Published in final edited form as:

Ann N Y Acad Sci. 2015 May ; 1344(1): 78–91. doi:10.1111/nyas.12742.

Rhythms and blues: modulation of oscillatory synchrony and the mechanism of action of antidepressant treatments

Andrew F. Leuchter^{1,2}, Aimee M. Hunter^{1,2}, David E. Krantz^{1,2}, and Ian A. Cook^{1,2,3}

¹Laboratory of Brain, Behavior, and Pharmacology, and the Depression Research and Clinic Program, Semel Institute for Neuroscience and Human Behavior at UCLA, Los Angeles, California

²Department of Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine, University of California, Los Angeles, California

³Department of Bioengineering, Henry Samueli School of Engineering and Applied Sciences, University of California, Los Angeles, California

Abstract

Treatments for major depressive disorder (MDD) act at different hierarchical levels of biological complexity, ranging from the individual synapse to the brain as a whole. Theories of antidepressant medication action traditionally have focused on the level of cell-to-cell interaction and synaptic neurotransmission. However, recent evidence suggests that modulation of synchronized electrical activity in neuronal networks is a common effect of antidepressant treatments, including not only medications, but also neuromodulatory treatments such as repetitive transcranial magnetic stimulation. Synchronization of oscillatory network activity in particular frequency bands has been proposed to underlie neurodevelopmental and learning processes, and also may be important in the mechanism of action of antidepressant treatments. Here, we review current research on the relationship between neuroplasticity and oscillatory synchrony, which suggests that oscillatory synchrony may help mediate neuroplastic changes related to neurodevelopment, learning, and memory, as well as medication and neuromodulatory treatment for MDD. We hypothesize that medication and neuromodulation treatments may have related effects on the rate and pattern of neuronal firing, and that these effects underlie antidepressant efficacy. Elucidating the mechanisms through which oscillatory synchrony may be related to neuroplasticity could lead to enhanced treatment strategies for MDD.

Keywords

major depressive disorder; oscillations; oscillatory synchrony; antidepressant treatment; antidepressant medication; mechanism of action; biomarkers; biosignatures; intermediate phenotype; thalamocortical dysrhythmia; quantitative electroencephalography; neuromodulation

Introduction

Major depressive disorder (MDD) is an illness that can be characterized at many different levels of biological organization. In addition to the clinical phenotype of depressive symptoms, physiologic differences between patients with MDD and healthy controls have been reported, for example, at the level of genetic polymorphism, gene expression, cellular signaling and metabolism, functional connectivity, and global brain function.^{1–4} Regulation of activity at each of these physiologic levels has a potential relationship to the mechanism of action (MOA) of an antidepressant treatment.

The functional linkages among these different levels of physiologic organization, and their possible relationship to antidepressant treatment efficacy, are not well understood. Here, we review evidence on the effects of antidepressant treatments on regulation of physiologic processes at levels ranging from the genome to brain networks, as well as the possible relationships between these effects and antidepressant MOA.

Antidepressant treatments may exert similar actions at different levels of biological organization

Pathogenic theories of MDD, and the MOA of antidepressant medications, traditionally have focused on synaptic neurotransmission. For much of the past 50 years, aminergic synapses have been the putative targets of antidepressant medications, and their MOA has been linked to increased extracellular availability of monoamines.³ Indeed, most antidepressant medications increase extracellular monoamine levels and change synaptic signaling, but these effects occur within hours of drug administration, whereas therapeutic effects do not occur for weeks.⁵ Other recently developed pharmacologic treatments for depression target a distinct set of synaptic proteins. These treatments include experimental, rapidly acting antidepressant medications, such as ketamine, which are hypothesized to act through a cascade of molecular and cellular events that are triggered by blockade of the *N*-methyl-D-aspartate receptor (NMDAR).² NMDAR blockade is hypothesized to lead to a decrease in γ -aminobutyric acid (GABA) inhibitory feedback on cortical pyramidal neurons and a resultant loss of tonic inhibition, thus increasing glutamatergic signaling in these circuits.⁶ Increased glutamatergic neurotransmission, in turn, is thought to activate synaptic α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors.⁷

A distinct set of treatments for MDD is neuromodulation techniques, through which external energy sources are applied to modify brain function. These techniques include electroconvulsive therapy (ECT) and repetitive transcranial magnetic stimulation (rTMS), as well as synchronized transcranial magnetic stimulation (sTMS), deep brain stimulation (DBS), transcranial direct current stimulation (tDCS), trigeminal nerve stimulation (TNS), and transcranial alternating current stimulation (tACS).^{8–11} Repetitive TMS in particular is an increasingly utilized treatment with efficacy and durability of improvement similar to that of antidepressant medication.¹² It is instructive to contrast rTMS with medication treatments for depression because it is delivered at a very different level of biologic organization, applied to defined cortical neuroanatomic targets. Interestingly, in stimulated cortex, rTMS has effects on GABAergic neurotransmission and cortical excitability that are analogous to

those of ketamine,¹³ with the effects of stimulation spreading rapidly to alter activity in multiple limbic structures, including the bilateral middle prefrontal cortex (PFC), right orbital frontal cortex, left hippocampus, and dorsomedial nucleus of the thalamus.¹⁴

Although the MOA of antidepressant treatments has not been fully elucidated, these varied treatments all lead to increased neuroplasticity,^{1,15} and recent theories have suggested that enhanced plasticity represents a common MOA of aminergic and glutamatergic antidepressants, as well as of neuromodulatory treatments such as rTMS.^{3,16} This idea builds on decades of parallel studies on the molecular mechanisms of learning and memory.¹⁷ For example, cellular models of learning involve integration of mechanisms including trafficking of synaptic glutamate receptors,^{18,19} remodeling of synaptic spines,²⁰ transcriptional upregulation (e.g., via the transcription factor CREB),^{21,22} local synaptic tagging,^{23,24} adult neurogenesis,²⁵ epigenetic remodeling via DNA methylation and histone modifications,²⁶ and the activity of neurotrophic factors.²⁷ Similar mechanisms may underlie the synaptic changes thought to occur in antidepressant therapies. For example, antidepressant medications, ECT, and rTMS have all been reported in human and animal models to increase the expression and signaling of brain-derived neurotrophic factor (BDNF, a trophic factor that mediates neuroplasticity) in the hippocampus and cortex.^{28–30} Repetitive TMS has been demonstrated to enhance neuroplasticity in cortical and corticospinal systems, possibly mediated through changes in expression of BDNF.^{30–32} Increased BDNF (either through direct injection into the brain or overexpression through transgenic manipulation) can produce changes in behavior similar to those induced by antidepressant medications.^{33,34} Increased BDNF expression may be induced by epigenetic processes, such as chromatin remodeling and histone methylation; alterations in intracellular signaling, such as phosphorylation of transcription factors affecting gene expression; and posttranslational modification of proteins.^{2,35,36} The downstream effects of BDNF in enhancing synaptic neuroplasticity are hypothesized to be involved in recovery from MDD.^{2–4}

Transduction of antidepressant effects across different levels of organization

The multiple levels of biological organization, ranging from the genome to brain networks and ultimately culminating in the phenotype(s) of MDD, represent a continuum of increasingly elaborate structures and processes. The continuum of biological structures that span the spectrum from genome to whole brain, and accompanying processes ranging from gene regulation to brain network function, can be conceived of as a spectrum of increasing biological complexity (Fig. 1). Broadly speaking, these structures and processes can be grouped into three general categories of organization: those existing at the level of the single cell, those involving cell-to-cell communication, and those that involve cell networks (Fig. 1).

