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Leveraging Neuroplasticity to Enhance Adaptive Learning: The Potential for Synergistic Somatic-Behavioral Treatment Combinations to Improve Clinical Outcomes in Depression

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Abstract

Until recently, therapeutic development in psychiatry was targeted solely toward symptom reduction. While this is a worthwhile goal, it has yielded little progress in improved therapeutics in the last several decades in the field of mood disorders. Recent advancements in our understanding of pathophysiology suggests that an impairment of neuroplasticity may be a critical part of the development of neuropsychiatric disorders. Interventions that enhance or modulate neuroplasticity often reduce depressive symptoms when applied as stand-alone treatments. Unfortunately, when treatments are discontinued, the disease state often returns as patients relapse. However, treatments that enhance or modulate plasticity not only reduce symptom burden, but also may provide an opportune window wherein cognitive or behavioral interventions could be introduced to harness a state of enhanced neuroplasticity and lead to improved longer-term clinical outcomes. Here, we review the potential of synergistically combining plasticity-enhancing and behavioral therapies to develop novel translational treatment approaches for depression. After reviewing relevant neuroplasticity deficits in depression, we survey biological treatments that appear to reverse such deficits in humans, including *N*-methyl-D-aspartate receptor modulators (ketamine, D-cycloserine), electroconvulsive therapy, and transcranial brain stimulation. We then review

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evidence that either directly or indirectly supports the hypothesis that a robust enhancement of neuroplasticity through these methods might promote the uptake of cognitive and behavioral interventions to enhance longer-term treatment outcomes through a synergistic effect. We identify key missing pieces of evidence and discuss future directions to enhance this emerging line of research.

Keywords

Depression; Electroconvulsive therapy; Ketamine; Neuromodulation; Neuroplasticity; Transcranial magnetic stimulation

Neuroplasticity, or the brain's capacity to flexibly adjust and reorganize itself in response to a changing environment, is fundamental to promoting adaptive functioning. Impairments of neuroplasticity characterize disorders of negative affect, including depression (1,2). Burgeoning evidence shows that traditional and novel treatments for depression exhibit plasticity-enhancing effects that at least partially underlie corresponding reductions in clinical symptoms observed in patients. While traditional pharmacological and psychotherapy approaches likely enhance neuroplasticity (3,4), novel treatments (5–7) seem to induce both clinical and neuroplastic effects more rapidly. Prominent among these newer approaches are glutamate-modulating agents [e.g., intravenous ketamine (1,2,8)]. In addition, noninvasive brain stimulation interventions (e.g., repetitive transcranial magnetic stimulation [rTMS]) may induce neuroplastic changes (9). One of the oldest and most efficacious treatments for depression, electroconvulsive therapy (ECT), also has potent acute plasticity-enhancing effects (10).

Each of these plasticity-enhancing approaches has the potential to exhibit therapeutic effects as monotherapies. However, clinical effects often dissipate once the intervention is removed (Figure 1A). This presents challenges for maintenance of gains, as long-term treatment may not be beneficial or feasible (11). Pharmacological/somatic therapies are challenging to maintain in the long term owing to patient discontinuation (11) and the rarity of follow-up opportunities in community practice (12). By contrast, findings suggest that gold-standard behavioral treatments such as cognitive behavioral therapy (CBT) can help prevent relapse of depression symptoms even in the absence of ongoing care (11,13–15), suggesting that the introduction of adaptive learning results in the long-term potential to buffer against negative affect. Finally, preclinical evidence suggests that unfavorable environmental factors may worsen mood symptoms in the setting of enhanced neuroplasticity by biological agents (16). Hence, a multimodal treatment approach may make use of this interaction between biological/somatic therapies that enhance neuroplasticity and cognitive behavioral interventions that harness, solidify, and guide this enhanced neuroplasticity, potentially resulting in lower rates of relapse (Figure 1B).

This review summarizes the potential for plasticity-enhancing somatic/biological agents to be leveraged in this multimodal approach, i.e., as short-term enhancers of cognitive flexibility and adaptive learning that may be combined with learning-based approaches to foster long-term relief from depression. After reviewing the role of neuro-plasticity in depression, we survey existing data in support of the notion that the introduction and

facilitation of new learning during somatically induced neuroplasticity “windows of opportunity” might provide an efficient path to enhance or extend symptom relief. We focus on therapies that have preclinical and clinical data supporting their potential to enhance neuroplasticity. We also identify key gaps in this emerging literature and conclude by proposing future research directions within this framework.

