Published in final edited form as:

Biol Psychiatry. 2015 June 15; 77(12): 1061–1070. doi:10.1016/j.biopsych.2015.01.002.

Multimodal Approaches to Define Network Oscillations in Depression

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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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DISCLOSURES
Other authors report no biomedical financial interests or potential conflicts of interest.

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 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 control subjects or nonresponders from responders (49). Intracranial recordings from implanted DBS electrodes in TRD patients provide new support for a subcortical role for alpha. Recordings from both the subcallosal cingulate (Brodmann area 25) and the nucleus accumbens acquired in different patients in separate studies report increases in resting alpha rhythm in TRD patients when compared with obsessive-compulsive disorder patients (50). While there are no healthy or nondepressed patient control subjects with comparable recordings in these studies, this is the first direct evidence of striatal and limbic alpha rhythm dysfunction in MDD. The presence of alpha asymmetry and its behaviorally specific clinical correlates remains to be determined. Source localization techniques applied to high-density scalp EEG data may provide a needed bridge between these unique invasive recording opportunities and the findings generated using more conventional lower resolution EEG techniques in larger patient and control cohorts.

Theta rhythms, often defined in humans as 4 Hz to 8 Hz oscillations, reflect another potential pathophysiological marker of MDD. Known primarily for its central role in hippocampal circuits, theta has been interpreted as a driving rhythm for downstream regional activity—a possible mechanism for coherent memory and attention processing (51). In addition, theta rhythms are involved in pattern recognition within the place and grid cell systems (52,53). Theta oscillations have also been shown to have properties of a traveling wave within the limbic system, hinting at a richer mechanism of distributed theta-dependent function (54), especially in the context of limbic-cortical interactions and network-level, synchronized activity. Interactions between medial temporal regions and prefrontal cortex appear to be mediated by theta oscillations, revealing a key communication mechanism between regions implicated in memory, executive function (55,56), and depression (44). To date, the focus of studies in MDD have centered on mid-frontal theta and how antidepressant therapy affects its properties.

Mid-frontal theta rhythms have been localized to the anterior cingulate cortex (ACC) in some studies (57), with demonstrations of abnormal theta correlations within corticolimbic networks in MDD using measures of absolute power and low resolution electromagnetic tomography (14,58). Cordance, a composite metric that relates relative power within a band (i.e., the ratio of theta power to total power) to absolute power within that band, has been used to further link theta oscillations to regional perfusion and metabolic activity (59). Cordance studies have demonstrated decreased frontal theta in MDD patients (26,60,61). Thought to reflect ACC activity (60), mid-frontal theta has been proposed as both a potential predictor of antidepressant medication response (61,62) as well as a target of change following treatment (63,64), mirroring findings demonstrated using PET measures of glucose metabolism and blood flow (44,48,65,66).

Expanding on these previous observations, increases in frontal theta cordance seen after 1 month of continuous DBS predicted long-term clinical efficacy (67). Evidence of cingulate asymmetry in resting-state PET and functional connectivity fMRI studies across depression subtypes (44,68,69) suggests that lateralized electrophysiology signals might also be present in theta; however, this has yet to be reported. Further investigation, ideally using bilateral midline cortical sampling using invasive methods, is needed to dissociate lateralized theta changes in ACC from those in adjacent medial prefrontal cortex. This approach might also help to integrate reports of frontal alpha asymmetries with limbic theta patterns. Nonetheless, despite the consistent evidence for theta involvement in MDD, validity of frontal midline theta as a biomarker of depression remains inconsistent (70); further efforts to identify MDD subtypes using localized rhythm abnormalities may be a useful next step.

NEUROMODULATION STUDIES OF BRAIN OSCILLATIONS IN MDD

Neuromodulation is generally designed to impact function of a specific brain target, in turn changing brain network function and corresponding brain rhythms via connections between the target and other brain areas (71). Neuromodulation treatment for TRD is commercially available using various approaches including electroconvulsive therapy (ECT) (72,73), transcranial magnetic stimulation (TMS) (74,75), and vagus nerve stimulation (VNS) (76), with ongoing research evaluating the utility of transcranial direct current stimulation (tDCS) (77,78), magnetic seizure therapy (73,79,80), cortical brain stimulation (81–83), and DBS (69,84–88). Based on the biophysics of each neuromodulation technique, it is likely that each has different effects on neural rhythms. Furthermore, different approaches have different time courses to induce initial and maximal clinical effects. For instance, ECT and TMS can produce acute changes but generally require ongoing multiple sessions over weeks to achieve sustained antidepressant effects (72–75) and maximal VNS effects are reported often after months of ongoing stimulation (89,90). In evaluating rhythm changes with different methods, one must consider target symptoms, time line, and interactions.

