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Neuropsychological Effects of Neuromodulation Techniques for Treatment-Resistant Depression: A Review

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Abstract

Electroconvulsive therapy (ECT) and ablative neurosurgical procedures are established interventions for treatment-resistant depression (TRD), but their use may be limited in part by neuropsychological adverse effects. Additional neuromodulation strategies are being developed that aim to match or exceed the efficacy of ECT/ablative surgery with a better neurocognitive side effect profile. In this review, we briefly discuss the neurocognitive effects of ECT and ablative neurosurgical procedures, then synthesize the available neurocognitive information for emerging neuromodulation therapies including repetitive transcranial magnetic stimulation, magnetic seizure therapy, transcranial direct current stimulation, vagus nerve stimulation, and deep brain stimulation. The available evidence suggests these procedures may be more cognitively benign relative to ECT or ablative neurosurgical procedures, though further research is clearly needed to fully evaluate the neurocognitive effects, both positive and negative, of these novel neuromodulation interventions.

Keywords

Major Depression; Neuromodulation; Neuropsychology; Antidepressant Treatment

Introduction

Up to half of patients with Major Depressive Disorder (MDD) do not respond to first-line antidepressant treatment (1), and one third do not respond to two or more treatments (2,3). Treatment-resistant depression (TRD) is therefore prevalent, resulting in added patient suffering, disability, and suicide risk (4,5). Established treatments for severe TRD include

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electroconvulsive therapy (ECT) and ablative neurosurgery – both of which are associated with cognitive side effects that may limit use. Over the past several years, a number of new neuromodulation techniques have been investigated with the goal of achieving or exceeding the efficacy of established TRD treatments with better cognitive safety. In this review, we describe the cognitive effects associated with ECT and ablative neurosurgical procedures and summarize available data on the neurocognitive safety of emerging neuromodulation techniques.

Electroconvulsive Therapy

ECT involves the serial administration of electrical current through the brain under general anesthesia to induce a generalized tonic-clonic seizure (6). ECT is one of the most effective acute treatments for a depressive episode (7), with response and remission rates as high as 79% and 75%, respectively, with brief pulse (1.0 ms) bitemporal (BT) electrode placement (Kellner et al., 2006; Husain et al., 2004). Recently, with the introduction of ultrabrief pulse (0.3 ms) ECT, studies have found varying efficacy results. For instance, Sackeim and colleagues found a high remission rate of 73% when using right-unilateral (RUL) electrode placement relative to 35% for a bilateral electrode configuration (8). However, Loo and colleagues found a modest remission rate of 27% with the use of ultrabrief pulse and RUL electrode placement (9). A possible explanation for this difference is that the latter study included a sample with greater treatment resistance. Seinaert and colleagues showed equivalent efficacy for ultrabrief pulse RUL and bifrontal (BF) ECT: response rate was 78.1% for both groups, remission rate was 43.75% for RUL and 34.38% for BF (10).

Balanced against its antidepressant efficacy, ECT results in significant cognitive sequelae including transient confusion, anterograde amnesia, and retrograde amnesia. Research has suggested that the confusion after each ECT treatment and the anterograde amnesia are time-limited (11-15), but retrograde amnesia has been found to persist up to and past 6-months in some cases (11-15). Patient-specific factors including greater age (16), lower education level, and lower premorbid intelligence (17) may increase the level of cognitive impairment associated with ECT. Also, concurrent use of certain psychotropic medications may either exacerbate (e.g., lithium, venlafaxine) or minimize (e.g., nortriptyline) adverse cognitive effects (18,19).

Procedural modifications have been developed to minimize the severity of adverse cognitive effects (12). The use of brief or ultra brief pulse width rather than sine wave current has been found to lessen the cognitive impact of ECT (11,20-22), and ultra brief pulse may be more cognitively advantageous than brief pulse (8). Dose titration – finding the smallest amount of energy required to elicit a seizure, then providing subsequent treatments relative to this threshold – has become a common practice that attempts to maximize efficacy while minimizing cognitive effects by treating at the lowest possible dose (23,24). Electrode configuration has also been shown to minimize adverse cognitive effects. RUL and BF ECT are associated with less severe retrograde amnesia compared to BT ECT (21,25). BF ECT has been reported to have a superior cognitive profile to BT ECT (26) and RUL ECT (27); however, these studies focused on memory (i.e., primarily temporal lobe tasks) rather than executive functions (i.e., primarily frontal lobe tasks) that might have been more affected (25).