NEUROPLASTICITY DEFICITS IN DEPRESSION

At the molecular level, depression has been characterized as a failure of neuroplasticity, including neuronal atrophy and synaptic depression in the prefrontal cortex (PFC) and hippocampus (1,2). Chronic stress contributes to sustained decreases in neuroprotective factors (e.g., brain-derived neurotrophic factor expression and signaling) that damage plasticity, fostering neuronal atrophy and synaptic depression (1,2). This results in deficient adaptation to the environment, compromised learning and stress coping, and downstream gain of activity in some affective processing regions (e.g., amygdala) regulated by the PFC. Conversely, when neuroplasticity is enhanced (e.g., by treatment), synaptic contacts increase, enhancing adaptability by allowing activity-dependent competition to stabilize the neural structures that best represent internal and external conditions (17–19).

In corresponding patterns of human neurocognition, depression and related conditions are associated with impaired cognitive flexibility (20,21) and decreased regulation of stimulus-driven affective processing (22,23). These behavioral deficits are linked to altered functional integration across the PFC and affective circuits (24–27). These alterations are posited to produce the rigid negative biases evident in depressed patients across a wide range of implicit information processing domains [e.g., negative appraisals of self, the environment, and the future (28); preferential attention and memory for negative stimuli (23,29,30)], which in turn maintain and reinforce a state of high negative affect by fostering overestimation of the personal shortcomings, dangers, and misfortunes inherent to the individual’s life (31). Somatic therapies that address neuroplasticity deficits may hold the potential to relax rigid patterns of processing and cognitive inflexibility, facilitating adaptive learning and promoting acquisition of effective emotion regulation skills.

SEARCH STRATEGY

To identify ongoing or completed trials to include in this review, we performed a systematic search in April 2018 of ClinicalTrials.gov. Search terms were (“ketamine” or “ECT” or “electroconvulsive therapy” or “TMS” or “transcranial magnetic stimulation” or “tDCS” or “transcranial direct current stimulation” or “DCS” or “D-cycloserine”) AND (“CBT” or “cognitive therapy” or “cognitive behavioral therapy” or “behavioral activation” or “cognitive training” or “neurocognitive training”). We also included trials if they were found among the references of included studies or relevant reviews in this area. We included studies in which a somatic treatment was used in combination with a behavioral intervention for the treatment of a depressive disorder.

HISTORICAL PRECEDENT IN CONVENTIONAL THERAPIES

While in this review we focus on emerging approaches to biological-behavioral treatment combination, the search for synergy across pharmacological and behavioral modalities has historical precedent. Although conventional (e.g., monoamine-based) oral antidepressants show compelling neuroplasticity-enhancing effects in both animals and humans (18,32), findings regarding synergistic effects in patients are equivocal, with meta-analyses supporting, at best, a modest benefit for combination treatment over either modality alone (33–35). Furthermore, it remains unclear whether any observed effects are truly synergistic; alternatively, the combination could reflect a simple group-level additive pattern whereby distinct (or partially overlapping) subsets of patients benefit from each of the two monotherapies. Burgeoning approaches would therefore benefit from the use of research designs that explicitly tackle this question, seeking to establish a clear synergistic benefit by exploiting rapid-onset biological effects, in the hopes of documenting a more efficient time course of recovery than has been previously possible.

GLUTAMATE-MODULATING AGENTS

Ketamine

Monomodal Neuroplasticity and Clinical Effects.—Ketamine is an *N*-methyl-D-aspartate (NMDA) antagonist used routinely for anesthesia. In randomized controlled trials, subanesthetic doses (0.5 mg/kg given over 40 minutes) of intravenous ketamine exhibit well-replicated, rapid antidepressant effects (i.e., meta-analytic Cohen's $d = 1.4$) (36), even in treatment-resistant depression (37) and bipolar depression(38). Antidepressant effects begin as soon as 2 hours post-infusion and continue far beyond the drug's elimination half-life of 2.5 to 3 hours. However, effects typically dissipate within 7 to 14 days following exposure of a single infusion, demonstrating that when plasticity-enhancing treatments are withdrawn, patients often experience a return of symptoms (Figure 1A). To date, the only strategy shown in replicated datasets to extend ketamine's rapid effects is to give repeated ketamine infusions (39–41). While an increasing number of clinicians now offer longer-term ketamine treatment in an effort to maintain antidepressant effects of the drug (42), there are feasibility and safety concerns for long-term use (43–45), including potential neurocognitive impact, neurotoxicity, and addiction/abuse liability.

