Review

Biological Psychiatry

Multimodal Approaches to Define Network Oscillations in Depression

Otis Lkuwamy Smart, Vineet Ravi Tiruvadi, and Helen S. Mayberg

ABSTRACT

The renaissance in the use of encephalography-based research methods to probe the pathophysiology of neuropsychiatric disorders is well afoot and continues to advance. Building on the platform of neuroimaging evidence on brain circuit models, magnetoencephalography, scalp electroencephalography, and even invasive electroencephalography are now being used to characterize brain network dysfunctions that underlie major depressive disorder using brain oscillation measurements and associated treatment responses. Such multiple encephalography modalities provide avenues to study pathologic network dynamics with high temporal resolution and over long time courses, opportunities to complement neuroimaging methods and findings, and new approaches to identify quantitative biomarkers that indicate critical targets for brain therapy. Such goals have been facilitated by the ongoing testing of novel invasive neuromodulation therapies, notably, deep brain stimulation, where clinically relevant treatment effects can be monitored at multiple brain sites in a time-locked causal manner. We review key brain rhythms identified in major depressive disorder as foundation for development of putative biomarkers for objectively evaluating neuromodulation success and for guiding deep brain stimulation or other target-based neuromodulation strategies for treatment-resistant depression patients.

Keywords: Depression, Electrophysiology, Neurocircuitry, Neuroimaging, Neuromodulation, Treatment-resistant

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Over 10% of the world population has major depressive disorder (MDD), a disorder associated with the dysregulation of mood, cognition, sensorimotor physiology, and homeostatic processes (1). While treatments are available and generally effective, not all patients respond, leading to continued disability and morbidity. These clinical treatment challenges require new integrative models of disease pathophysiology and treatment effects. Complementary neuroimaging and electrophysiology techniques have emerged as critical contributors to meeting these challenges, providing a versatile platform to characterize brain circuit dysfunction underlying specific symptoms, as well as changes associated with their successful treatment. Discussed here are converging neuroimaging and electrophysiological findings with an eye toward the future application of multimodal network biometrics used in conjunction with targeted neuromodulation interventions for patients with treatment-resistant depression (TRD).

About 10% to 30% of MDD patients develop TRD, defined as MDD unresponsiveness to multiple standard antidepressant interventions (e.g., monotherapies or multiple drugs, psychotherapy) (2). Neuromodulation therapies (3–6) have taken on an increasingly primary role in the treatment of these patients, with the most invasive strategies, such as deep brain stimulation, providing a unique platform to directly modulate and record within specified neural circuits. Brain imaging has been critical to identifying the specific neural circuits to be targeted for neurostimulation.

Neuroimaging studies to date using different MDD cohorts and various interventions have defined a putative depression brain network mediating active symptoms and treatment effects (1,7–15). The most replicable findings involve limbic and cortical regions, notably frontal, ventral, and dorsal anterior cingulate; amygdala; hippocampus; and nucleus accumbens (Figure 1) [reviewed in (1,16)]. Recent studies further identify differential patterns in different patient subgroups using such diverse methods as glucose metabolism positron emission tomography (PET) (17,18), connectivity-based functional magnetic resonance imaging (fMRI) (19,20), diffusion tensor/tractography imaging (21–24), glutamate concentration magnetic resonance spectroscopy (25), and source-localized scalp electroencephalography (EEG) power spectra (26,27). These pattern variations suggest that further TRD subtyping, as well as subtype-specific target selection, may be necessary to optimize the various evolving neuromodulation strategies. Electrophysiology can extend this spatially grounded foundation by characterizing, with high temporal resolution, dynamic activity within putative disease networks determined from neuroimaging (Figure 1). As direct measures of neuron population activity, electrophysiology measures provide valuable windows into region-specific oscillations at millisecond time scales, with distinct oscillations carrying information from different brain processes (28,29). Particularly, for invasive interventions such as deep brain stimulation (DBS), precise anatomical targeting can be combined with simultaneous multimodal EEG and/or intracranial

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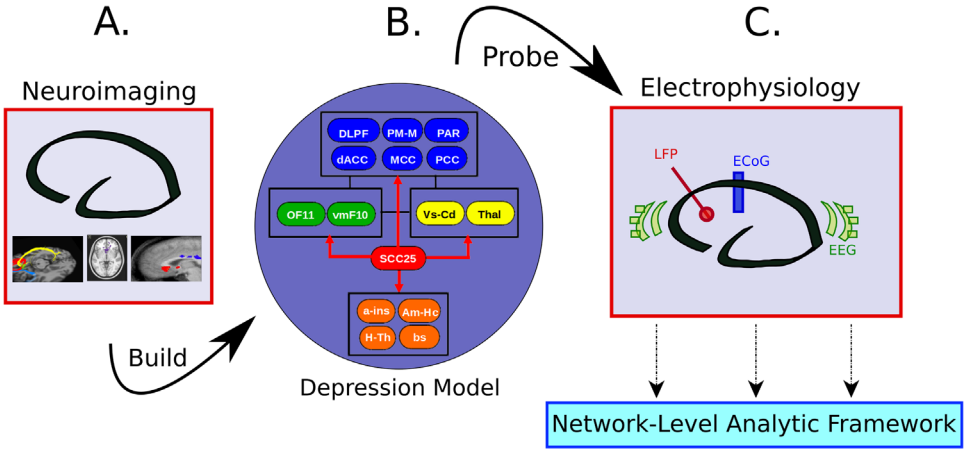

