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Special Review

Brain Oscillations and Their Implications for Neurorehabilitation

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HIGHLIGHTS

- Neural oscillation is rhythmic or repetitive neural activity in the central nervous system.
- With brain oscillation, we diagnose, prognosticate and treat the neurological disease.

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ABSTRACT

Neural oscillation is rhythmic or repetitive neural activities, which can be observed at all levels of the central nervous system (CNS). The large-scale oscillations measured by electroencephalography have long been used in clinical practice and may have a potential for the usage in neurorehabilitation for people with various CNS disorders. The recent advancement of computational neuroscience has opened up new opportunities to explore clinical application of the results of neural oscillatory activity analysis to evaluation and diagnosis; monitoring the rehab progress; prognostication; and personalized rehabilitation planning in neurorehabilitation. In addition, neural oscillation is catching more attention to its role as a target of noninvasive neuromodulation in neurological disorders.

Keywords: Neurological Disorders; Brain Waves; Brain-computer Interface; Event Related Potential; Transcranial Magnetic Stimulation

WHAT ARE NEURAL OSCILLATIONS?

Neural oscillations, which are also known as brainwaves, are rhythmic or repetitive neural activity in the central nervous system (CNS). Oscillatory activity originates either from individual neurons or from inter-neural interactions. At the individual neuronal level, oscillations can appear either as fluctuations in resting potential or as a rhythm of action potentials, which can induce post-synaptic neuronal oscillations [1-3]. At the level of neural ensembles, the synchronized activity of multiple neurons evokes macroscopic oscillations, which can be observed on an electroencephalogram. Macroscopic neural oscillations generally arise from inter-neuronal connections that can affect multiple neuronal firing patterns. These inter-neuronal interactions can cause oscillations at various frequency bands.

The intrinsic neuronal properties of neural oscillations have been explored by many researchers. The well-known Hodgkin-Huxley model shows how ion channel dynamics contribute to the initiation and propagation of action potentials or periodic spiking [4]. In addition to their role in periodic spikes, subthreshold membrane potentials may also contribute to oscillatory activity by facilitating the synchronous activity of neighboring neurons [5]. Lastly, some subtypes of cortical cells fire bursts (i.e., brief clusters) of spikes

rhythmically at preferred frequencies. These cells are also known as bursting neurons, and these rhythmic spikes are candidates for triggering synchronous network oscillations [6,7].

Neural oscillatory activity can also be affected by neurotransmitters [7]. Specifically, the concentrations of certain neurotransmitters can regulate the amount of neural oscillations. For example, gamma-aminobutyric acid (GABA) levels have been shown to be positively correlated with oscillation frequencies in response to induced stimuli [8]. In addition, a number of nuclei in the brainstem have various projections throughout the brain and can influence the concentrations of neurotransmitters such as norepinephrine, acetylcholine, and serotonin. These projection systems can affect the activity of brainwaves (e.g., alpha, beta, and delta waves) [9]. Therefore, brain oscillations can be a useful tool for determining brain status and can be used to assess the prognosis of patients with brain disorders [9].

In contrast to neuronal-level neural oscillations, large-scale neural oscillations have been studied only using electrocorticography, electroencephalography (EEG), or magnetoencephalography (MEG). The electric potentials generated by single neurons are too small to be recorded outside the scalp, and EEG or MEG activity always mirrors the summations of the synchronous activity of thousands or millions of neurons with similar spatial orientations [10]. Neurons in a neural ensemble do not fire at exactly the same time (i.e., full synchronization). Neuronal firing is rhythmically modulated through local interactions between excitatory and inhibitory interneurons. In particular, inhibitory interneurons play an important role in producing neural ensemble synchrony by generating a narrow window for effective excitation and rhythmically modulating the firing rate of excitatory neurons. If the probability of a large group of neurons is modulated at a common frequency, they will fire and generate oscillations at the same frequency, providing insights into brain entrainment [11,12].