The rapid nature of ketamine's effects have been attributed to its ability to rapidly and profoundly reverse neuroplasticity deficits (1,2,8). Ketamine induces neuroplastic changes (increases in spine density, synaptic strengthening) over periods of hours to days following exposure in animals (5,46). As glutamate receptors are ubiquitous throughout the brain, such findings suggest the potential for far-reaching, rapid functional reorganization, as observed in patients (47) and monkeys (48) 24 hours postketamine administration. It was originally believed that these downstream effects were mediated through ketamine's antagonism of NMDA receptors (5); however, recent evidence suggests that mechanisms independent of NMDA receptor antagonism could also mediate these effects (8).

Consistent with a broad effect on cognitive flexibility and plasticity in human patients, there is evidence that a single infusion of ketamine may enhance cognitive abilities or at least

resolve depression-related cognitive impairment in the short term (49–51). Notably, this is in contrast to the detrimental effects of long-term exposure to ketamine on cognition in rodent models (52) and high-frequency (HF) substance abusers (53). Ketamine also exhibits delayed but enhancing effects on synaptic potentiation in humans (6). Furthermore, ketamine induces rapid plasticity in implicit processing patterns relevant in depression (54,55). At the neural network level, neuroimaging investigations in depressed patients have linked ketamine's antidepressant effects to increased activity and connectivity in PFC and striatal/reward circuits (47,56–58). Connectivity decreases within affective and default mode networks have also been observed after ketamine [in magnetoencephalography (59) and in functional magnetic resonance imaging of primates (48)], interpreted as reversal of the maladaptive affective- and default mode network–driven hyperconnectivity that typifies depression (60).

Potential for Synergistic Effects.—Given that synaptic plasticity involving glutamatergic receptors is considered the major molecular substrate of learning and memory in the brain (61,62), ketamine-induced neuroplasticity could open a clinical "window of opportunity" for new, protective learning. A preliminary pilot study supports this notion, suggesting that CBT may sustain the antidepressant effects of ketamine. In a small sample ($N = 16$) of patients with treatment-resistant depression, in those who demonstrated clinical response to ketamine ($n = 8$) and then received 12 sessions of CBT over 10 weeks (open label), 75% maintained their response for 8 weeks following ketamine (63). This compares favorably to historical rates of 29% to 45% retaining ketamine response at 4 weeks in prior studies (40,64). More definitive tests of ketamine's synergistic potential in combination with behavioral treatments are the focus of an ongoing randomized trial as follow-up to this study (NCT03027362) (see Table 1). Another ongoing study (NCT03237286) focuses on automated cognitive training as a potentially efficient, portable, dissemination-friendly, and low-cost behavioral intervention (65–67) using a computer-based paradigm [appetitive conditioning (68)]. The combination of intravenous ketamine followed promptly by active cognitive training is compared with relevant control treatments (saline followed by active training; ketamine followed by sham computer training). Results from these studies, as well as similar multimodal approaches in other affective conditions (69,70), will speak directly to the potential for ketamine to promote adaptive learning when combined with behavioral treatment paradigms.

D-Cycloserine

Monomodal Treatment: Neuroplasticity and Clinical Effects.—D-cycloserine is a glutamate modulating agent that can act as either an NMDA partial agonist at low doses or an NMDA antagonist at higher doses. In patients, low and intermediate doses (50–250 mg/day) do not appear to have robust effects on mood (71). However, at higher doses (1000 mg/day), D-cycloserine exhibited robust antidepressant effects in a pilot trial of 26 depressed patients, with significant effects over placebo after 6 weeks (Cohen's d range = 0.91–0.99) (72). This dose also shows initial promise in extending the rapid anti-depressant effects of ketamine when given subsequently (73), and several ongoing investigations are pursuing this sequenced approach (i.e., NCT02772211, NCT02974010, NCT03395392). In the cognitive domain, at an intermediate dose (250 mg), D-cycloserine has shown enhancement effects for

declarative memory in healthy humans, which was linked to increased functional magnetic resonance imaging activation in the hippocampus (74), consistent with a potential facilitative effect on learning.