Ablative Neurosurgery

Ablative neurosurgical procedures represent the earliest surgical attempts to treat TRD. Procedures in use today primarily include anterior capsulotomy, anterior cingulotomy, subcaudate tractotomy, and limbic leucotomy. Ablative surgery may be effective in 30%-70% of patients (28) – rigorous safety and efficacy data are lacking. In addition to the

risks inherent to any neurosurgical procedure, undesirable personality changes and cognitive functioning have been reported with each approach. In terms of cognitive change, the processes mediated by the site of ablation are most likely to be affected.

Anterior Capsulotomy

Anterior capsulotomy severs a portion of the white matter tracts in the anterior section of the internal capsule that connects the thalamus to the frontal cortex (29). When combined with anterior cingulotomy it may cause greater reductions in emotion recognition than anterior cingulotomy alone (30). Anterior capsulotomy has primarily been used for treatment-refractory obsessive compulsive disorder (OCD) and is less-studied in TRD patients (31). One study of anterior capsulotomy for treating OCD found a long term (about 10 year) mild impairment in set-shifting and verbal fluency (32). Set shifting and working memory deficits have also been reported in treatment-refractory anxiety disorders patients receiving anterior capsulotomy (33). In sum, available data suggest possible, but not definitive, modest negative effects of anterior capsulotomy on neurocognitive function, particularly executive functioning.

Anterior Cingulotomy

Anterior cingulotomy involves bilateral lesions of the dorsal anterior cingulate gyrus (34). There is conflicting information regarding the neurocognitive effects related to anterior cingulotomy. Two studies have found impaired executive functions (e.g., emotional recognition, response inhibition, and mental image rotation (30,35)). However, another found no impairment using a computerized neurocognitive battery and showed that patients improved on certain measures of executive functioning and spatial working memory (36).

Stereotactic Subcaudate Tractotomy (SST)

Stereotactic subcaudate tractotomy (SST) severs a portion of nerve fibers anterior to the head of the caudate nucleus connecting prefrontal cortex to hippocampus, amygdala, thalamus, and hypothalamus (37). There are limited neuropsychological data for patients undergoing SST. One group found SST to be associated with widespread frontal impairment at 2 weeks, but not 6 months, after surgery (38). It was concluded that these transient deficits were due to post-operative edema as opposed to the surgical lesions *per sé* (38).

Limbic Leucotomy

Limbic leucotomy combines anterior cingulotomy with SST (29). Neuropsychological data are limited, but preliminary results from a study of 88 patients showed no impairment on the Wechsler Adult Intelligence Scale (WAIS) 6 weeks after surgery (39). Improvements were noted on the Verbal, Performance and Full Scale IQ scores, but these changes may have been related to practice effects.

Emerging Neuromodulation Techniques

Repetitive Transcranial Magnetic Stimulation (rTMS)

Repetitive transcranial magnetic stimulation (rTMS) uses a focal, rapidly changing magnetic field to induce an electrical current in a targeted brain region. Meta-analyses have shown high-frequency (5-20 Hz) rTMS of the left dorsolateral prefrontal cortex (DLPFC) to be an effective antidepressant therapy with moderate to large effect size (40-43). A recent sham-controlled, multi-site study confirmed the statistically significant antidepressant effects of rTMS (44). A growing database supports the antidepressant efficacy of low-frequency (≤1 Hz) rTMS applied to the right DLPFC (45-47); however, these data are limited relative to left DLPFC studies. Some studies have suggested left DLPFC rTMS might have similar

efficacy to ECT (48-50). However, there are conflicting data (51), and it is notable that a secondary analysis of the recent multi-site study showed that active rTMS was statistically more effective than sham rTMS only in patients failing no more than one adequate antidepressant treatment (52).