Neural oscillations have been one of the most widely studied areas in research on the mechanism of human behavioral activity using neural activity generated by large groups of neurons and measured by techniques such as EEG or MEG; that is, the raw data of EEG or MEG are the result of continuous composite signals in each electrode or sensor from large groups of neurons. Oscillatory activity in groups of neurons involves feedback or feedforward connections between neurons that result in the synchronization of their firing activity. Associations between various neurons can cause oscillations among different frequencies in different situations [13-16]. Both EEG and MEG have been used as neurophysiological techniques to collect data on brain activity. However, there are some important differences between these 2 techniques. MEG can lead to a better understanding of the functioning of the brain due to its enhanced potential to determine the spatial source of the recorded activity. With this technology, signal detection is practically unaffected by the conductivity and structure of the skull and scalp tissue. In addition, compared to EEG systems, MEG systems allow higher spatial sampling resolution. Under favorable conditions, the spatial localization of current sources with whole-head MEG is on the order of 2–3 mm at a temporal resolution better than 1 ms [17]. From the perspective of source measurements, scalp EEG is sensitive to both the tangential and radial components of a current source in a spherical volume conductor. MEG detects only its tangential components, and is therefore most sensitive to activity from sulci. In contrast to MEG, EEG can detect signals both in the sulci and at the top of the cortical gyri. Therefore, MEG is sensitive to activity in more brain areas, but activity that is visible using MEG can also be localized with greater accuracy [18,19]. Scalp

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EEG methods also have restrictions in terms of measuring the neural source with high spatial precision, as the scalp form a barrier between electrodes and the neural cortex that distorts the neural signal from the neural generator to the electrode. Modern EEG systems have many more sensors than earlier systems (i.e., up to 512) and can use more robust and accurate source modeling techniques with an emphasis on time-domain signal processing. By contrast to MEG, advances in EEG recording technology (e.g., dry electrodes and high-density EEG) made it a feasible tool for detecting subjects' intentions and for neurorehabilitation in the clinical field, as exemplified by brain-computer interface (BCI) systems and closed loop neuromodulation systems.

After preprocessing, the EEG or MEG signal looks like a continuous line, resembling pink noise, that has broad spectral content and also reveals oscillatory activity. After time-frequency analysis, this noise is decomposed into various frequency band components, such as alpha (7.5–12.5 Hz), delta (1–4 Hz), theta (4–8 Hz), beta (13–30 Hz), low gamma (30–70 Hz), and high gamma (70–150 Hz) frequency bands [13-16]. The most well-known frequency band is alpha activity, which can be acquired from the occipital montage during relaxed wakefulness and increases when the eyes are closed. During sleep, the EEG signal shows a transition from faster frequencies to increasingly slower frequencies such as alpha waves. Using the spectral alpha content of EEG signals, various stages during sleep can be classified [13]. Lasaponara et al. [20] suggested that alpha-band EEG activity in the affected hemisphere during orienting of attention in patients with reduced awareness of the left side of space showed pathological enhancement compared to healthy subjects. They concluded that right-hemispheric lesions or lesions of the white matter pathway could interfere with the frontal modulation of alpha activity in posterior brain areas. Another deeply studied frequency band is the changing patterns of beta activity, which can be acquired from the sensorimotor cortex area before and during motor performance. In studies of beta-band activity, researchers have tried to detect subjects' motor intentions and motor performance time, motor learning, and motor memory consolidation [19]. Several studies focused on biological mechanisms beyond gamma oscillations within the cerebral cortex and hippocampus [7,21-26], associated with cognitive processes, including attention, sensory perception, and memory formation [2,7,16,27,28], and various pathological conditions [29-31]. Some researchers have also suggested that gamma oscillations are closely related to several biophysical properties of neurons, including the time constant of $GABA_A$ and a-amino-3-hydroxy-5-methyl-4-sioxazolepropionic acid receptors [32], the membrane time constant of cortical pyramidal cells [33], and the critical time window of spike-timing-dependent plasticity [34]. Kujala et al. [35] recently investigated potential correlations between gamma oscillations in the primary visual cortex (V1) and $GABA_A$ receptor density using multi-modal MEG. Their findings suggested that the gamma-band response of V1 was shaped by GABA-receptor mediated inhibitory neurotransmission. Despite numerous contributions to our understanding of gamma oscillations, there remains a large gap between bench research and clinical rehabilitation in neurological disorders.

Neural oscillations are a cornerstone for identifying several neurological disorders; for example, excessive synchronization is observed during seizure activity in epilepsy and tremors in Parkinson's disease [36,37]. Neural oscillatory activity can also be used to modulate the external devices of BCIs, in which subjects can control an external device by changing the amplitude of a particular brain rhythm [38,39].

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HOW CAN THE EFFICACY OF NEUROREHABILITATION USING BRAIN OSCILLATIONS BE IMPROVED? THE ASSOCIATION BETWEEN BRAIN OSCILLATIONS AND NEUROREHABILITATION

Brain oscillations have been categorized into spontaneous oscillations at rest and event-related oscillations during a task according to the circumstances of recording. When recording a spontaneous signal at rest, subjects are seated on a chair with their eyes open or closed. They are generally asked not to think about any specific ideas. Brain oscillations can also be measured during tasks such as body movement and specific cognitive activity.