Potential for Synergistic Effects.—Though the current review focuses on depression, it is noteworthy that a large clinical literature has examined the potential for low-dose D-cycloserine (50 mg) to facilitate extinction learning during exposure therapy for anxiety conditions. Based on promising initial findings, this approach was pursued to synergistically capitalize on neuroplasticity by combining pharmacology with behavioral treatment (75). Unfortunately, subsequent research in this area suggests that D-cycloserine may not produce a reliable and clinically meaningful increase in the overall response rate above that achieved through gold-standard exposure therapy protocols alone (76). We are not aware of published findings that directly test whether D-cycloserine enhances behavioral treatments in the context of depression. One ongoing study (NCT02376257) is designed to test the hypothesis that an intermediate dose of D-cycloserine (250 mg) can enhance memory retention of computer-administered cognitive therapy session material among depressed patients (see Table 1) (77,78). While learning enhancement has been found at this intermediate dose, mood effects are robust only at higher doses. If such mood effects are an important clinical marker of neuroplasticity in depression, higher doses (i.e., 1000 mg) could be needed to maximize synergistic effects with behavioral learning, though this hypothesis has not been tested.

BRAIN STIMULATION THERAPIES

Electroconvulsive Therapy

Monomodal Treatment: Neuroplasticity and Clinical Effects.—ECT is the gold-standard therapy for severe depression (79). Whereas standard antidepressant therapies achieve remission in 13% to 14% of patients with treatment-resistant major depressive disorder (MDD) (80), ECT reliably achieves remission rates of 50% to 70% (81). ECT involves passing an electrical current through the brain to induce a generalized seizure under general anesthesia. During an acute treatment course, ECT is typically given several times per week (three times per week in the United States), with the average patient requiring a range of six to 12 treatments (81–83).

While the mechanism of action of ECT remains incompletely understood, its potent effects on neuroplasticity may underlie its antidepressant effects (10,84), though critical gaps in this literature remain. Electroconvulsive seizures (the analog of ECT in animal models) affect many neuroplastic processes, including gliogenesis, increased axospinous synapses in the CA1 pyramidal layer, increase in number of mushroom spines, axonal sprouting in the dentate gyrus, neurogenesis, as well as regulation of neurotrophic factors (85,86). Cognitive flexibility, operationalized as the ability to flexibly learn new and unlearn old associations as novel situations arise, has been shown to improve following electroconvulsive seizure in rodents (86). Studies of ECT in humans have also shown effects on neuroplasticity markers, including changes in hippocampal and amygdala volumes (10,84,87), peripheral brain-derived neurotrophic factor (88), and default mode network connectivity (89).

Notably, as with most antidepressant treatments, a major clinical problem related to ECT is the high probability of relapse following an index treatment course [as high as 84% during the subsequent 6 months when ECT is abruptly discontinued (90)]. Even with adjunctive continuation pharmacotherapy and other biological strategies, relapse rates approach 50% within the first year (91), with most patients relapsing 2 to 3 months following an index ECT course (90,92). These findings support the hypothesis that when plasticity-enhancing treatments are withdrawn, patients often experience a return of symptoms.

Potential for Synergistic Effects.—Early work on ECT did not typically probe the combined effect of psychotherapy (93), possibly reflecting the thinking that ECT patients were too impaired to effectively engage in psychotherapy. However, advancements in technique have improved cognitive outcomes substantially. In fact, many studies demonstrate that a number of cognitive domains improve post-ECT compared with baseline, likely as a result of improvements in mood and other related symptoms (92,94–96). A large meta-analysis of the effects of ECT on cognitive domains (N = 2981, k = 84) (97) found that while some cognitive domains show impairment in the subacute period (<3 days since last ECT), many domains showed improvement compared with baseline in the acute period (4–15 days) as well as on longer-term follow-up (>28 days) posttreatment. In fact, 1 month after treatment, approximately half of neurocognitive measures showed statistically significant improvement, with effect sizes (within subject) ranging from 0.37 to 0.75, and no assessment showed a decline compared with baseline (97).

Given potent effects of ECT on plasticity, the subacute post-ECT period may be an opportune time for cognitive and behavioral interventions to improve longer-term outcomes. Several studies suggest that the combination of ECT and psychotherapy may lead to improved longer-term outcomes (98–100) (see Table 1). The largest study to date (N = 60) showed that ECT followed by CBT was more efficacious at maintaining response (77% sustained response) than either continued ECT alone (40%) or pharmacotherapy alone (44%) (98).