These three categories are not entirely independent. The literature reviewed above indicates that the brain has intrinsic mechanisms to transduce biological signals along this continuum from the most fundamental level of complexity to the most elaborate, and vice versa: genetic polymorphisms influence learning processes at the level of brain functional networks, and

the activity of brain functional networks influences synaptic function and epigenetic processes. Physiologic signal transduction in the brain must be a “two-way street,” with one or more physiologic mechanisms transmitting salient information through both bottom-up (i.e., neuron to network) and top-down (i.e., network to neuron) modes of communication, across multiple levels of biological complexity. Evidence indicates that this bidirectional signal transduction is an essential part of learning and memory and, more broadly, neuroplasticity, although the precise mechanisms underlying this signal transduction have not been fully elucidated (Fig. 1).

Similarly, it is not well understood how the neuroplastic effects of antidepressant medication treatments are transduced from the cellular level of action to the level of brain functional networks, and reciprocally, how the neuroplastic effects of treatments such as rTMS are transduced from the level of cortical neuronal networks to the level of cellular function. Therapeutic interventions that act at either basic or more elaborate levels of complexity have been reported to yield similar changes in plasticity and gene expression in humans and/or in animal models, in peripheral blood or brain. These interventions include antidepressant medication and exercise,³⁷ cognitive behavioral therapy for posttraumatic stress disorder,³⁸ ECT,³⁹ altering emotional and physical stress exposure,⁴⁰ and cues that entrain circadian rhythms.⁴¹ The effects of these interventions may be transduced through similar mechanisms that subserve signal transduction in learning and memory processes, although this has not been established. Regardless of whether the mechanism(s) for transducing antidepressant treatment effects is similar or distinct, the effects of medication treatments that alter neuronal function or synaptic transmission must be transduced in a bottom-up fashion to influence cognitive and emotional processing in brain systems. Conversely, the influence of neuromodulation treatments that are administered to small ensembles of cortical neurons must be transduced in a top-down fashion to the synapse and the individual neuron, where it can influence synaptic plasticity (Fig. 1).

For treatments that are delivered at the level of higher-order brain networks, or to the organism as a whole,^{35,40} it also remains unclear how neuroplastic changes are induced across brain regions in order to achieve remission from MDD. Some treatments such as rTMS can be effective when delivered to one of several neuroanatomic targets, and cognitive behavioral therapy is directed at behaviors and thought processes rather than at any specific neuroanatomic structure. Depression affects multiple physiological functions and behaviors controlled by distinct brain regions. It is possible that all brain regions undergo neuroplastic changes induced by a global neurochemical process. Alternatively, a more circumscribed area of the brain or a subset of neurons may initiate the antidepressant response that is then transmitted more broadly.

Use of intermediate phenotypes to examine antidepressant action

We have previously proposed that intermediate phenotypes (IPs) may be useful for understanding antidepressant MOA and the relationship between treatment modalities that act along a broad spectrum of complexity, ranging from cellular processes to the organism as a whole.⁴² In particular, those IPs with an intermediate position along this spectrum, proximal to possible loci of action both at the level of the cell and the organ level of the

brain, may help to bridge the gap between neuronal and more global brain function in MDD, transducing signals in both bottom-up and top-down directions (Fig. 1).

Modulation of cerebral oscillatory activity appears to fulfill the criteria for this type of IP, reflecting the activity of both brain circuits and cellular processes at the level of the neuron. In human studies, oscillatory synchrony regulates information flow in brain circuits and networks in response to environmental inputs and task demands,^{43,44} while at the same time reflecting genetic influences: for example, oscillatory reactivity during cognitive tasks is correlated with a human Val66Met polymorphism that also affects BDNF secretion.⁴⁵ In animal models, oscillatory regulation also appears to represent a crucial step in context-dependent fear learning. Disruption of hippocampal θ rhythms (4–8 Hz) through blockade of neuronal gap junctions in the dorsal hippocampus impairs context-dependent memory formation as well as c-fos expression, suggesting a functional link between θ frequency oscillations and a neuroplastic process mediated by electrical synapses.⁴⁶ In the circuits that mediate circadian rhythms, changes in oscillatory synchrony correlate with changes in dopaminergic tone⁴⁷ and, through voltage- and ligand-gated ion channels, with cyclical changes in gene expression.⁴¹ In the context of antidepressant treatment, ultradian oscillatory synchrony has been observed to be related to fluctuation in serotonergic tone and has been hypothesized to play a prominent role in antidepressant medication efficacy, as well as to affect expression of genes related to serotonin synthesis.⁴⁸ Changes in brain oscillatory synchrony measured with quantitative electroencephalography (qEEG) have been shown to be a reproducible predictor of response and remission after 8 weeks with a variety of treatments, including monoamine reuptake inhibitors, bupropion, DBS, rTMS, and the experimental antidepressant ketamine.^{42,49–56}

How can oscillatory synchrony link brain processes from cellular to network levels?

Although the processes regulating synchronous oscillations are not fully understood, they represent a compelling potential mechanism for integrating the activity of individual neurons into microcircuits and larger-scale functional networks, as well as coordinating processing of information across brain regions.^{44,57–60} Synchronous oscillations yoke the function of neighboring individual neurons into small microcircuits,^{44,57–60} and phase-locked oscillations of multiple microcircuits can link physically distant areas of the brain.^{57,60} Entrainment of neuronal oscillations in a phase-locked manner plays a central role in regulation of blood flow and metabolism, the control of sleep and other autonomic processes, and the formation of neural networks for higher-order information processing (Fig. 2).^{57,61–64} This broad role for oscillatory synchrony in coordinating brain activity suggests that disturbed oscillatory regulation may play a key role in the emergence of depression and related neuropsychiatric phenotypes.⁶⁰

Recent experimental work using neuromodulation methods provides strong evidence that alteration of oscillatory synchrony alters activity in brain functional networks, with measurable changes in cognition and behavior. Helfrich *et al.*⁶⁵ applied tACS to the occipital cortex during a visual perception task, and applied stimulation either in or out of phase with endogenous oscillations in order to manipulate brain network function. They

demonstrated that the two forms of stimulation had different effects on visual network function measured using qEEG and elicited distinct alterations in perceptions of movement in visual stimuli. The linkage between modulation of network oscillations and measurable perceptual consequences indicates that oscillatory brain activity coordinates functional brain networks for visual perception.⁶⁶ These findings are consistent with a growing body of literature indicating that manipulation of oscillations in neuronal networks alters perception and behavior in multiple systems: low-frequency tACS applied to the frontotemporal region enhances slow-wave oscillations during sleep and memory consolidation;⁶⁷ in-phase tACS θ stimulation of left prefrontal and parietal cortices enhances, whereas out-of-phase stimulation diminishes, performance on a visual memory-matching reaction-time task;⁶⁸ TMS stimulation of parietal cortex alters spatial tactile perception;^{69–71} and, tACS applied to the motor cortex alters oscillatory frequency and changes the speed and accuracy of motor activity^{66,72,73}

Findings regarding the effects of oscillatory modulation on perceptual, memory, and motor systems are likely to generalize beyond application of neuromodulation techniques to a variety of other processes that involve regulation of brain function. In the context of task performance, data suggest that an individual's selective attention, expectancy, and planning to achieve a goal modulates oscillatory synchrony in brain networks, and this in turn mediates top-down neuroplastic processes.⁵⁹ These experimental findings in humans also are consistent with a large body of experimental literature from *in vitro* and animal models showing that neuroelectric information is transmitted in a bidirectional manner, such that top-down and bottom-up factors are not readily separable.^{44,60,74} The firing of individual neurons summates and contributes to rhythmic oscillations, and the electrical field generated by oscillations of ensembles of cells influences individual neuronal activity through local field potentials and ephaptic coupling.^{57,74,75} There is an endogenous resonant frequency in neuronal circuits, with neurons responding selectively to inputs at preferred frequencies.⁷⁶ The timing of neuronal firing input in relation to the resonant frequency of a neural circuit helps determine whether the input will strengthen the synapse (e.g., long-term potentiation (LTP)) or weaken the synapse (e.g., long-term depression (LTD)).⁷⁷ This phenomenon of spike timing-dependent plasticity (STDP)⁷⁸ indicates that neuroelectric regulation is an important complement to neurochemical regulation of neuroplasticity.⁷⁷