In general, studies of rTMS have been found it to be safe and well-tolerated (44). The most severe potential adverse effect is seizure (53), but implementation of established safety guidelines (54) has substantially reduced this risk (53). rTMS also appears safe in patients taking concurrent antidepressant medications (55). Based on its novelty and the possibility that rTMS might offer an alternative to ECT, neurocognitive assessment has been common in rTMS treatment trials. The vast majority of studies have found rTMS to have no deleterious effects on cognition (47,56-60). Some studies have reported minimal deficits in sustained attention (61), spatial planning, and verbal retention (62), but the treatment protocols used in these studies were relatively nonstandard: one utilized a twice-daily treatment schedule instead of a more typical once-daily treatment schedule (61), while the other used bilateral DLPFC rTMS (62). Direct comparison of 10 Hz left DLPFC rTMS to brief-pulse RUL ECT suggests that rTMS has a superior cognitive effect profile (63,64), though one study using less sensitive neurocognitive measures failed to find such a difference (51).

Many studies have noted improvements in aspects of cognitive functioning over the course of rTMS treatment. Specific areas of improvement have included manual motor speed, simple reaction time, verbal and visual learning, attention, processing speed, verbal fluency, autobiographical memory, working memory, and executive functioning (47,56-58,60-62,65,66). However these findings must be interpreted with caution due to various methodological factors that could have mediated the findings, including use of select cognitive instruments without alternate forms, practice effects, cohort characteristics (i.e., age, education level), statistical chance, and lack of a control group (58,65,67,68). As a whole, the available neurocognitive safety data for rTMS in TRD are insufficient to formulate conclusive hypotheses regarding the presence or absence of neurocognitive improvements. Future studies with larger sample sizes and stricter methodological controls may clarify this issue more definitively.

Magnetic Seizure Therapy (MST)

Magnetic seizure therapy (MST) uses an rTMS device to administer a series of rTMS pulses delivered at high intensity to induce a single seizure under general anesthesia and muscle relaxation. A series of seizures is given over several weeks, analogous to ECT. Efficacy is supported by two case reports (69,70), and two small studies comparing MST and ECT (71,72). These data suggest MST has antidepressant effects, but not necessarily equivalent to ECT (72). Compared to ECT, MST is associated with fewer somatic side effects, most notably headaches and muscle aches (73). A two-center controlled trial comparing MST to RUL ECT (administered with ultra-brief pulse) is ongoing.

MST results in fewer adverse cognitive effects than ECT (69), perhaps due to the more focal nature of acute stimulation (71) and less generalized impact on cortical regions subserving neurocognitive functions. In nonhuman primates, MST (administered at 50 Hz) caused little anterograde or retrograde amnesia relative to electroconvulsive shock (ECS) (74,75); MST administered at 100 Hz retained its cognitive advantage over ECS and was comparable to sham (anesthesia only) (76). In depressed patients, cognitive data suggest that, compared to ECT, MST is associated with fewer subjective memory complaints and fewer objective cognitive side effects (73). Specifically, cognitive advantages of MST included preserved face recognition (both neutral and affective), sentence recognition, and category fluency (Lisanby, Luber et al., 2003). Only delayed figure reproduction was worse in patients

receiving MST than in those receiving ECT. Following a complete course of 50 Hz MST in a controlled trial with 20 patients, there was little to no change in neurocognitive performance on measures of auditory or visuospatial learning and memory, retrograde memory for public information, and global cognitive function (77). A consistent finding with both 50 Hz and 100 Hz MST is rapid recovery of orientation after treatment (73,78).

Transcranial Direct Current Stimulation (tDCS)

In transcranial direct current stimulation (tDCS), a relatively low intensity, nonconvulsive electrical current is non-invasively applied to the brain (79). tDCS for depression focuses electrical current through the DLPFC with a supraorbital grounding (80), but likely differs from rTMS in mechanism of action (80). Preliminary antidepressant efficacy is supported by two randomized, sham-controlled studies (81,82). A comparison study of tDCS and fluoxetine found both treatments significantly reduced depressive symptoms, though tDCS showed a faster antidepressant effect (83). Side effects of tDCS have included slight tingling at the electrode sites, headache, fatigue, and nausea (84).

tDCS studies including neurocognitive assessment have focused on global cognitive function, processing speed, working memory, attention, and executive functions (85). Of importance, no decreases were noted in any neurocognitive test following treatment, and a statistically significant improvement was found in the domain of working memory. This improvement was only observed in patients who received active DLPFC stimulation. Improvement in working memory has also been observed following DLPFC tDCS in healthy controls (86) and individuals with idiopathic Parkinson's disease (87). Additionally, improvement in verbal recognition memory has been observed following tDCS in individuals with Alzheimer's disease (88). However, one recent investigation of tDCS in individuals with depression found no effects on verbal working memory, recognition memory, or attention (89). The authors posited the interference effects from medications, differences in stimulation parameters, and cognitive battery administration time as the reason for the lack of improvement in verbal working memory observed in other studies (89).