Repetitive TMS

Monomodal Treatment: Neuroplasticity and Clinical Effects.—Transcranial magnetic therapy involves the noninvasive application of rapidly changing magnetic fields to induce focused electrical currents in the cortex. When stimulation is delivered in rapid succession (e.g., several pulses per second), this is called rTMS. Studies focused on stimulation of the motor cortex suggest that HF stimulation (5–20 Hz) leads to increased local cortical excitability whereas low-frequency stimulation (0.1–1.0 Hz) leads to local cortical inhibition (101).

The efficacy of rTMS for the treatment of depression was established in three large, multisite trials of adult patients with MDD who had failed to respond to one to four standard antidepressants. In these trials of HF rTMS, 703 subjects were randomized to active or sham rTMS (102–104), with modest effect sizes. Following a large industry-sponsored study (104,105), the Food and Drug Administration cleared the first rTMS device in 2008 for therapeutic clinical use in MDD. The Food and Drug Administration–approved treatment

protocols involve 20 to 30 sessions of 10-Hz rTMS delivered to the left dorsolateral PFC (DLPFC). However, a small but substantial literature also supports the antidepressant efficacy of low-frequency rTMS applied to the right DLPFC (106) as well as bilateral rTMS (107). As with other acute treatments for depression, relapse following a successful course of rTMS is relatively high (108).

In depressed patients, a course of rTMS has been associated with improvement in cognitive function, though this is not clearly distinct from an overall antidepressant effect (109). TMS exhibits cognitive performance enhancement in healthy humans across numerous domains, including motor learning, attention, memory, and language (110). Another systematic review focused on HF rTMS targeting the PFC reported that rTMS was more likely to lead to cognitive improvements when applied over the left DLPFC (111).

It is hypothesized that TMS operates by modulating the function of neural circuits involved in emotion regulation, cognition, and attention control (112,113). As the primary target of TMS as a treatment for depression is the DLPFC, it has been suggested that TMS may specifically alter activity of a cognitive control network that includes this region, potentially enhancing cognitive control of emotion (114). Studies in human participants, animal models, and in vitro work have all demonstrated that rTMS affects synaptic plasticity in a relatively enduring way (9). In clinical populations, most but not all studies show that rTMS-induced changes in cortical excitability and brain activity (positron emission tomography, functional magnetic resonance imaging, electroencephalography) last beyond the immediate period of stimulation (9). Human brain imaging studies show effects of rTMS on regional cerebral blood flow (115), blood oxygen level–dependent activity patterns (116), and electroencephalography responses (117), which last up to several days beyond the stimulation period (118,119). In rodents, neuroplasticity markers—including brain-derived neurotrophic factor and alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor phosphorylation—remain upregulated in the hippocampus 3 days following HF-rTMS (120).

Potential for Synergistic Effects.—Despite the potential synergistic effect of modulating the cognitive control network via rTMS and engaging patients in a cognitively based psychotherapy, few studies have combined the two approaches for any disorder. In depression, a large, nonrandomized naturalistic study treated patients for a minimum of 10 weeks with simultaneous rTMS and CBT (CBT sessions were conducted during TMS) and demonstrated relatively strong response (66%) and remission (56%) rates. A majority of individuals who achieved response or remission acutely maintained these outcomes at 6 months posttreatment (65% of responders retained response; 60% of remitters retained remission) (121). These findings await validation with a randomized controlled trial. While this review focuses on depression, it is worth noting that rTMS in combination with CBT in posttraumatic stress disorder showed enhanced clinical outcomes in two small (Ns = 9, 30) (122,123) and one relatively large (N = 103) (124) sham-controlled studies. Although still preliminary, these studies suggest that response to existing psychotherapeutic strategies for PTSD might be enhanced with concurrent focal brain stimulation.

Transcranial Direct Current Stimulation

Monomodal Treatment: Neuroplasticity and Clinical Effects.—Transcranial direct current stimulation (tDCS) passes a low-intensity electrical current through the brain between two electrodes (cathode and anode). tDCS does not directly depolarize cortical neurons but does result in lasting changes in cortical excitability, with increased cortical excitability occurring under the anode and decreased excitability occurring under the cathode. Some have proposed that tDCS induces neuroplasticity through NMDA-dependent mechanisms (125–127). Preliminary studies suggest that the NMDA antagonist dextromethorphan prevents lasting effects of tDCS on motor evoked potentials, while tDCS-induced excitability is potentiated by the partial NMDA agonist D-cycloserine (at a low dose of 100 mg) (127,128). tDCS has been studied as a potential treatment for several psychiatric disorders, including depression, and as a cognitive enhancer in healthy individuals. To date, the clinical data on tDCS are mixed. Although there is some evidence for antidepressant effects (129), these are modest at best, and a large clinical trial was negative (130). A quantitative review found no support for cognitive enhancing effects of a single session of tDCS in healthy individuals (131).