Top-down and bottom-up effects of oscillatory modulation in depression

It is challenging to fully elucidate the role of the rate and pattern of neuronal firing and oscillatory synchrony in the phenotype of depression and the MOA of antidepressant treatments: neither the brain systems regulating mood nor the MOA of treatment are well understood. One pathogenic theory of depression is based on the network hypothesis, which suggests that MDD arises from defects in modulating activity-dependent neuronal communication.⁷⁹ This is consistent with evidence from animal models, indicating that oscillatory synchrony may be linked both to depressive behaviors and their resolution through the rate and pattern of neuronal firing in deep-brain gray matter structures. Altering the rate and pattern of firing of dopaminergic neurons in the ventral tegmental area (VTA) can either induce susceptibility or increase resilience to social stress-induced behaviors in rodent models of depression.⁸⁰ Activation of phasic firing in VTA neurons projecting to the

nucleus accumbens (NAc) induces susceptibility to depressive behaviors; induction of phasic firing in VTA neurons projecting to the medial PFC (mPFC) does not have this effect. Furthermore, inhibition of the VTA–NAc projection induces resilience, whereas inhibition of the VTA–mPFC projection promotes susceptibility to depressive behavior.⁸⁰ Further work demonstrates that inhibition or excitation of specified mid-brain dopamine neurons can either accentuate or attenuate multiple independent depressive behaviors caused by chronic stress, suggesting that processes affecting depressive symptoms may involve alterations in neuroelectric information transfer in limbic circuitry.⁸¹ Importantly, in mice expressing a marked depressive phenotype in a social defeat paradigm, stimulation of phasic mPFC firing also exerted potent antidepressant-like effects.⁸²

Studies suggest that patients with MDD have a diminished ability to adaptively modulate brain network activity, with greatly increased oscillatory synchrony on qEEG in the resting state,⁸³ as well as diminished modulation of network function during task performance as measured by blood flow on functional magnetic resonance imaging (fMRI) or qEEG.^{84–87} The marked increase in oscillatory synchrony seen in patients with MDD may help explain the aberrant increases in thalamocortical and corticocortical connectivity seen in these patients.^{88,89} Abnormal oscillatory modulation has been implicated in the genesis of MDD through the mechanism of thalamocortical dysrhythmia (TCD), which complements neurotransmitter-based models of pathogenesis.^{90–93} TCD is characterized by persistent, highly resonant oscillatory activity in thalamocortical loops (thalamocortical oscillations) primarily within the high δ (2.5–4 Hz) and θ (4–8 Hz) frequency band as assessed with qEEG and magnetoencephalography^{90–92,94} Like the dopaminergic cells projecting from the VTA, pacemaker cells in thalamocortical circuits have distinct firing modes:⁹⁴ in TCD, pacemaker cells fire in lower-frequency bursting mode, which is associated with increased slow-wave oscillatory activity and defective modulation of cortical rhythms; when these cells shift to higher-frequency burst firing, normal dynamics of oscillatory modulation are restored.^{90–92}

Oscillatory modulation and the MOA of antidepressant treatments

A role for top-down control of oscillatory synchrony in neuroplasticity is consistent with the effects of rTMS as a treatment modality for MDD. Repetitive TMS creates a weak, local electrical current in the cortical area underlying the stimulating magnet through magnetic induction. Although the MOA of rTMS remains incompletely understood, the most immediate effect of high-frequency rTMS stimulation (>5 Hz) on brain function is synchronization (entrainment) of the oscillations of brain tissue to the frequency of the stimulating magnet directly overlying this cortical area.^{95–99} This oscillatory entrainment is not sustained: once stimulation has ceased, rTMS enhances emergence of the natural, intrinsic rhythms of underlying cortex, which, in the PFC, represent high-frequency (β or 12–20 Hz; and γ or 20–80 Hz) activity^{95,96,100} These oscillatory changes in stimulated cortex may contribute to enhanced plasticity in stimulated cortex,¹⁰ as well as the rapid spread of functional changes through network activity to multiple limbic structures,¹⁰¹ consistent with the mechanism of STDP.⁷⁸

Repetitive TMS has been hypothesized to achieve therapeutic benefit in MDD through manipulating oscillatory synchrony to reduce abnormal low-frequency resonance in thalamocortical loops.^{10,101} Repeated entrainment of corticothalamic oscillations to the frequency of stimulation, and the follow-on facilitated reemergence of normal β and γ endogenous rhythms, has been hypothesized to “reset” oscillatory circuits and brain network function and the processes that regulate normal mood.^{10,99,101} TCD has been implicated not only in MDD, but also in related neuropsychiatric illnesses, including obsessive–compulsive disorder (OCD), Parkinson’s disease (PD), and central pain syndromes—sharing the common characteristic that treatments that disrupt persistent resonance within thalamocortical feedback loops can ameliorate symptoms. These treatments include: for central pain syndromes, neurosurgical lesions in thalamic nuclei;^{102,103} for tinnitus, rTMS¹⁰⁴ or direct cortical stimulation;¹⁰⁵ and, for OCD, MDD, and PD, administration of DBS.^{91,106}

Resolution of TCD also may be related to the MOA of antidepressant medications. A variety of neurochemical and ionic mechanisms govern both the firing pattern of individual neurons and resonant oscillatory frequency of neuronal circuits.^{76,107} Medications may alter the pattern of firing of pacemaker cells (i.e., burst firing mode) and the resonant frequency of neural circuits through both indirect (i.e., increasing extracellular monoamine and glutamate levels)^{93,94,108,109} and direct effects (e.g., pharmacologic inhibition of T-type calcium channels).^{110,111} The activation level of voltage-gated T-type calcium channels is a key molecular determinant of the firing rate and pattern of thalamic pacemaker cells¹¹² and, in addition to their neurochemical effects, many antidepressant and antipsychotic medications (including ketamine) bind to and modulate the activity of these channels at concentrations similar to those used for pharmacotherapy^{110,111,113–115} T-type calcium channels have been reported to play a key role in mediating synaptic plasticity in the cortex,¹¹⁶ in the reticular nucleus of the thalamus¹¹⁷ and thalamocortical circuits,^{118,119} in spinal projection neurons,¹²⁰ in the cerebellar system,¹²¹ and in hippocampal systems involved in learning.¹²²

Although the modulation of tonic and phasic firing patterns of VTA neurons has been explored in animal models of depression,^{80,82,123} the firing patterns of cells in thalamocortical circuits have not been extensively studied in these models. It is known, however, that the shift in firing modes in thalamocortical neurons has pronounced effects on excitability in brain networks,¹²⁴ levels of arousal and behavior,¹²⁵ and sensory processing.¹²⁶ Although the role of modulation of thalamocortical cell firing patterns in the MOA of antidepressants remains speculative, this possible mechanism for ameliorating symptoms of depression merits further investigation.¹¹⁰

Toward an integrated theory of neurochemical and neuroelectric antidepressant MOA

The syndrome of MDD is complex and pleomorphic and may, in fact, consist of syndromes with similar phenotypes that arise from physiologic dysfunction at different levels of biological complexity. In a parallel manner, treatments for MDD exert a range of effects at multiple physiologic levels. We have focused here on neurochemical, neuroelectric, and neuroplastic effects, but this is not an exhaustive list of possible MOA. Treatments could, in

fact, act at any level along the translational spectrum from genome to illness phenotype, with significant interactions among regulatory processes along this spectrum. We suggest that antidepressant treatments such as rTMS may modulate oscillatory synchrony and, in a top-down fashion, act at the level of large-scale networks to influence neuronal firing rates and patterns, and eventually downstream cellular processes. Conversely, medications would appear to act in a bottom-up fashion, first to induce changes at the level of cell-to-cell communication followed by changes in neuronal firing rates and patterns, and eventually modulation of oscillatory synchrony and network activity (Fig. 3). Modulation of oscillatory synchrony appears to be a central component of both top-down and bottom-up processes, reflecting the influence of chemical neurotransmission, electrical synapses, genetic polymorphisms, and environmental influences, among other factors.