While similarities and differences of the various neuromodulation approaches have not been explicitly investigated, differential patterns in oscillatory measures and network function have been identified that correlate with decreased depressive symptoms. ECT decreases ACC-dorsolateral pre-frontal cortex connectivity (91), increases connectivity within frontal cortices (92), and increases subcallosal cingulate cortex (SCC) and frontal theta oscillations (93,94). VNS increases delta oscillations in prefrontal, frontal, and central regions (90,95). TMS reduces connectivity between frontal and deep-brain nuclei (13,96,97); increases prefrontal gamma activity (98); decreases precuneus gamma activity (98); increases alpha rhythms in frontal (99) and dorsal ACC (100) areas; decreases and increases theta oscillations in SCC (101) and prefrontal cortex (102), respectively; decreases prefrontal delta signals (102); and alters activations in other structures (103). Likely due to differences in techniques (cortical targeting, parameters, duration and number of sessions), there is not yet a clear relationship between antidepressant effects and specific brain rhythms for tDCS (104–106). However, tDCS can decrease delta, theta, and alpha rhythms in frontal and cingulate areas in addition to both midline theta increases and alpha decreases (104–106). Such studies might be further extended using longer longitudinal time lines and

standardized, multiple signal-acquisition modalities to track the chronology of clinical changes in depressive symptoms.

NETWORK ANALYSES TO STUDY OSCILLATIONS IN MDD

Together, resting-state and neuromodulation studies of MDD oscillations reflect the diseased network's baseline activity and the network's response to an induced state change, respectively. The next step is the development of analytic tools and models to integrate these various recording modalities across stimulation techniques within a network perspective.

Toward this goal, higher-order metrics and network-level analyses can extend band-limited power results by explicitly incorporating activity timing information present in rhythm phase. Oscillations have frequencies and magnitudes, often well characterized in basic electrophysiological methods, but oscillation phase may also contribute to region-region interactions and is thought to contain a large portion of the information content of neuronal oscillations (107). Many phase-based analysis techniques have been applied to neural systems, revealing previously unseen dynamics within and between brain regions during physiology and disease (108–110). Here, we will focus on phase locking, coherence, and cross-frequency coupling (CFC) as vital tools for multimodal, multiregional electrophysiological studies in MDD.

Phase locking is an analysis to examine the rapid dynamics in regional brain rhythms that are often lost in power-based analyses; such losses are attributed to large averaging epochs, on the order of minutes. In support of this general observation, longer-range temporal correlation in theta rhythms, occurring at rapid time scales on the order of seconds, has been found to be absent in MDD patients (111). Some phase-based methods have shown transient intervals of phase-locked alpha asymmetry, requiring smaller epoch lengths and a characterization of the phase of ongoing EEG activity (112). Abnormal phase relationships between distinct MDD network nodes may further give rise to mistimed communication between regions, even with unchanged power.

Coherence can quantify spectral synchrony between brain oscillations from distinct regions. Coherence is currently used to determine functional connectivity within distributed electrophysiology channels (47,113). Applied to MDD, long-distance coherence between regions has been shown to increase in alpha and theta rhythms (47,114). Coherence has already demonstrated utility as a functional metric, but extending its use to track neuromodulation effects can more fully probe node-to-node communication at millisecond time scale.