Vagus Nerve Stimulation (VNS)

In vagus nerve stimulation (VNS), a bipolar electrode wrapped around the cervical vagus nerve (typically left) transmits low-frequency electrical pulses originating from a pulse generator implanted subcutaneously in the anterior chest wall (90). The treatment has been used to treat refractory epilepsy (US FDA approved in 1997) and the US FDA approved its use as an adjunctive treatment of refractory depression in 2005 (91). In a placebo-controlled clinical trial, VNS did not show a statistically significant acute (10-week) antidepressant effect compared to sham treatment. After 12 months of VNS plus treatment-as-usual (TAU), response and remission rates were 27% and 16%, respectively (92), which were statistically significantly higher than a non-randomized observation-only, TAU group (93). Side effects included voice alteration, dyspnea, and neck pain, all of which are generally mild and restricted to time of stimulation (91,94).

Cognitive safety data on VNS are limited. Only one study of VNS for TRD reported cognitive effects: patients receiving open-label VNS showed no decrements on measures of processing speed, psychomotor function, verbal fluency, attention, memory, or executive functioning (95). Patients showed improved performance on measures of psychomotor speed, language, and executive function. These results were not attributable to practice effects, though may have been associated with mood improvement. In studies of patients treated with VNS for epilepsy, no impairments were found in the domains of attention, motor function, short-term memory, learning and memory, IQ, processing speed, and

executive function (96-98). However, Helmstaedter et al. (2001) reported that poor performance on measures of visual-spatial memory and increased time to task completion was related to higher intensity (1-2.5 mA) VNS stimulation.

Deep Brain Stimulation (DBS)

For deep brain stimulation (DBS), electrodes are stereotactically implanted at a specific neuroanatomical target and focal stimulation is delivered. Use is currently widespread for movement disorders, with several subcortical regions including the thalamic ventral intermediate nucleus (VIM) for tremor, the globus pallidus internus (GPi) for dystonia, and the subthalamic nucleus (STN) and GPi for Parkinson's disease (PD) (99). DBS offers a revisable, adjustable, and reversible alternative to ablative procedures. However, DBS is not simply a reversible lesion (100). Therefore, this treatment may reasonably have a different cognitive side effect profile compared to ablation of the same targets (101).

Although the majority of PD DBS patients experience a safe and effective outcome, potential site-related side effects have been reported (102). DBS applied to the STN has been associated with reductions in verbal fluency and, less consistently, verbal memory, conditional associative learning, conceptual reasoning, and global cognitive function (102). DBS applied to the GPi has been associated with relatively mild reductions on measures of verbal fluency and visuospatial construction (102). However, while it may seem from the available literature that DBS applied to the STN relative to the GPi might be associated with more cognitive side effects, methodological differences between studies (e.g. sample size and medication effects) weaken this conclusion (102). For example, a recent study has found that in patients receiving STN DBS for PD, variables such as surgical trajectory and electrode placement may be associated with differences in neurocognitive side effects experienced (103). Importantly, DBS of either the STN or GPi is considered relatively safe from a cognitive standpoint.

For studies of DBS in TRD, the three best-studied targets are the subcallosal cingulate white matter (SCCwm), the ventral caudate/ventral striatum (VC/VS), and the nucleus accumbens (NAc). Open-label DBS of the SCCwm has shown six month response and remission rates of approximately 60% and 35% respectively (104,105). VC/VS DBS emerged as a potential target for TRD when patients with treatment-resistant OCD also showed an antidepressant response (106). Six month response and remission rates of open-label VC/VS DBS for TRD have been reported to be 40% and 20%, respectively (107). Finally, the antidepressant response rate for twelve months of DBS applied to the NAc (a target anatomically similar to the VC/VS) has recently been reported as 50% (108). The most common side effects of SCCwm DBS treatment for TRD are wound infection, perioperative headache, and worsening/irritable mood (105). Increased suicidality was seen in 13% of TRD patients receiving VC/VS DBS (107), and 20% of patients receiving NAc DBS (108).