Future research should aim to elucidate how these multiple possible neurochemical and neuroelectric MOA interact to effect recovery from MDD. There are several possible mechanisms by which synaptic neurotransmission might affect oscillatory network properties, and vice versa. It is tempting to speculate that this may occur via changes in ion channel expression or activity. Monoamines have been shown to regulate potassium and calcium channel activity, and it is conceivable that aminergic antidepressants indirectly regulate neuronal excitability in this way.^{127–129} Antidepressant drugs may also modulate oscillatory synchrony and induce neuroplasticity at the cellular level through more direct effects on voltage-gated ion channels. The current that occurs in the extracellular space between neuronal processes is also mediated by voltage- and ligand-gated ion channels, and is the primary determinant of the intrinsic resonance and oscillation of the membrane potentials that account for EEG.⁵⁷ Neurochemically mediated synaptic transmission is the major source of excitatory signaling in the brain, but gap junction-mediated electrical synapses are the major source of connection between neurons that subserve neural synchronization and form oscillatory networks.^{74,130} Modulation of the activity of these ion channels may similarly contribute to the activities of antidepressant therapies^{110,113,114} and simultaneously effect both synaptic function and network rhythmicity. Interestingly, expression of genes encoding for T-type calcium channels is increased by ECT in an animal model,¹³¹ consistent with a role for expression of these channels in neuroplasticity induced by neuromodulation treatments, but changes in expression of these genes have not yet been reported with rTMS or other neuromodulation treatments.

The molecular mechanisms that link spontaneous oscillations to neuroplastic changes during learning and development may also be relevant to the MOA of antidepressant treatment. The initiation of NMDA-dependent LTP in the hippocampus is regulated by θ and α frequency oscillations (4–12 Hz). One mechanism that allows these rhythms to be transduced to glutamatergic synapses involves regulated changes in the activity of GABAergic interneurons.¹³² The oscillations induced by rTMS can potentiate either glutamatergic or GABAergic signaling, depending on their frequency. It is possible that further study will elucidate how different patterns, frequencies, and routes of administration of neuromodulatory treatment will influence neuroplasticity at cellular and molecular levels. Although the role of oscillations in MOA remains speculative, modulation of oscillatory synchrony represents a useful construct to link the various levels at which antidepressant therapies exert their effects, bridging the molecular and cellular levels to that of whole-brain

networks. A greater understanding of the mechanism through which synchronized oscillations may contribute to neuroplastic changes may provide important insight for understanding how multiple MOA may interact to affect clinical outcomes.

Conclusion

There is a range of effective antidepressant treatments that appear to work through disparate mechanisms to achieve a common goal, namely relief of depressive symptoms. The theory that restoration of plasticity in brain networks is a common pathway for disparate antidepressant treatments is speculative,^{3,4,16,28,29,33,34,133} but is consistent with a range of findings on impaired network function and neuroplasticity in MDD, as well the known effects of antidepressant treatments.^{134,135} Adaptive flexibility is an essential feature of normal brain network function, and impairments with respect to flexibility in oscillatory control may result in different phenotypes of neuropsychiatric illnesses,¹³⁶ including MDD.⁷⁹

Rates and patterns of neuronal firing and resultant oscillatory synchrony constitute a continuum of neuroelectric activity that may play a central role in the emergence of depressive phenotypes, as well as in the transfer of information bridging the level of brain networks with cellular processes. Evidence indicates that antidepressant therapies induce plastic changes in the brain at the levels of the individual neuron, cell-to-cell connections, and oscillatory synchrony in brain networks. All of these forms of enhanced flexibility and plasticity in the brain help to restore normal modulation of the mechanisms that regulate mood, cognitive function, and autonomic regulation.^{10,133,135} The framework proposed here may help integrate these neuroplastic processes across multiple levels of physiologic regulation, ranging from the processes regulating gene expression to oscillations in large-scale brain networks. Future studies that bridge the gap between neuroplasticity on a cellular level and the level of brain networks may not only elucidate the MOA of antidepressant treatments, but also may serve as a guide for the development of new and more effective treatment interventions for MDD.

Acknowledgments

The authors thank Ms. Nikita Vince-Cruz and Ms. Jennifer Villalobos for expert assistance in preparation of the manuscript and figures, and Mr. Brian Kobayashi for his assistance with the figures.

Conflicts of interest

Andrew F. Leuchter, M.D., has received research support from the National Institutes of Health (NIH), Wyeth Pharmaceuticals, Novartis Pharmaceuticals, Seaside Therapeutics, Genentech, Shire Pharmaceuticals, Neuronetics, Eli Lilly and Company, and NeuroSigma; served as a consultant to NeoSync, Inc., Brain Cells, Inc., Taisho Pharmaceuticals, Eli Lilly and Company, and Aspect Medical Systems/Covidien; is Chief Scientific Officer of Brain Biomarker Analytics LLC (BBA); owns stock options in NeoSync, Inc.; and has equity interest in BBA.

Ian A. Cook, M.D., received grant support from Aspect Medical Systems/Covidien, Cyberonics, Eli Lilly and Company, High Q Foundation, John E. Fetzer Foundation, John A. Hartford Foundation, MedAvante, Merck, Brain and Behavior Research Foundation (formerly NARSAD), NIH, NeoSync, Neuronetics, Novartis, Pfizer, Sepracor/Sunovion, Seaside Therapeutics, and the West Coast College of Biological Psychiatry; served as an advisor or consultant to Allergan, Ascend Media, Bristol-Myers Squibb, Cyberonics, Eli Lilly and Company, Forest Laboratories, Janssen, Neuronetics, NeuroSigma, Pfizer, Scale Venture Partners, the U.S. Departments of Defense and Justice, Interventions Committee for Adult Disorders (ITVA) Study Section of the NIH, and a Data Safety Committee for the U.S. Department of Veterans Affairs; has spoken on behalf of Bristol-Myers Squibb, CME LLC,

Eli Lilly and Company, Medical Education Speakers Network, Pfizer, Neuronetics, NeuroSigma, and Wyeth; has active biomedical device patents, which are assigned to the University of California; and has been granted stock options in NeuroSigma, the licensee of some of his inventions.