CFC, while not yet applied to MDD, provides a set of methods to quantify the interaction of different brain oscillations. Phase-amplitude coupling (PAC), a type of CFC, determines the statistical relationship between the phase of low-frequency oscillations and the amplitude of high-frequency oscillations (115). PAC is hypothesized to reflect a mechanism by which different subcortical regions exchange control over cortical targets (116). PAC studies have shown rapid changes during learning (117), decision making and reward encoding (118,119), and even disease correction (120). A recent study in Parkinson's disease

demonstrated large clinically relevant changes in coupling between beta and gamma rhythms in the pathway connecting motor cortex and subthalamic nucleus pathway with acute subthalamic nucleus stimulation. This study is particularly noteworthy as it leveraged intraoperative DBS to record multiple structures to link oscillatory changes to clinical effects (120). Furthermore, demonstrations of distinct phase-amplitude couplings across different networks may indicate communication responsible for binding specific regions to elements of a single task (116). Similar methods can be applied in MDD, and animal models have already taken this approach using both multiregion unit activity and field potentials in both genetic and stress models of disease (117,121–126).

INTEGRATED MULTIMODAL FRAMEWORK USING DBS FOR TRD

DBS provides a highly versatile platform to access, test, integrate, and extend these disparate oscillatory findings identified in previous neuromodulation and electrophysiological studies of MDD. Like other neuromodulation techniques, network effects can be electrically triggered, recorded by diverse noninvasive or invasive modalities, and quantified by multiple signal processing techniques within and across modalities over time. Unique to DBS is the anatomical precision of both stimulation and recording within deep network structures. To date, research groups have examined six different DBS targets in TRD patients: the SCC white matter (69), the ventral striatum/ventral anterior internal capsule (84), the nucleus accumbens (85), the inferior thalamic peduncle (87), the lateral habenula (86), and the medial forebrain bundle (88). While there is anatomical evidence that these regions share many structural connections (127–129), it is untested if DBS at these various targets evoke similar quantitative neurophysiology effects. As such, measuring local and remote brain oscillations for each electrically stimulated target will provide important opportunities to test shared and disjoint attributes of different DBS approaches within different theoretical depression models (Figure 2). Further, different targets may optimally impact specific depressive symptoms: inhibiting negative mood may be best achieved with stimulation of the SCC white matter, while motivation and learning may be optimally induced using stimulation of the ventral striatum/ventral anterior internal capsule or medial forebrain bundle. A target comparison strategy addressing the time course of stimulation-induced changes in distinct symptoms or behaviors may also be required to fully delineate DBS effects in MDD toward optimizing the selection of a procedure most likely to result in clinical remission for a given patient (130–132).

There are several examples of DBS studies in MDD patients utilizing scalp or intracranial electrophysiology, but none to date address DBS-specific antidepressant mechanisms. One study found that an increase in frontal theta cordance after 1 month of DBS correlated with the eventual magnitude of long-term antidepressant response to chronic DBS but found no additional differential changes with actual response (67). Other studies have exploited the opportunity to directly measure activity at the DBS target, allowing for direct linking of behavior to the activity of the brain region being modulated, independent of actual stimulation effects (131–134). Such studies have generally been performed in the operating room or in the days thereafter. In separate studies, SCC alpha power was positively correlated with baseline depression severity scores (50); single neurons in the SCC were shown to be preferentially activated by negatively relative to positively valenced emotional

images (131); SCC beta coherence changes predicted subsequent decisions in an affective valuation task (134); and the accumbens activity increased in anticipation of an impending reward (118,132). These studies generally confirm previous findings using other imaging modalities. While first observations of the chronology of response-specific changes in negative bias with DBS have been recently reported using scalp EEG (130), longitudinal studies of subcortical electrophysiological changes are not yet available knowledge. Nonetheless, such findings do inform on node and network properties of MDD and perhaps more specifically on TRD dysfunction, but studies thus far provide limited information about mechanisms mediating either acute stimulation-induced rhythmic effects or long-term antidepressant response.

Evolving strategies to address antidepressant mechanisms of DBS are now undergoing testing and development. For example, in studies of SCC DBS for TRD, it has been shown that precise localization of the intended DBS implantation target can be optimized using preoperative diffusion imaging and white matter tractography to define the intersection of the uncinate fasciculus, cingulum, and forceps minor as in and around the SCC (21). Immediately upon implantation of DBS therapy electrodes, detailed measurements of basal activity at the precise target of stimulation can be recorded, confirming localization of the intended contact within the gray-white matter junction. In addition, potential behavioral correlates and changes in local activity with and without therapeutic doses of stimulation can be characterized. Until recently, SCC recordings were restricted to intraoperative recordings or those performed in the immediate postoperative period with externalized leads (50,131,133,134). Devices are now available that not only deliver therapeutic stimulation but also record ongoing oscillations directly off the implanted DBS electrodes (135–138). Consequently, studies can now measure activity changes in targeted regions of interest longitudinally at a high temporal resolution. Integration of signals from multiple regions of interest will require multielectrode data acquisition and multichannel analyses to fully capture mechanistic interactions within the MDD network (Figure 2). Additionally, such studies can be combined with complementary sampling of whole-brain activity changes using scalp EEG, PET, and fMRI (139–141) to define a more comprehensive view of DBS effects throughout the network over time.