Evoked signals are another type of brain oscillation that has a relatively long latency from the signal-evoking event. Unlike spontaneous neural oscillations, evoked signals are recorded in response to any stimulus, including light and auditory or cognitive activity. The underlying mechanism and clinical usefulness of the data depend strongly on the recording method.

Spontaneous neural oscillations

Using brain oscillations for predicting recovery and prognostication

During analyses of spontaneous neural oscillation data by EEG, computational techniques such as Fourier transformation could be useful to determine the brain asymmetry and neuronal imbalance after the diagnosis of a neuronal disorder such as stroke or Parkinson's disease. Several reports have shown that certain values calculated from time-frequency analyses with resting-state neural oscillation data are associated with stroke patients' recovery process and can reflect their recovery. Furthermore, post-stroke measurements of initial brain wave patterns (known as the resting state brain network), such as the brain symmetry index and delta/alpha ratio, have been shown to have prognostic value for patient recovery [40,41].

Association between brain oscillations and post-stroke seizure

Epilepsy is a common chronic neurological disorder characterized by seizures. EEG has been a very important tool for diagnosing and managing epilepsy. Psychiatrists often encounter this neurological condition in patients with various underlying neurological diseases such as stroke, traumatic brain injury, hypoxic brain injury, and Parkinson's disease. These neurological disorders can be a primary origin of epileptic events. In particular, ischemic stroke is undoubtedly one of the most frequent causes of epilepsy in adults. Galovic et al. [42] recently developed a multivariate model named “SeLECT,” which uses 5 risk factors (i.e., severity of stroke, large-artery atherosclerotic etiology, early seizures, cortical involvement, and territory of middle cerebral artery involvement) to predict the risk of late seizures within the first year after stroke. However, the uncertainty of that model has been pointed out [43]. The prediction of poststroke seizure could draw upon EEG findings such as asymmetry. A recent study attempted to show that the first EEG asymmetry could independently presume unprovoked seizures or epilepsy in the year following anterior circulation ischemic stroke [44]. Seizures are transient signs and/or symptoms of hypersynchronous neuronal activity in the brain. If psychiatrists were able to meet patients with these types of disorders and then to characterize the patient's brain oscillatory activities, they could determine whether epilepsy is a barrier to a patient's neurorehabilitation journey and whether patients need antiepileptic drug treatment [37].

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Event-related brain activities

Event-related desynchronization (ERD) and event-related synchronization (ERS)

The activity change in the beta-band frequency associated with movement is one of the most impressive changes among the characteristics of brain oscillations. In the motor cortex immediately prior to the start of movement, the beta-band amplitude is temporarily reduced and then shows a rebounding pattern after movement is terminated. Changes in the brain oscillatory characteristics associated with this movement are referred to as ERD or event-ERS. It is also important to note that similar brain oscillation characteristics have been reported even if subjects only imagine moving a joint. BCI techniques using this concept are being actively developed [45-51].

Analytic approach to brain oscillatory activity (decoding)

Researchers have attempted to understand how brain oscillatory properties can be simultaneously changed by the subject's movement or intention to move. EEG has a very small temporal resolution (approximately 1 ms), which can enhance researchers' understanding of temporal changes during each step of motor skill learning. Bönstrup et al. [52] reported a new form of motor consolidation during sequential motor skill learning. In their study, researchers examined EEG activity and performance change during the rest period between 2 trials. The change in performance during the rest period suggested a novel rapid form of motor skill learning during the training session. They also reported that the beta-band frequency activity in some specific parcellated cortical areas was associated with performance improvement during the rapid form of motor skill learning. These findings suggest several future research directions. In particular, it may be possible to modulate brain activity during a specific period of behavioral or cognitive performance, such as storage, consolidation, or retrieval. In addition, brain oscillation decoding could reflect a patient's brain state in real time, which may determine the best time to apply neuromodulation. Alternatively, decoding could contribute to determining the optimal treatment parameters.