References

1. Duman RS. Pathophysiology of depression and innovative treatments: remodeling glutamatergic synaptic connections. *Dialogues Clin. Neurosci.* 2014; 16:11–27. [PubMed: 24733968]
2. Duman RS, Aghajanian GK. Synaptic dysfunction in depression: potential therapeutic targets. *Science.* 2012; 338:68–72. [PubMed: 23042884]
3. Krishnan V, Nestler EJ. Linking molecules to mood: new insight into the biology of depression. *Am. J. Psychiatry.* 2010; 167:1305–1320. [PubMed: 20843874]
4. Tardito D, Perez J, Tiraboschi E, et al. Signaling pathways regulating gene expression, neuroplasticity, and neurotrophic mechanisms in the action of antidepressants: a critical overview. *Pharmacol. Rev.* 2006; 58:115–134. [PubMed: 16507885]
5. Tanti A, Belzung C. Open questions in current models of antidepressant action. *Br. J. Pharmacol.* 2010; 159:1187–1200. [PubMed: 20132212]
6. Chowdhury GM, Behar KL, Cho W, et al. ¹H-¹³C-nuclear magnetic resonance spectroscopy measures of ketamine's effect on amino acid neurotransmitter metabolism. *Biol. Psychiatry.* 2012; 71:1022–1025. [PubMed: 22169441]
7. Autry AE, Adachi M, Nosyreva E, et al. NMDA receptor blockade at rest triggers rapid behavioral antidepressant responses. *Nature.* 2011; 475:91–95. [PubMed: 21677641]
8. Fröhlich F. Endogenous and exogenous electric fields as modifiers of brain activity: rational design of noninvasive brain stimulation with transcranial alternating current stimulation. *Dialogues Clin. Neurosci.* 2014; 16:93–102. [PubMed: 24733974]
9. Cook IA, Espinoza R, Leuchter AF. Neuromodulation for depression: invasive and noninvasive (deep brain stimulation, transcranial magnetic stimulation, trigeminal nerve stimulation). *Neurosurg. Clin. N. Am.* 2014; 25:103–116. [PubMed: 24262903]
10. Leuchter AF, Cook IA, Jin Y, et al. The relationship between brain oscillatory activity and therapeutic effectiveness of transcranial magnetic stimulation in the treatment of major depressive disorder. *Front. Human Neurosci.* 2013; 7:1–12.
11. Brunoni AR, Teng CT, Correa C, et al. Neuromodulation approaches for the treatment of major depression: challenges and recommendations from a working group meeting. *Arq. Neuropsiquiatr.* 2010; 68:433–451. [PubMed: 20602051]
12. George MS, Taylor JJ, Short EB. The expanding evidence base for rTMS treatment of depression. *Curr. Opin. Psychiatry.* 2013; 26:13–18. [PubMed: 23154644]
13. Radhu N, Ravindran LN, Levinson AJ, et al. Inhibition of the cortex using transcranial magnetic stimulation in psychiatric populations: current and future directions. *J. Psychiatry Neurosci.* 2012; 37:369–378. [PubMed: 22663947]
14. Li X, Nahas Z, Kozel FA, et al. Acute left prefrontal transcranial magnetic stimulation in depressed patients is associated with immediately increased activity in prefrontal cortical as well as subcortical regions. *Biol. Psychiatry.* 2004; 55:882–890. [PubMed: 15110731]
15. Sanacora G, Treccani G, Popoli M. Towards a glutamate hypothesis of depression: an emerging frontier of neuropsychopharmacology for mood disorders. *Neuropharmacology.* 2012; 62:63–77. [PubMed: 21827775]
16. Racagni G, Popoli M. Cellular and molecular mechanisms in the long-term action of antidepressants. *Dialogues Clin. Neurosci.* 2008; 10:385–400. [PubMed: 19170396]
17. Stuchlik A. Dynamic learning and memory, synaptic plasticity and neurogenesis: an update. *Front. Behav. Neurosci.* 2008; 8:106. [PubMed: 24744707]
18. Huganir RL, Nicoll RA. AMPARs and synaptic plasticity: the last 25 years. *Neuron.* 2013; 80:704–717. [PubMed: 24183021]
19. Malenka RC. Synaptic plasticity and AMPA receptor trafficking. *Ann. N.Y. Acad. Sci.* 2003; 1003:1–11. [PubMed: 14684431]

20. Holtmaat A, Svoboda K. Experience-dependent structural synaptic plasticity in the mammalian brain. *Nat. Rev. Neurosci.* 2009; 10:759.
21. Kida S, Serita T. Functional roles of CREB as a positive regulator in the formation and enhancement of memory. *Brain Res. Bull.* 2014; 105:17–24. [PubMed: 24811207]
22. Alberini CM. Transcription factors in long-term memory and synaptic plasticity. *Physiol. Rev.* 2009; 89:121–145. [PubMed: 19126756]
23. Rogerson T, Cai DJ, Frank A, et al. Synaptic tagging during memory allocation. *Nat. Rev. Neurosci.* 2014; 15:157–169. [PubMed: 24496410]
24. Ch'ng TH, Martin KC. Synapse-to-nucleus signaling. *Curr. Opin. Neurobiol.* 2011; 21:345–352. [PubMed: 21349698]
25. Aimone JB, Li Y, Lee SW, et al. Regulation and function of adult neurogenesis: from genes to cognition. *Physiol. Rev.* 2014; 94:911–1026.
26. Jiang Y, Langlet B, Lubin FD, et al. Epigenetics in the nervous system. *J. Neurosci.* 2008; 28:11753–11759. [PubMed: 19005036]
27. Chen LY, Rex CS, Sanaiha Y, et al. Learning induces neurotrophin signaling at the hippocampal synapses. *Proc. Natl. Acad. Sci. USA.* 2010; 107:7030–7035. [PubMed: 20356829]
28. Russo-Neustadt AA, Beard RC, Huang YM, et al. Physical activity and antidepressant treatment potentiate the expression of specific brain derived neurotrophic factor transcripts in the rat hippocampus. *NeuroScience.* 2000; 101:305–312. [PubMed: 11074154]
29. Nibuya M, Morinobu S, Duman RS. Regulation of BDNF and trkB mRNA in rat brain by chronic electroconvulsive seizure and antidepressant drug treatments. *J. Neurosci.* 1995; 15:7539–7547. [PubMed: 7472505]
30. Dall'Agnol L, Medeiros LF, Torres IL, et al. Repetitive transcranial magnetic stimulation increases the corticospinal inhibition and the brain-derived neurotrophic factor in chronic myofascial pain syndrome: an explanatory double-blinded, randomized, sham-controlled trial. *J. Pain.* 2014; 15:845–855. [PubMed: 24865417]
31. Esslinger C, Schöler N, Sauer C, et al. Induction and quantification of prefrontal cortical network plasticity using 5 Hz rTMS and fMRI. *Hum. Brain Mapp.* 2014; 35:140–151. [PubMed: 22965696]
32. Morellini N, Grehl S, Tang A, et al. What does low-intensity rTMS do to the cerebellum? *Cerebellum.* 2014; 14:23–26. [PubMed: 25346177]
33. Shirayama Y, Chen AC, Nakagawa S, et al. Brain-derived neurotrophic factor produces antidepressant effects in behavioral models of depression. *J. Neurosci.* 2002; 22:3251–3261. [PubMed: 11943826]
34. Siuciak JA, Lewis DR, Wiegand SJ, et al. Antidepressant-like effect of brain-derived neurotrophic factor (BDNF). *Pharmacol. Biochem. Behav.* 1997; 56:131–137. [PubMed: 8981620]
35. Baudry A, Mouillet-Richard AS, Launay JM, et al. New views on antidepressant action. *Curr. Opin. Neurobiol.* 2011; 21:858–865. [PubMed: 21530233]
36. Castrén E, Vöikar V, Rantamäki T. Role of neurotrophic factors in depression. *Curr. Opin. Pharmacol.* 2007; 7:18–21. [PubMed: 17049922]
37. Huang GJ, Ben-David E, Tort Piella A, et al. Neurogenomic evidence for a shared mechanism of the antidepressant effects of exercise and chronic fluoxetine in mice. *PLoS One.* 2012; 7:e35901. [PubMed: 22558262]
38. Levy-Gigi E, Szabó C, Kelemen O, et al. Association among clinical response, hippocampal volume, and FKBP5 gene expression in individuals with posttraumatic stress disorder receiving cognitive behavioral therapy. *Biol. Psychiatry.* 2013; 74:793–800. [PubMed: 23856297]
39. Jacob E, Tadler SC, Light KC, et al. Leukocyte gene expression in patients with medication refractory depression before and after treatment with ECT or isoflurane anesthesia: a pilot study. *Depress. Res. Treat.* 2014; 2014:1–12.
40. Lesch KP. When the serotonin transporter gene meets adversity: the contribution of animal models to understanding epigenetic mechanisms in affective disorders and resilience. *Curr. Top. Behav. Neurosci.* 2011; 7:251–280. [PubMed: 21225411]
41. Colwell CS. Linking neural activity and molecular oscillations in the SCN. *Nat. Rev. Neurosci.* 2011; 12:553–569. [PubMed: 21886186]