The ultimate end product of such multimodal studies will be reliable and sensitive biomarkers of antidepressant response at the cellular and systems levels that guide the optimization of current DBS protocols and facilitate the development of next generation research strategies and medical devices. Toward these goals, current generation devices are now being leveraged using multiple measurements at strategic time points within an individual clinical research trial. Preoperative multi-modal neurophysiology (e.g., PET, fMRI, diffusion tensor/tractography imaging, and EEG) combined with behavioral and psychophysiological measures provides first estimates of the network of interest and eventually of the most appropriate DBS stimulation target based on combined behavioral biometrics and imaging-based inclusion criteria (17,18,142) (Figure 1). Surgical implantation utilizes predefined network maps of individualized white matter pathways to ensure optimal network targeting (21,24) with new methods developing more refined models of likely electrophysiological effects (24,143). Lastly, preoperative, intraoperative, and postoperative multimodal encephalography define, confirm, and help to track acute,

subacute, and chronic changes indicative of target engagement (Figures 1 and 2) (136,144,145). Such applications of multimodal encephalography can thus directly inform on mechanisms mediating DBS-induced antidepressant effects at the neuronal level with implications for ongoing, evidence-based modification of algorithms for treatment delivery. Availability of next generation devices for longterm intra-cranial EEG monitoring has already demonstrated feasibility and clinical utility in studies of epilepsy and Parkinson's disease (120,146,147). Such studies further serve as models for advancing studies of DBS for MDD and for rational development of noninvasive approaches (12). Determining the least invasive and most reliable combination(s) of brain signal modalities, neuromodulation methods, and stimulation targets to achieve the most effective antidepressant response for a given patient is the ultimate goal.

Acknowledgments

Supported in part by Grants from the Dana Foundation, Woodruff Fund, Stanley Medical Research Institute, and Hope for Depression Research Foundation and the National Institute of Neurological Disorders and Stroke (3R01NS079268-02S1) with work performed under Food and Drug Administration physician-sponsored investigational device exemptions G060028 and G130107.

Dr. Mayberg has received consulting and intellectual property licensing fees from St. Jude Medical, Inc.

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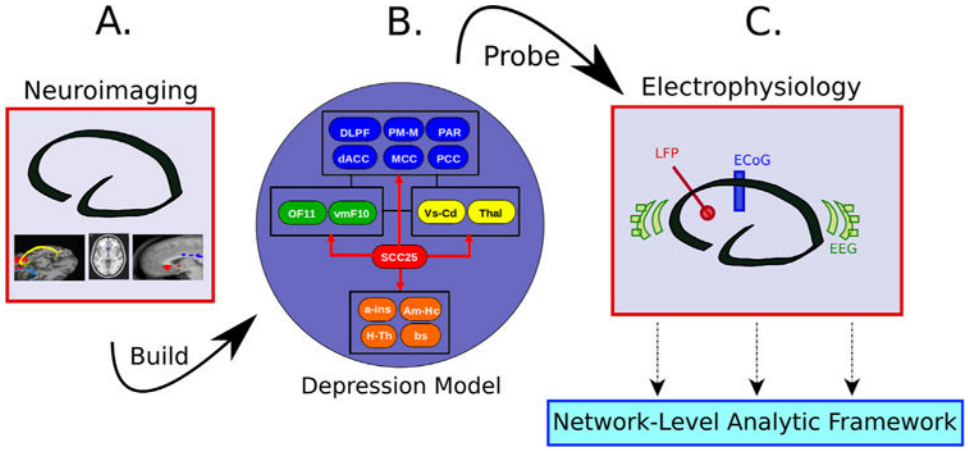

Figure 1.