Figure 1. Operational pipeline for imaging-informed electrophysiology studies of depression. A multiregion model of depression **(B)** is constructed from the synthesis of structural and functional imaging findings (i.e., positron emission tomography, structural magnetic resonance imaging, functional magnetic resonance imaging, diffusion tensor/tractography imaging) **(A)**, providing foundation for hypothesis-driven electrophysiological analyses **(C)**. a-ins, anterior insula; Am-Hc, amygdala-hippocampus; bs, brainstem; dACC, dorsal anterior cingulate cortex; DLPF, dorsolateral prefrontal; ECoG, electrocorticography; EEG, electroencephalography; H-Th, hypothalamus; LFP, local field potential; MCC, mid-cingulate; OF11, orbitofrontal (Brodmann area 11); PAR, parietal; PCC, posterior cingulate; PM-M, premotor-motor; SCC25, subcallosal cingulate (Brodmann area 25); Thal, thalamus; vmF10, ventromedial frontal; Vs-Cd, ventral striatum-caudate.

EEG to measure both local and remote network effects before, during, and after acute and chronic stimulation.

In this article, we review 1) past studies of brain oscillations in MDD, 2) mechanistic studies of neuromodulation interventions, and 3) strategies for optimizing neuromodulation for TRD using integrated multimodal brain imaging and brain electrophysiology.

RESTING-STATE STUDIES OF BRAIN OSCILLATIONS IN MDD

Historically, noninvasive electrophysiology was the primary probe of brain activity in MDD and thus foundational for later studies using functional imaging methods such as PET, single-photon emission computed tomography, and fMRI. Particularly, alpha and theta rhythms dominated the published literature measured using primarily scalp EEG, findings that continue to guide and influence electrophysiology studies using contemporary tools.

Alpha rhythms, often defined in humans as 8 Hz to 12 Hz oscillations, reflect a potentially important mechanism of depression. The first rhythm seen by EEG discoverer Hans Berger, alpha oscillations have since been ascribed to decreased cortical activity or processing. Early models of depression posited differential activation of positive and negative affect systems (30) located in left and right frontal cortex, respectively (31,32). Demonstration of left frontal alpha increases and right frontal alpha decreases tracked with symptoms of depression (26). Since then, prefrontal rhythm asymmetries have been investigated as biomarkers of depression (33).

Resting alpha asymmetry between the frontal cortices has been shown to predict affective responses to emotive stimuli (34). Studies have also shown an association between increased left frontal alpha and greater depression severity scores (26,35). In a study investigating fluoxetine responder-nonresponder differences, alpha power was found to be similar between the groups, while alpha asymmetry demonstrated decreased alpha in the right hemispheres when compared with the left in the nonresponders (36). These results were seen to support alpha asymmetry as a putative biometric of depressive disease (37). However, enthusiasm for the use of this alpha asymmetry as a clinical biometric was somewhat attenuated by failure to demonstrate a consistent correlation between alpha activity and clinical state over the course of a depressive episode (38). On the other hand, the argument that variability in frontal alpha asymmetries represents a trait marker for depression risk, even outside actual episodes of illness (39), has had more direct support. While reports of alpha abnormalities in depression are among the most robust findings, the temporal instability of alpha asymmetry findings relative to depressive state (39,40) limits current reliance on alpha findings as trait marker of the illness (41,42). Alpha asymmetry over the parietotemporal regions has also been reported (38,43), again paralleling studies with other neuroimaging methods (44,45). Early investigations of whole-brain functional connectivity across the EEG spectrum have further demonstrated increased parietal-temporal alpha coherence (46,47) and distributed cortical synchrony in MDD (47). Such whole-brain level approaches are now the emerging standard, with a focus on identifying diagnostic and prognostic biometrics (48).

Recent investigations of alpha have examined functional connectivity (46), with elevated alpha coherence demonstrated in long-range connections between frontopolar and temporal regions in MDD patients (47). These studies, relying on EEG modalities with higher-order quantitative capabilities, represent a new approach for studying the role of alpha in distributed MDD networks.

More recent investigations using magnetoencephalography have thus far failed to confirm the utility of alpha asymmetry as a diagnostic marker, since both depressed and nondepressed subjects exhibit asymmetries at statistically similar rates (49). Notably, frontal alpha asymmetry, when present, was stable following clinically effective repetitive transcranial magnetic stimulation, suggesting an important role for alpha asymmetry variability as a reflection of depression trait but not in differentiating TRD from healthy