Potential for Synergistic Effects.—tDCS has been tested in combination with cognitive control training (CCT), an automated intervention designed to engage the PFC, increase cognitive control, and decrease symptoms through working memory exercises (132). A pilot study randomized 27 MDD participants into three groups: 1) tDCS combined with CCT, 2) sham brain stimulation combined with CCT, and 3) sham CCT plus active tDCS. In all three groups, there were similar immediate antidepressant effects, but the tDCS combined with the CCT group exhibited sustained and increased antidepressant effect at 3 weeks posttreatment (see Table 1) (133). In a similar double-blinded study ($N = 37$), depressed patients received active tDCS and CCT or sham tDCS and CCT for 10 consecutive days. Depressive symptoms posttreatment and at 2-week follow-up did not differ across groups; this may have been due to specific individual differences, though this hypothesis needs further confirmation (134). One additional, similar randomized controlled trial of tDCS combined with CCT is underway (see Table 1). Finally, three randomized controlled trials examining tDCS combined with CBT for depression are underway, with results anticipated shortly (see Table 1) (135).

tDCS combined with behavioral treatment has also been explored in other disorders of negative affect. For instance, using a fully crossed (2 × 2) randomized controlled design, tDCS (active or sham) over the DLPFC was combined with a single session of one of two forms of automated attention retraining (designed to train attention either toward or away from threat cues) in 77 participants with mild anxiety. Active tDCS facilitated the uptake of the trained attentional patterns (136). Additionally, a small case series ($N = 4$) has shown that tDCS combined with working memory training may improve cognitive and emotional function in patients with posttraumatic stress disorder and poor working memory (137).

SUMMARY AND FUTURE DIRECTIONS

The current review focuses on the potential of behavioral interventions to leverage plasticity-enhancing approaches to address pathological neural circuits in depression and hence improve longer-term outcomes. While the theoretical basis and indirect evidence for this strategy are compelling, few clinical studies directly test these approaches using critical control conditions, including each intervention component (somatic and behavioral) in the absence of the other (Table 1). Such studies are necessary to provide definitive evidence of synergy—ideally by showing not only that the combination treatment outperforms each intervention component on its own, but also that the clinical advantages of the multimodal treatment are not simply additive. These fully crossed designs are likely scarce because they present challenges to consider from both pragmatic (e.g., sufficient sample sizes required in each cell) and ethical (e.g., withholding gold-standard treatments) standpoints. Nevertheless, well-controlled designs are important to show definitively that neuroplasticity enhancement increases the impact of the behavioral treatment, and likewise that the behavioral treatment extends and/or magnifies the acute effect of the neuroplasticity intervention.

The somatic therapies reviewed above have the largest evidence base in humans with regard to stand-alone clinical and neuroplasticity effects and are the subject of preliminary or ongoing clinical studies testing their potential for synergistic combination with behavioral approaches. Countless other interventions may have similar plasticity-enhancing potential yet to be leveraged in clinical research. These include numerous other glutamate-modulating drugs that have been pursued in the wake of intravenous ketamine. The field anxiously anticipates the results of several phase II and III trials of these glutamate-modulating drugs with hypothesized potential for potent and rapid enhancements in neuroplasticity (esketamine, rapastinel, tulrampator/S-47445, AV-101, NRX-1074, CERC-301), many of which are completed or near completion [see (138)].

Nonpharmacological options to enhance plasticity are also important to consider. These include alternatives such as exercise, which exhibits plasticity and procognitive effects (139). Unfortunately, in the current system of Food and Drug Administration approval and new drug development, researchers investigating nonpharmacological approaches and older, well-established drugs without patent protection have considerably less opportunities for funding well-powered clinical trials compared with pharmacological agents with industry sponsorship.

In summary, a range of neuroplasticity enhancers have the potential to facilitate the uptake of adaptive cognitive patterns that may effectively buffer against depression over time. While this thesis is currently indirectly supported by robust animal and human literatures, the development and rigorous clinical validation of synergistic, neuroplasticity-based somatic-behavioral treatment combinations remains in an early stage.

