Review



# Magnetoencephalography as a Tool in Psychiatric Research: Current Status and Perspective

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**ABSTRACT**

The application of neuroimaging to provide mechanistic insights into circuit dysfunctions in major psychiatric conditions and the development of biomarkers are core challenges in current psychiatric research. We propose that recent technological and analytic advances in magnetoencephalography (MEG), a technique that allows measurement of neuronal events directly and noninvasively with millisecond resolution, provides novel opportunities to address these fundamental questions. Because of its potential in delineating normal and abnormal brain dynamics, we propose that MEG provides a crucial tool to advance our understanding of pathophysiological mechanisms of major neuropsychiatric conditions, such as schizophrenia, autism spectrum disorders, and the dementias. We summarize the mechanisms underlying the generation of MEG signals and the tools available to reconstruct generators and underlying networks using advanced source-reconstruction techniques. We then surveyed recent studies that have used MEG to examine aberrant rhythmic activity in neuropsychiatric disorders. This was followed by links with preclinical research that has highlighted possible neurobiological mechanisms, such as disturbances in excitation/inhibition parameters, that could account for measured changes in neural oscillations. Finally, we discuss challenges as well as novel methodological developments that could pave the way for widespread application of MEG in translational research with the aim of developing biomarkers for early detection and diagnosis.

*Keywords:* Biomarker, Brain imaging, Magnetoencephalography, Neural oscillations, Psychiatry, Translational Research

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Neuroimaging has played a fundamental role in psychiatric research in recent decades, shaping a new conceptualization of major brain disorders as impairments in neural circuits through the interrogation of the anatomical and functional architecture of large-scale networks (1,2). These important insights have been largely supported through studies conducted with magnetic resonance imaging (MRI), a brain imaging technique with excellent spatial resolution, which also allows for functional imaging of neurovascular signals. However, research into the underlying pathophysiology of psychiatric conditions has been impeded by the fact that these imaging techniques allow only indirect links to cellular and physiological mechanisms underlying observed signal changes and thus only limited relationships to preclinical research. Moreover, MRI approaches are unable to capture neural processes with high temporal resolution, which is essential for measuring fast rhythmic fluctuations of neuronal events that have been recently implicated in major psychiatric conditions (3).

## NEURONAL DYNAMICS IN LARGE-SCALE NETWORKS

It is conceivable that mechanistic insights into circuit dysfunctions require a stronger focus on noninvasive techniques that allow a direct assessment of neuronal dynamics at high temporal resolution. This is because recent data highlight that cognitive and executive processes during normal brain functioning emerge from the coordinated activity of distributed neuronal populations that are dynamically configured on the backbone of anatomical connections (4–6). Measurements from invasive as well as noninvasive electrophysiology support this hypothesis through demonstrating close relationships between modulations in the amplitude and synchrony of rhythmic activity and task-dependent and state-dependent parameters and cognitive and perceptual processes (7–9).

In addition to the functional significance of such rhythmic fluctuations, much work has been devoted to the analysis of synaptic mechanisms and circuits that support the generation of oscillatory activity and its synchronization (10). Establishing

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relationships between levels of organization, from cellular physiology to large-scale networks, will be a fundamental prerequisite for translational research. Only with these links does it become possible to quantify neural measures in the human brain that can be compared with observations in animal models and patient data to discover pathophysiological mechanisms and to target intervention to correct circuit dysfunctions (3).

## MAGNETOENCEPHALOGRAPHY AS A TOOL IN BRAIN RESEARCH

Electroencephalography (EEG) and magnetoencephalography (MEG) provide noninvasive measurements of fluctuations in the excitability of neuronal populations with high temporal resolution that can provide potential direct links with preclinical research. Although EEG has been widely applied in the investigation of psychiatric disorders for many decades, MEG has been applied only more recently in the identification of pathophysiological mechanisms.