Evoked potential

Evoked potentials have frequently been reported as measures of recovery status and prognosis after stroke. Motor evoked potentials (MEPs) are a representative evoked brain oscillation that is used to predict the integrity of a patient's corticospinal pathway. For example, an absent lower-extremity MEP response following transcranial magnetic stimulation was reported to predict a poor prognosis for independent walking after stroke [53]. We have also reported that the somatosensory evoked potential (SSEP) from the lower extremities could be a prognostic candidate for independent walking after stroke [54]. However, MEP and SSEP have not yet been compared. Furthermore, the most important parameter using evoked potentials from brain oscillations could be the transcranial magnetic stimulation evoked potential (TEP), which has been reported in recent studies using high-resolution EEG and transcranial magnetic stimulation [55,56]. TEPs showed a larger P30 amplitude in stroke patients than in healthy controls. There was a negative correlation between the N45 peak amplitude and functional performance in stroke patients [55].

Event-related potentials

Several studies have investigated the role of event-related potentials (ERPs) such as P300, N100, and P200, in working memory [57-59], attention in healthy patients [60], stroke [61], Parkinson's disease [62-64], and dementia [65,66]. The properties of ERPs are similar to those of brain oscillations (e.g., amplitude and latency). It is possible to collect amplitude and latency data, which are known to be highly correlated with cognitive performance.

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For example, changes in the P300 amplitude have been used to report the underlying mechanisms of improvement in walking memory after transcranial direct stimulation of the dorsolateral prefrontal cortex in healthy people [59,67]. ERPs can also be used to monitor improvement after cognitive training or rehabilitation [68,69].

Neuromodulation

Neuromodulation increases or decreases brain cortical activity using electrical or magnetic stimulation. These stimuli can be delivered transcranially or intracortically and can affect either neuronal activity or interneuronal transmission.

Although these techniques have been approved by the Food and Drug Administration to treat depression, they have not yet been approved for other indications. There are many controversies regarding the efficacy of noninvasive neuromodulation, and one suggested reason is the doubtful efficacy of neuromodulation. With our improved understanding of neuroscience, we now know that cortical activities have oscillatory properties that could affect the efficacy of neuromodulation. However, to date, there is no sophisticated protocol or technique that adapts to an individual's brain oscillatory status. Existing protocols are relatively fixed, depending on the purpose of stimulation. Studies using these stimulatory techniques have reported that the phase of beta oscillatory activity in the motor cortex consistently affects the MEP amplitude. Therefore, researchers have suggested that brain oscillatory activity should be used to determine aspects of the stimulation protocol, such as the stimulation start point or stimulation frequency. To this end, the concept of closed-loop neuromodulation may be capable of detecting an individual's oscillatory activity and thereby determining the optimal stimulation time point.

A closed-loop system can already detect the frequency of individual brain oscillatory activities in specific situations, such as finger tapping. By using this parameter, we can select the stimulation frequency with repetitive transcranial magnetic stimulation (TMS) or transcranial alternative current stimulation. Recently, some studies have reported that TMS could be a representative tool for evoking brain activity with EEG recordings, in so-called TMS-EEG studies. With this technology, we can explore the connectivity between several brain regions and obtains new insights into brain oscillatory activity from TMS-EEG studies [70]. Research on this topic has suggested that there are links between brain oscillatory activity at specific frequencies and cognitive performance. Researchers could use a specific stimulation frequency for repetitive TMS based on these linkages between brain oscillations and cognitive function [70].

BCI (neuroprosthetics)

A BCI is a type of closed-loop system, as this technique can monitor brain activity, determine the subject's intention using a decision algorithm based on artificial intelligence, and control external devices to perform various activities depending on the direction. A BCI platform consists of 1) a monitoring device that assesses the subject's intentions; 2) a process that analyzes multiple signals from various sensors including brain activity, which then decides whether or not to conduct the pre-programmed activity; and 3) an external device. Brain oscillations are the best-known signal type to detect a subject's intention. Although BCI systems can also use other human signals such as electromyography, pressure sensors, and audio signals, brain signals have very high temporal resolution, which can be useful in the real-time detection of the subject's intention. In particular, P300 signals and ERD/ERS at the beta-band frequency have been reported to be closely associated with movement and

attention. A BCI detects a change in P300 to determine the subject's intention to control the external device or cursor [71-74]. The BCI accepts and delivers brain oscillatory signals combined with EMG to the processor. The decision algorithm in the processor determines the subject's intention by using recent advances in machine learning.

CONCLUSION

The results of neural oscillatory activity analysis can help improve the evaluation and diagnosis; monitoring the rehab progress; prognostication; and personalized rehabilitation planning in neurorehabilitation. In addition, therapeutic usage of neural oscillation signals is drawing more attention due to the recent advancement of noninvasive neuromodulation technologies. Additional studies are warranted to confirm whether the clinical use of neural oscillation signals is associated with functional improvement in patients with various neurological disorders.

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