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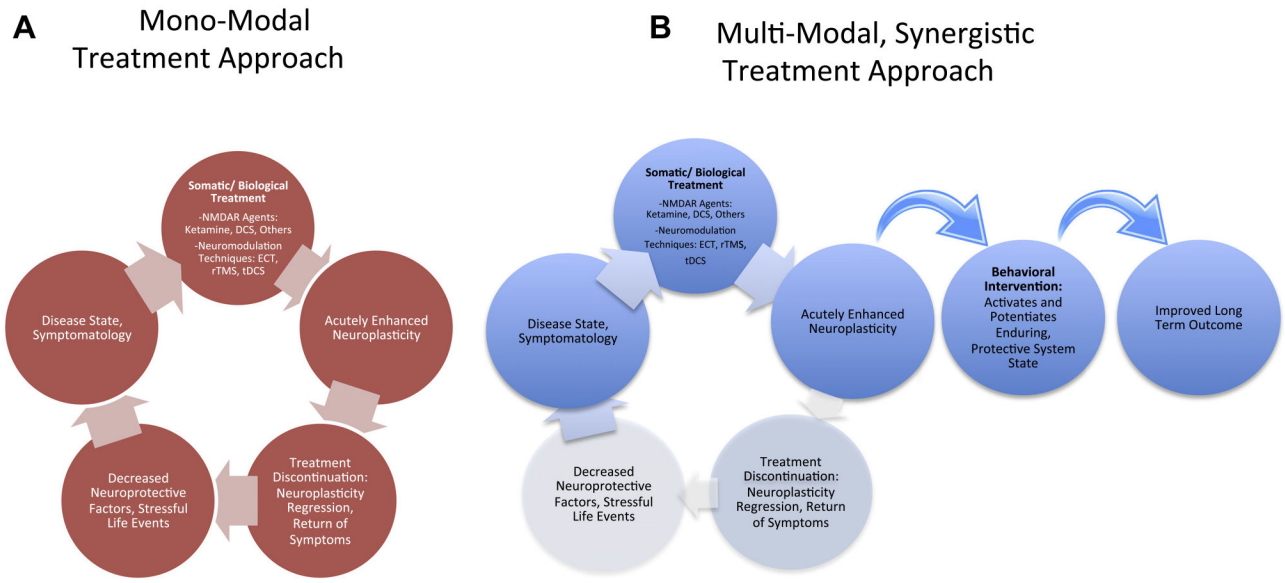

Figure 1.

(A) The monomodal approach often leads to a return of the symptomatic state once treatment is discontinued. **(B)** The proposed, multimodal approach may combine treatment modalities synergistically to enhance and subsequently harness a state of neuroplasticity to lead to improved longer-term outcomes. DCS, D-cycloserine; ECT, electroconvulsive therapy; NMDAR, *N*-methyl-D-aspartate receptor; rTMS, repetitive transcranial magnetic stimulation; tDCS, transcranial direct current stimulation.

Table 1.

Completed and Ongoing Clinical Trials Investigating Combinations of Somatic/Biological Treatments With Cognitive Behavioral Interventions in Depression

NCT Identifier, Study Status	Trial Design and Description	Expected Completion Date, Projected/Actual Enrollment	Primary Outcome Measure or Results	RCT?	Includes Comparison Condition for Somatic Treatment Without Behavioral?	Includes Comparison Condition for Behavioral Treatment Without Somatic?
Ketamine						
NCT03237286, ongoing	3-arm RCT: IV ketamine + 4 days of computer-based cognitive training; IV ketamine + sham training; IV saline + cognitive training	Oct 2023, *N* = 150	**1** Depression severity (MADRS) **2** fMRI measure (executive-salience network functional connectivity) **3** Implicit-association test **4** Cognitive flexibility	Y	Y	Y
NCT03027362, ongoing	2-arm RCT: ketamine responders randomized to CBT or psychoeducation	Jul 2019, *N* = 28	**1** Time to relapse **2** Changes in cognitive flexibility/ executive functioning	Y	Y	N
NCT02289248, completed	Open label, single arm: IV ketamine followed by CBT (8 weeks following ketamine)	Oct 2016, *N* = 16	Among responders, 75% retained response 8 weeks following ketamine, though the majority eventually relapsed on longer-term, naturalistic follow-up (63)	N	N	N
D-cycloserine						
NCT02376257, completed	3-arm RCT: 250-mg DCS + CBT, 100-mg modafinil + CBT, or placebo + CBT	May 2017, *N* = 85	Delayed memory recall for CBT content; results submitted but not yet published	Y	N	Y
ECT						
NCT02176473, completed	Single arm, open label: ECT responders undergo computer-based CBT	Dec 2016, *N* = 15	At 6 months, the relapse rate was 33% (100)	N	N	N
NCT00487500, completed	3-arm RCT: ECT responders were randomized (1:1:1) to continuation phase medication (MED), CBT + MED, or ECT + MED	2010, *N* = 60	At 6 months, CBT/MED group had 77% sustained response, ECT/MED group had 40% sustained response, and MED-alone group had 44% sustained response (98)	Y	Y	N
No number, completed	Single arm, open label: ECT responders undergo CBT	2005, *N* = 9	At 12-month follow-up, 3 patients withdrew; mean BDI scores among completers were lower (11.7) compared to the end of ECT (18.8) (99)	N	N	N