42. Leuchter AF, Hunter AM, Krantz DE, et al. Intermediate phenotypes and biomarkers of treatment outcome in major depressive disorder. *Dialogues Clin. Neurosci.* 2014; 16:525–537. [PubMed: 25733956]
43. Xu X, An L, Mi X, et al. Impairment of cognitive function and synaptic plasticity associated with alteration of information flow in theta and gamma oscillations in melamine-treated rats. *PLoS One.* 2013; 8:e77796. [PubMed: 24204970]
44. Buzsáki G, Draguhn A. Neuronal oscillations in cortical networks. *Science.* 2004; 304:1926–1929. [PubMed: 15218136]
45. Soltész F, Suckling J, Lawrence P, et al. Identification of BDNF sensitive electrophysiological markers of synaptic activity and their structural correlates in healthy subjects using a genetic approach utilizing the functional BDNF Val66Met polymorphism. *PLoS One.* 2014; 9:e95558. [PubMed: 24760076]
46. Bissiere S, Zelikowsky M, Ponnusamy R, et al. Electrical synapses control hippocampal contributions to fear learning and memory. *Science.* 2011; 331:87–91. [PubMed: 21212357]
47. Frederick A, Bourget-Murray J, Chapman CA, et al. Diurnal influences on electrophysiological oscillations and coupling in the dorsal striatum and cerebellar cortex of the anesthetized rat. *Front. Syst. Neurosci.* 2014; 8:145. [PubMed: 25309348]
48. Salomon RM, Cowan RL. Oscillatory serotonin function in depression. *Synapse.* 2013; 67:801–820. [PubMed: 23592367]
49. Bares M, Novak T, Kopecek M, et al. The effectiveness of prefrontal theta cordance and early reduction of depressive symptoms in the prediction of antidepressant treatment outcome in patients with resistant depression: analysis of naturalistic data. *Eur. Arch. Psychiatry Clin. Neurosci.* 2014; 265:73–82. [PubMed: 24848366]
50. Broadway JM, Holtzheimer PE, Hilimire MR, et al. Frontal theta cordance predicts 6-month antidepressant response to subcallosal cingulate deep brain stimulation for treatment-resistant depression: a pilot study. *Neuropsychopharmacology.* 2012; 37:1764–1772. [PubMed: 22414813]
51. Horacek J, Brunovsky M, Novak T, et al. Sub-anesthetic dose of ketamine decreases prefrontal theta cordance in healthy volunteers: implications for antidepressant effect. *Psychol. Med.* 2010; 40:1443–1451. [PubMed: 19995475]
52. Leuchter AF, Cook IA, Hamilton SP, et al. Biomarkers to predict antidepressant response. *Curr. Psychiatry Rep.* 2010; 12:553–562. [PubMed: 20963521]
53. Bares M, Brunovsky M, Kopecek M, et al. Changes in QEEG prefrontal cordance as a predictor of response to antidepressants in patients with treatment resistant depressive disorder: a pilot study. *J. Psychiatr. Res.* 2007; 41:319–325. [PubMed: 16889798]
54. Bares M, Brunovsky M, Kopecek M, et al. Early reduction in prefrontal theta QEEG cordance value predicts response to venlafaxine treatment in patients with resistant depressive disorder. *Eur. Psychiatry.* 2008; 23:350–355. [PubMed: 18450430]
55. Kopecek M, Bares M, Horacek J, et al. Low-dose risperidone augmentation of antidepressants or anxiolytics is associated with hyperprolactinemia. *Neuro. Endocrinol. Lett.* 2006; 27:803–806. [PubMed: 17187006]
56. Cook IA, Leuchter AF, Morgan M, et al. Early changes in prefrontal activity characterize clinical responders to antidepressants. *Neuropsychopharmacology.* 2002; 27:120–131. [PubMed: 12062912]
57. Buzsáki G, Anastassiou CA, Koch C. The origin of extracellular fields and currents—EEG, ECoG, LFP and spikes. *Nat. Rev. Neurosci.* 2012; 13:407–420. [PubMed: 22595786]
58. Fries P. A mechanism for cognitive dynamics: neuronal communication through neuronal coherence. *Trends Cogn. Sci.* 2005; 9:474–480. [PubMed: 16150631]
59. Engel AK, Fries P, Singer W. Dynamic predictions: oscillations and synchrony in top-down processing. *Nat. Rev. Neurosci.* 2001; 2:704–716. [PubMed: 11584308]
60. Varela F, Lachaux JP, Rodriguez E, et al. The brain-web: phase synchronization and large-scale integration. *Nat. Rev. Neurosci.* 2001; 2:229–239. [PubMed: 11283746]
61. Cain SM, Snutch TP. T-type calcium channels in burst-firing, network synchrony, and epilepsy. *Biochim. Biophys. Acta.* 2013; 1828:1572–1578. [PubMed: 22885138]

62. Guenther T, Schönknecht P, Becker G, et al. Impact of EEG-vigilance on brain glucose uptake measured with [(18)F]FDG and PET in patients with depressive episode or mild cognitive impairment. *Neuroimage*. 2011; 56:93–101. [PubMed: 21276863]
63. Feige B, Scheffler K, Esposito F, et al. Cortical and subcortical correlates of electroencephalographic alpha rhythm modulation. *J. Neurophysiol*. 2005; 93:2864–2872. [PubMed: 15601739]
64. Kubota Y, Sato W, Toichi M, et al. Frontal midline theta rhythm is correlated with cardiac autonomic activities during the performance of an attention demanding meditation procedure. *Brain Res. Cogn. Brain Res*. 2001; 11:281–287. [PubMed: 11275489]
65. Helfrich RF, Knepper H, Nolte G, et al. Selective modulation of interhemispheric function connectivity by HD-tACS shapes perception. *PLoS Biol*. 2014; 12:e1002031. [PubMed: 25549264]
66. Thut G. Modulating brain oscillations to drive brain function. *PLoS Biol*. 2014; 12:e1002032. [PubMed: 25549340]
67. Marshall L, Helgadottir H, Molle M, et al. Boosting slow oscillations during sleep potentiates memory. *Nature*. 444:610–613. [PubMed: 17086200]
68. Polania R, Nitschke MA, Korman C. The importance of timing in segregated theta phase-coupling for cognitive performance. *Curr. Biol*. 2012; 22:1314–1318. [PubMed: 22683259]
69. Ruzzoli M, Soto-Faraco S. Alpha stimulation of the human parietal cortex attunes tactile perception to external space. *Curr. Biol*. 2014; 24:329–332. [PubMed: 24440394]
70. Thut G, Veniero D, Romei V, et al. Rhythmic TMS causes local entrainment of natural oscillatory signatures. *Curr. Biol*. 2011; 21:1176–1185. [PubMed: 21723129]
71. Romei V, Gross J, Thut G. On the role of prestimulus alpha rhythms over occipito-parietal areas in visual input regulation: correlation or causation? *J. Neurosci*. 2010; 30:8692–8697. [PubMed: 20573914]
72. Pogosyan A, Gaynor AD, Eusebio A, et al. Boosting cortical activity at beta-band frequencies slows movement in humans. *Curr. Biol*. 2009; 19:1637–1641. [PubMed: 19800236]
73. Joundi RA, Jenkinson N, Brittain JS, et al. Driving oscillatory activity in the human cortex enhances motor performance. *Curr. Biol*. 2012; 22:403–407. [PubMed: 22305755]
74. Wang XJ. Neurophysiological and computational principles of cortical rhythms in cognition. *Physiol. Rev*. 2010; 90:1195–1268. [PubMed: 20664082]
75. Anastassiou CA, Perin R, Markram H, et al. Ephaptic coupling of cortical neurons. *Nat. Neurosci*. 2011; 14:217–223. [PubMed: 21240273]
76. Hutcheon B, Yarom Y. Resonance, oscillation and the intrinsic frequency preference of neurons. *Trends Neurosci*. 2000; 23:216–222. [PubMed: 10782127]
77. Zaehle T, Rach S, Herrmann CS. Transcranial alternating current stimulation enhances individual alpha activity in human EEG. *PLoS One*. 2010; 5:e13766. [PubMed: 21072168]
78. Markram H, Lübke J, Frotscher M, et al. Regulation of synaptic efficacy by coincidence of postsynaptic APs and EPSPs. *Science*. 1997; 275:213–215. [PubMed: 8985014]
79. Castrén E. Is mood chemistry? *Nat. Rev. Neurosci*. 2005; 6:241–246. [PubMed: 15738959]
80. Chaudhury D, Walsh JJ, Friedman AK, et al. Rapid regulation of depression-related behaviors by control of midbrain dopamine neurons. *Nature*. 2013; 493:532–536. [PubMed: 23235832]
81. Tye KM, Mirzabekov JJ, Warden MR, et al. Dopamine neurons modulate neural encoding and expression of depression-related behavior. *Nature*. 2013; 493:537–541. [PubMed: 23235822]
82. Covington HE, Lobo MK, Maze I, et al. Antidepressant effect of optogenetic stimulation of the medial prefrontal cortex. *J. Neurosci*. 2005; 30:16082–16090. [PubMed: 21123555]
83. Leuchter AF, Cook IA, Hunter AM, et al. Resting-state quantitative electroencephalography reveals increased neurophysiologic connectivity in depression. *PLoS One*. 2012; 7:1.
84. Delvecchio G, Fossati P, Boyer P, et al. Common and distinct neural correlates of emotional processing in bipolar disorder and major depressive disorder: a voxel-based meta-analysis of functional magnetic resonance imaging studies. *Eur. Neuropsychopharmacol*. 2012; 22:100–113. [PubMed: 21820878]

