported to be robust to recording method (Edgar et al., 2018). Lastly, increased alpha band power during emotional face processing (Safar et al., 2018) and reduced general gamma power in motor areas (An et al., 2018) were among the changes that have been observed in autism spectrum disorder.

4. Pre-Surgical Planning and Navigation

Pre-surgical planning procedures are performed on patients who will receive neurosurgical operations and it usually involves mapping of the somatosensory, motor and language areas of the brain in order to preserve patients' cognitive and other brain functions before the operations. Cortical stimulation mapping, Wada procedure, and invasive ECoG are among the methods that are used for this purpose, but all of these methods are invasive. Therefore, the medical community has been focusing on replacing these methods with non-invasive imaging techniques such as fMRI, TMS, and MEG (Papanicolaou et al., 2018). The mapping procedures should be carefully conducted since some lesions are known to cause functional reorganizations in the brain due to plasticity (Lee et al., 2009). fMRI is quite common for these procedures since it has an excellent spatial resolution, but studies have shown that some lesions can also distort blood oxygen-level dependent (BOLD) making the results of fMRI potentially misleading for functional mapping (Holodny et al., 2000; de Abreu et al., 2016). Since MEG is a direct measure of brain functions, it could be used as an alternative method for functional mapping without being affected by the changes in BOLD. A study comparing two different MEG systems has reported no bias for localization of S1 showing the consistency of MEG measurements with different systems (Bardouille et al., 2018). However, the best results in functional reorganization cases could be obtained by using MEG and fMRI together in a multimodal approach (Zimmerman et al., 2019). One study has compared fMRI, MEG, TMS, and high gamma ECoG to predict postoperative language outcome by using the support vector regression and reported that the best trade-off between model complexity and accuracy was achieved by the fMRI and MEG combination (Babajani-Feremi et al., 2018).

2. Conclusion

MEG is increasingly becoming popular among clinicians. It is attracting considerable interest due to its rapid development. It is currently used to aid the diagnosis and treatment of several conditions ranging from epilepsy to psychiatric conditions. Since multimodal imaging approach is the gold standard in medical diagnosis MEG becomes a powerful tool, especially when used in conjunction with other methods. Because it is a non-invasive method which has a better spatial resolution compared to EEG and a higher temporal resolution compared to fMRI, it has a lot to offer to both of these techniques as well as the others that are not mentioned in this review.

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