NCT Identifier, Study Status	Trial Design and Description	Expected Completion Date, Projected/Actual Enrollment	Primary Outcome Measure or Results	RCT?	Includes Comparison Condition for Somatic Treatment Without Behavioral?	Includes Comparison Condition for Behavioral Treatment Without Somatic?
rTMS						
NCT03289923, ongoing	2-arm RCT: active rTMS + CBT vs. sham rTMS + CBT	Jan 2019, *N* = 50	**1** Change in fMRI bold signal **2** Changes in clinical rating scales and MEG/EEG	Y	N	Y
No number, completed	Single-arm, open-label, naturalistic study of rTMS + CBT (CBT performed during TMS sessions)	2016, *N* = 196	Posttreatment response and remission rates of 66% and 56%, respectively; sustained response and remission rates were seen in 65% and 60% of those originally attaining response/remission, respectively (121)	N	N	N
tDCS						
NCT03548545, ongoing	2-arm RCT: active tDCS 1 CBT vs. sham tDCS 1 CBT	Dec 2020, *N* = 72	Change in depression severity (MADRS) at 4 weeks	Y	N	Y
NCT03518749, Ongoing	3-arm RCT: 1-mA tDCS 1 CCT, 2-mA tDCS 1 CCT, sham tDCS 1 CCT	Mar 2019, *N* = 57	Change in depression severity (MADRS) at 4 weeks	Y	N	Y
NCT02633449, ongoing	3-arm RCT: active tDCS and CBT, sham tDCS and CBT, or CBT alone	Dec 2018, *N* = 192	Primary outcome measure is change in MADRS scores from baseline to 6, 18, and 30 weeks (135)	Y	N	Y
NCT01974076, ongoing	2-arm RCT: active tDCS 1 CBT vs. sham tDCS 1 CBT	Sep 2018, *N* = 135	Depression severity (MADRS) at 3 weeks	Y	N	Y
NCT01875419, completed	2-arm RCT: active tDCS 1 CBT vs. sham tDCS 1 CBT (tDCS immediately prior to CBT)	Oct 2017, *N* = 30	Change in depression severity at 8 weeks (BDI and HDRS); results not yet published	Y	N	Y
ACTRN12613000050752[a], completed	3-arm RCT: tDCS 1 CCT, sham tDCS 1 CCT, vs. tDCS 1 sham CCT	June 2013, *N* = 27	Depression severity (MADRS), with significant group-by-time interaction (p = .003), with tDCS 1 CCT group showing best clinical outcome at follow-up (133)	Y	Y	Y
NCT01434836, completed	2-arm RCT: tDCS 1 CCT vs. sham tDCS 1 CCT	May 2013, *N* = 37	Depression severity at 4 weeks; no group-by-time interaction was observed (134)	Y	N	Y

BDI, Beck Depression Inventory; CBT, cognitive behavioral therapy; CCT, cognitive control training (a computer-based intervention); ECT, electroconvulsive therapy; EEG, electroencephalography; fMRI, functional magnetic resonance imaging; HDRS, Hamilton Depression Rating Scale; IV, intravenous; MADRS, Montgomery–Åsberg Depression Rating Scale; MED, antidepressant medication; MEG, magnetoencephalography; N, no; NCT, national clinical trial; RCT, randomized controlled trial; rTMS, repetitive transcranial magnetic stimulation; tDCS, transcranial direct current stimulation; Y, yes.

[a]Registered via the Australian New Zealand Clinical Trials Registry.