85. Manna CB, Tenke CE, Gates NA, et al. EEG hemispheric asymmetries during cognitive tasks in depressed patients with high versus low trait anxiety. *Clin. EEG Neurosci.* 2010; 41:196–202. [PubMed: 21077571]
86. Segrave RA, Thomson RH, Cooper NR, et al. Upper alpha activity during working memory processing reflects abnormal inhibition in major depression. *J. Affect. Disord.* 2010; 127:191–198. [PubMed: 20579742]
87. Henriques JB, Davidson RJ. Brain electrical asymmetries during cognitive task performance in depressed and nondepressed subjects. *Biol. Psychiatry.* 1997; 42:1039–1050. [PubMed: 9386856]
88. Sheline YI, Price JL, Yan Z, et al. Resting-state functional MRI in depression unmasks increased connectivity between networks via the dorsal nexus. *Proc. Natl. Acad. Sci. USA.* 2010; 107:11020–11025. [PubMed: 20534464]
89. Greicius MD, Flores BH, Menon V, et al. Resting-state functional connectivity in major depression: abnormally increased contributions from subgenual cingulate cortex and thalamus. *Biol. Psychiatry.* 2007; 62:429–437. [PubMed: 17210143]
90. Llinás RR, Ribary U, Jeanmonod D, et al. Thalamo-cortical dysrhythmia: a neurological and neuropsychiatric syndrome characterized by magnetoencephalography. *Proc. Natl. Acad. Sci. USA.* 1999; 96:15222–15227. [PubMed: 10611366]
91. Llinás R, Urbano FJ, Leznik E, et al. Rhythmic and dysrhythmic thalamocortical dynamics: GABA systems and the edge effect. *Trends Neurosci.* 2005; 28:325–333. [PubMed: 15927689]
92. Schulman JJ, Cancro R, Lowe S, et al. Imaging of thalamocortical dysrhythmia in neuropsychiatry. *Front. Hum. Neurosci.* 2011; 5:1–11. [PubMed: 21283556]
93. Perez-Reyes E, Lory P. Molecular biology of T-type calcium channels. *CNS Neurol. Disord. Drug Targets.* 2006; 5:605–609. [PubMed: 17168745]
94. Hughes SW, Crunelli V. Thalamic mechanisms of EEG alpha rhythms and their pathological implications. *Neuroscientist.* 2005; 11:357–372. [PubMed: 16061522]
95. Johnson JS, Hamidi M, Postle BR. Using EEG to explore how rTMS produces its effects on behavior. *Brain Topogr.* 2010; 22:281–293. [PubMed: 19915972]
96. Hamidi M, Slagter HA, Tononi G, et al. Repetitive transcranial magnetic stimulation affects behavior by biasing endogenous cortical oscillations. *Front. Integr. Neurosci.* 2009; 3:14. [PubMed: 19587850]
97. Brignani D, Manganotti P, Rossini PM, et al. Modulation of cortical oscillatory activity during transcranial magnetic stimulation. *Hum. Brain Mapp.* 2008; 29:603–612. [PubMed: 17557296]
98. Fuggetta G, Pavone EF, Fiaschi A, et al. Acute modulation of cortical oscillatory activities during short trains of high-frequency repetitive transcranial magnetic stimulation of the human motor cortex: a combined EEG and TMS study. *Hum. Brain. Mapp.* 2008; 29:1–13. [PubMed: 17318833]
99. Paus T, Sipila PK, Strafella AP. Synchronization of neuronal activity in the human primary motor cortex by transcranial magnetic stimulation: an EEG study. *J. Neurophysiol.* 2001; 86:1983–1990. [PubMed: 11600655]
100. Rosanova M, Casali A, Bellina V, et al. Natural frequencies of human corticothalamic circuits. *J. Neurosci.* 2009; 29:7679–7685. [PubMed: 19535579]
101. Fuggetta G, Noh A. A neurophysiological insight into the potential link between transcranial magnetic stimulation, thalamocortical dysrhythmia and neuropsychiatric disorders. *Exp. Neurol.* 2012; 248:393–397.
102. Jeanmonod D, Magnin M, Morel A. Low-threshold calcium spike bursts in the human thalamus. Common physiopathology for sensory, motor and limbic positive symptoms. *Brain.* 1996; 119:363–375. [PubMed: 8800933]
103. Jeanmonod D, Sarnthein J, Magnin M, et al. Chronic neurogenic pain: thalamocortical dysrhythmic mechanisms and their surgical treatment. *Thalamus Related Syst.* 2005; 3:6370.
104. De Ridder D, Song JJ, Vanneste S. Frontal cortex rTMS for tinnitus. *Brain Stim.* 2013; 6:355–62.
105. De Ridder D, VanDer Loo E, Vanneste S, et al. Theta-gamma dysrhythmia and auditory phantom perception. *J. Neurosurg.* 2011; 114:912–921. [PubMed: 21235308]