Both MEG and EEG record a signal that is based primarily on postsynaptic potentials of pyramidal cells (11). However, there are important differences between both techniques (Table 1). MEG measures magnetic fields, whereas EEG measures electric potentials at the scalp. Electric signals are significantly distorted as they pass through different tissues with varying conductivities (cerebrospinal fluid, skull, skin). In contrast, magnetic fields are hardly affected by different tissues, which leads, for example, to improved estimates of high-frequency oscillations (Figure 1B) (12). Moreover, localization of generators of neural activity is more accurate for MEG than for EEG—especially if the complex geometries of these different tissues are not modeled correctly (13). Another difference between MEG and EEG is their sensitivity to the spatial orientation of the underlying generators (14). Whereas MEG is largely insensitive to radial sources that point toward the center of the head or away from it, EEG is sensitive to all orientations, although the amount of cortex truly silent to MEG may be relatively small (15). It should also be noted that EEG records signals relative to a reference electrode, the definition of which requires adequate consideration. In contrast, MEG recordings are reference free. MEG is also less susceptible to contamination by muscle artifacts, particularly those that result from volume conduction across electrodes, including the reference (16).

Optimal use of the rich information content of MEG signals often benefits from reconstruction of the generators of these signals. Source reconstruction relies on the combination of information represented in different MEG channels and combines with volume conductor models typically derived from individual anatomical MRI scans to compute tomographic estimates of activation on a three-dimensional grid covering the whole brain or the cortical surface. Source reconstruction has several benefits. It increases the signal-to-noise ratio, and it leads to more interpretable results because it reveals the location of the generators underlying the measured MEG signals (17). However, the sensitivity of MEG systems depends not only on the orientation of the generator but also on its location. MEG sensors are more sensitive to cortical generators than to subcortical generators (18).

## MEG STUDIES DURING NORMAL BRAIN FUNCTIONING

### Neural Oscillations During Cognitive Processes

Until recently, the noninvasive measurement of rhythmic activity in cognitive neuroscience has largely relied on sensor or electrode estimates of neural activity that provided correlative evidence with cognitive processes. Advances in MEG approaches have now allowed for the noninvasive mapping of the neuronal dynamics in large-scale networks, which have provided novel insights into the role of neural oscillations during perceptual and higher cognitive processes (19). Importantly for clinical research and development of biomarkers, such networks can be recreated in MEG measurements with high test-retest reliability (17,20).

Recent MEG studies have shown that top-down, attention-related signals are critical to the selection and integration of information that is relevant given the goals of an individual in a particular context (21). These biasing signals are readily measured using MEG, and it is possible to identify the sources of attention-related control in the distributed network of high-level associative areas and their modulatory consequences in perceptual areas (22,23). MEG studies have also contributed to our understanding of how attentional control and modulation guide perception of individuals (24) as well as how individuals flexibly focus on specific contents within memory (8,25). These processes of dynamic prioritization and selective routing of information processing are ubiquitous to healthy brain function and cognition (26), and their disruption is a major factor in many neuropsychiatric conditions (27). Importantly, MEG data have sufficient information content to allow decoding of cognitive states (Figure 1C) (8), highlighting the mechanistic involvement of MEG-measured oscillations in cognitive processes. Finally, emerging data suggest close relationships between rhythmic activity as assessed with MEG and the anatomical expression profile of neural oscillations (28) as well as with spectral characteristics of local field potentials from invasive electrophysiology (29), raising the exciting prospect of measuring physiologically realistic neuronal dynamics in extended networks.

### Resting-State Networks

Recent applications of MEG have led to novel insights into the complex dynamics of resting-state networks, which are an important target for psychiatric research (30). The networks disclosed by MEG-informed source reconstruction closely resemble the resting-state networks delineated using functional MRI (fMRI) (31), such as the default mode network, dorsal attention networks, and motor networks, but provide additional information on the contribution of distinct frequencies to the organization of the dynamic connectome (32). The high temporal resolution of MEG in principle allows many different approaches to quantifying coupling between spatially distinct brain regions, including power-power coupling, phase-phase correlations, and cross-frequency phase-amplitude coupling. Recent work has also extended the application of MEG to the investigation of cortical-subcortical networks during rest. Contributions from deeper sources should be detectable in MEG data, given that their fields are strong