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.

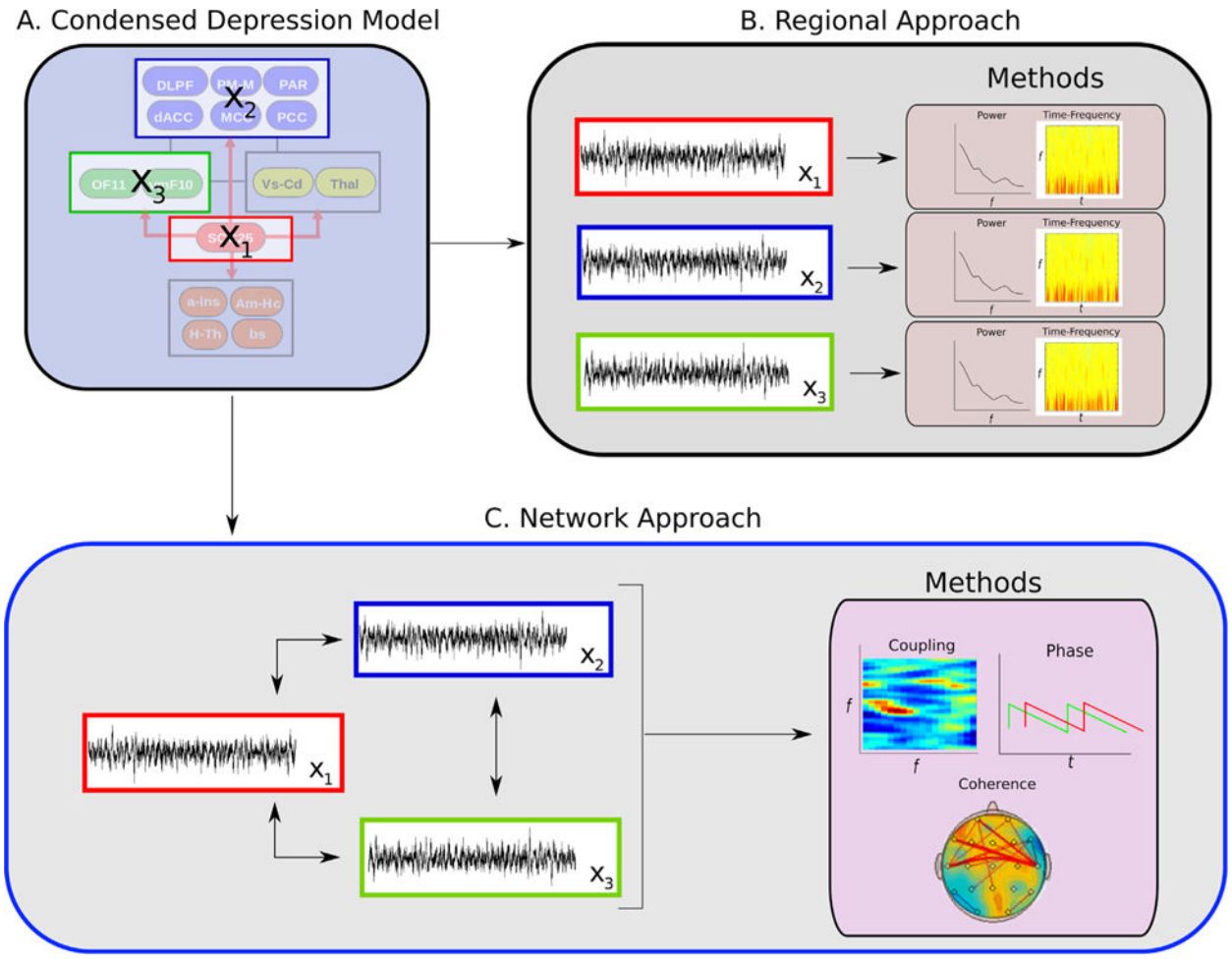

Figure 2.

Analytic framework for characterizing regional interactions within a given depression model. Following selection of putative targets **(A)** derived from a designated multiregion model, two signal processing strategies are implemented: an intraregion approach **(B)** that uses methods that analyze each node independently and an interregion network approach **(C)** that considers the interaction between multiple nodes.