106. Kopell B, Greenberg BD. Anatomy and physiology of the basal ganglia: implications for DBS in psychiatry. *Neurosci. Behav. Rev.* 2008; 32:408–422.
107. Izhikevich EM, Desa NS, Walcott EC, et al. Bursts as a unit of neural information: selective communication via resonance. *Trends Neurosci.* 2003; 26:161–167. [PubMed: 12591219]
108. Varela C, Sherman SM. Differences in response to serotonergic activation between first and higher order thalamic nuclei. *Cereb. Cortex.* 2009; 19:1776–1786. [PubMed: 19029063]
109. Celada P, Puig MV, Artigas F. Serotonin modulation of cortical neurons and networks. *Front Integral Neurosci.* 2013; 7:25.
110. Bianchi MT. Non-serotonin antidepressant actions: direct ion channel modulation by SSRIs and the concept of single agent poly-pharmacy. *Med. Hypoth.* 2008; 70:951–956.
111. Traboulsie A, Chemin J, Kupfer E, et al. T-type calcium channels are inhibited by fluoxetine and its metabolite norfluoxetine. *Mol. Pharm.* 2006; 69:1963–1968.
112. Yunker AM, McEnery MW. Low-voltage-activated (“T-Type”) calcium channels in review. *J. Bioenerg. Biomembr.* 2003; 35:533–575. [PubMed: 15000520]
113. Bianchi MT, Botzolakis EJ. Targeting ligandgated ion channels in neurology and psychiatry: is pharmacological promiscuity an obstacle or an opportunity? *BMC Pharmacol.* 2010; 10:3. [PubMed: 20196850]
114. Rammes G, Rupprecht R. Modulation of ligandgated ion channels by antidepressants and antipsychotics. *Mol. Neurobiol.* 2007; 35:160–174. [PubMed: 17917105]
115. Todorovic SM, Perez-Reyes E, Lingle CJ. Anti-convulsants but not general anesthetics have differential blocking effects on different T-type current variants. *Mol. Pharmacol.* 2000; 58:98–108. [PubMed: 10860931]
116. Uebele VN, Nuss CE, Fox SV, et al. Positive allosteric interaction of structurally diverse T-type calcium channel antagonists. *Cell Biochem. Biophys.* 2009; 55:81–93. [PubMed: 19582593]
117. Astori S, Lüthi A. Synaptic plasticity at intrathalamic connections via CaV3.3 T-type Ca^{2+} channels and GluN2B-containing NMDA receptors. *J. Neurosci.* 2013; 33:624–630. [PubMed: 23303941]
118. Lambert RC, Bessa'ih T, Crunelli V, et al. The many faces of T-type calcium channels. *P flügers Arch.* 2014; 466:415–423.
119. Hsu CL, Yang HW, Yen CT, et al. A requirement of low-threshold calcium spike for induction of spike-timing-dependent plasticity at corticothalamic synapses on relay neurons in the ventrobasal nucleus of rat thalamus. *Chin. J. Physiol.* 2012; 55:380–389. [PubMed: 23286445]
120. Ikeda H, Heinke B, Ruscheweyh R, et al. Synaptic plasticity in spinal lamina I projection neurons that mediate hyperalgesia. *Science.* 2003; 299:1237–1240. [PubMed: 12595694]
121. Ly R, Bouvier G, Schonewille M, et al. T-type channel blockade impairs long-term potentiation at the parallel fiber-Purkinje cell synapse and cerebellar learning. *Proc. Natl. Acad. Sci. USA.* 2013; 110:20302–20307. [PubMed: 24277825]
122. Chen LY, Rex CS, Sanaiha Y, et al. Learning induces neurotrophin signaling at hippocampal synapses. *Proc. Natl. Acad. Sci. USA.* 2012; 107:7030–7035. [PubMed: 20356829]
123. Tye KM, Mirzabekov JJ, Warden MR, et al. Dopamine neurons modulate neural encoding and expression of depression-related behavior. *Nature.* 2013; 493:537–541. [PubMed: 23235822]
124. Dreyfus FM, Tschertter A, Errington AC, et al. Selective T-type calcium channel block in thalamic neurons reveals channel redundancy and physiological impact of I(T)window. *J. Neurosci.* 2008; 30:99–109. [PubMed: 20053892]
125. Crunelli V, Tóth TI, Cope DW, et al. The ‘window’ T-type calcium current in brain dynamics of different behavioral states. *J. Physiol.* 2005; 562(Part 1):121–129. [PubMed: 15498803]
126. Hartings JA, Temereanca S, Simons DJ. State-dependent processing of sensory stimuli by thalamic reticular neurons. *J. Neurosci.* 2003; 23:5264–5271. [PubMed: 12832551]
127. Dragicevic E, Schiemann J, Liss B. Dopamine midbrain neurons in health and Parkinson’s disease: Emerging roles of voltage-gated calcium channels and ATP-sensitive potassium channels. *NeuroScience.* 2015; 284C:798–814. [PubMed: 25450964]
128. Ji X, Martin GE. BK channels mediate dopamine inhibition of firing in a subpopulation of core nucleus accumbens medium spiny neurons. *Brain Res.* 2014; 1588:1–16. [PubMed: 25219484]

129. Yang K, Dani JA. Dopamine D1 and D5 receptors modulate spike timing-dependent plasticity at medial perforant path to dentate granule cell synapses. *J. Neurosci.* 2014; 34:15888–15897. [PubMed: 25429131]
130. Niculescu D, Lohmann C. Gap junctions in developing thalamic and neocortical neuronal networks. *Cereb. Cortex.* 2014; 24:3097–3106. [PubMed: 23843439]
131. Sun W, Park KW, Choe J, et al. Identification of novel electroconvulsive shock-induced and activity-dependent genes in the rat brain. *Biochem. Biophys. Res. Commun.* 2005; 327:848–856. [PubMed: 15649423]
132. Clarke VR, Collingridge GL, Lauri SE, et al. Synaptic kainate receptors in CA1 interneurons gate the threshold of theta-frequency-induced long-term potentiation. *J. Neurosci.* 2012; 32:18215–18226. [PubMed: 23238735]
133. Castrén E. Neuronal network plasticity and recovery from depression. *JAMA Psychiatry.* 2013; 70:983–939. [PubMed: 23842648]
134. Price JL, Drevets WC. Neurocircuitry of mood disorders. *Neuropsychopharmacology.* 2010; 35:192–216. [PubMed: 19693001]
135. Price JL, Drevets WC. Neural circuits underlying the pathophysiology of mood disorders. *Trends Cogn. Sci.* 2012; 16:61–71. [PubMed: 22197477]
136. Ramocki MB, Zoghbi HY. Failure of neuronal homeostasis results in common neuropsychiatric phenotypes. *Nature.* 2008; 455:912–918. [PubMed: 18923513]

Figure 1.

Spectrum of factors that influence expression of the depressive phenotype in MDD. A continuum of factors contributes to the depressive phenotype in MDD, ranging from genetic polymorphisms through function in brain networks. The multiple levels of biological structures, ranging from the genome to brain networks and ultimately culminating in the phenotype(s) of MDD, represent a spectrum of increasing biological complexity (shown in the center of the diagram from bottom left to top right). These structures can be grouped into three general categories of organization: those existing at the level of the single cell, those involving cell-to-cell communication, and those involving ensembles of cells that form circuits and networks. Each of these categories of structural organization is characterized by certain physiologic functions, shown on the right. The three levels of structural and functional organization are not entirely autonomous: the effects of genetic and molecular factors are translated bottom up to influence the clinical phenotype of MDD, whereas the influence of brain functional networks are translated top down to influence cellular communication and intracellular processes. The spectrum of structures and functions presented here are intended to be illustrative of general physiologic principles and are not an

exhaustive list of structural and functional features of interest in MDD. Reproduced from www.brain.ucla.edu. © 2015 UCLA Laboratory of Brain, Behavior, and Pharmacology.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Figure 2.

Central role of rhythmic oscillations in regulating brain processes. Oscillatory synchrony integrates the activity of individual neurons into microcircuits and larger-scale functional networks. Modulation of activity in these networks helps regulate information processing, cerebral blood flow and metabolism, and autonomic functions.

Figure 3.

Hypothesized action of antidepressant treatments at different levels of biological complexity in the brain. Antidepressant treatments act along a continuum of structures and processes ranging from the level of a single cell to ensembles of neurons in brain networks.

Neuromodulatory and medication treatments for MDD are shown graphically in relation to the hypothesized level of action along this continuum. Neuromodulatory treatments (such as rTMS) may modulate oscillations in higher-order brain networks (arrow at top left), whereas medication treatments may affect synaptic neurotransmission or neuroelectric communication at the level of cell-to-cell communication (arrow at middle left). Treatments acting at any level along this continuum may increase neuroplasticity and exert physiologic effects in a bidirectional manner. Treatments acting on intracellular processes or intercellular communication may transmit their effects bottom up to affect brain functional networks, whereas treatments that directly modulate function in brain networks or microcircuits may transmit their effects top down to influence cellular processes or intercellular communication. Evidence indicates that, in addition to synaptic neurotransmission, neuroelectric communication plays a central role in mediating top-down and bottom-up effects across multiple levels of biological complexity in the brain. Modulation of neuronal firing rates and patterns and oscillatory synchrony may represent a

mechanism through which treatment effects are transduced across multiple levels of physiologic action to increase neuroplasticity. We hypothesize that modulation of oscillatory synchrony plays an important role in the MOA of antidepressant treatments. Reproduced from www.brain.ucla.edu. © 2015 UCLA Laboratory of Brain, Behavior, and Pharmacology.