McNeely et al. (2008) evaluated the neurocognitive safety of SCCwm DBS for TRD using tests of verbal IQ, attention, psychomotor speed, risk taking, memory, and executive functioning and found no deterioration on any measure. Improvements were noted in verbal and visual memory, manual motor speed, and verbal learning in the subset of patients who were performing these tasks at below-average levels at baseline, moving them closer to average levels after 12 months of treatment (109). These changes did not correlate with changes in mood over the same time period, leading the authors to conclude that there might exist separate neural circuits for cognitive function and depression (109). Limitations of this study included small sample size (six patients) and the fact that patients at below-average baseline levels of cognitive functioning have the most room for improvement from practice effects.

Patients receiving VC/VS DBS for TRD were found to have no negative effects from stimulation on measures of general intellectual ability, language, processing speed, executive function, or learning and memory (107). Notably, the cognitive adverse effects reported with anterior capsulotomy were not seen with acute or chronic stimulation. Similar to the study of SCCwm DBS for TRD, improvement was observed in verbal memory that was statistically unrelated to change in depression severity (107). In the study of patients receiving NAc DBS, stimulation was not associated with any impairment of general intellectual ability, language, processing speed, executive functioning, learning, and memory (108).

Additional DBS targets for TRD are under investigation, though neurocognitive data are limited. A case report of DBS of the inferior thalamic peduncle reported efficacy in TRD, and neurocognitive data showed either no change or improvement in a number of domains (110). Finally, DBS of the white matter adjacent to the lateral habenula has shown an antidepressant effect in a single case report (111). While cognitive effects were not reported, animal data suggest habenular DBS may adversely affect associative learning and spatial working memory in rats (112,113). Therefore testing in these domains should be considered in future clinical studies of habenular DBS.

In sum, DBS of the SCCwm, the VC/VS, and the NAc for TRD do not appear associated with any adverse cognitive side effects, and slight improvements in certain domains have been reported for SCCwm and VC/VS DBS. However, the available clinical data are quite limited, and results from ongoing large clinical trials will be needed to verify the cognitive safety of these treatments. Data are even more limited for other emerging targets. Given that DBS for TRD is still in the early stages of development, it is strongly recommended that comprehensive neuropsychological evaluation – paying particular attention to which domains might be affected by stimulation at a specific target – should be incorporated into ongoing and future clinical trials.

Summary

Challenges in interpreting cognitive effects related to antidepressant therapies

In interpreting the cognitive effects of antidepressant therapies, three issues must be carefully considered: practice effects, neurocognitive impairments associated with depression (that may or may not improve with treatment), and substantial methodological variations between studies. These issues complicate interpretation of neurocognitive findings to date with various focal brain stimulation therapies.

Practice effects are improvements in test performance solely due to prior test exposure. For example, individuals who complete intelligence tests at multiple time points tend to show improved scores, even with lengthy intervals between test administration (114). Moreover, the use of alternate test forms, a strategy commonly used to minimize practice effects, does not completely remove the influence of these effects (115). Thus, with tests where practice effects are expected to improve performance (e.g., Digit Span, Stroop Color Word Test), the *lack* of improvement (without obvious worsening) could indicate cognitive impairment. In designing neuropsychological testing for future studies, a potentially beneficial strategy may be to administer the battery to a control group at identical time points to clarify whether the specific battery and testing conditions used were associated with practice effects.

Studies of neurocognitive side effects of antidepressant therapies are additionally complicated by the cognitive impairments associated with depression. A systematic review of data from individuals with MDD published between 1980 and 2008 suggested a pattern of global-diffuse impairment in many cognitive domains including processing speed, attention,

memory, and executive function (116). For example, investigations have reported associations between MDD and impairment in divided attention (117), short-term and long-term memory (118), and executive functions including cognitive flexibility, inhibition, and problem solving (119-122).

Collectively, the available evidence suggests that cognitive deficits observed in MDD occur with more demanding (e.g., measures of cognitive flexibility) relative to less challenging tests (e.g., measures of simple reaction time) (123-125). Particularly relevant to treatment studies, these deficits may resolve as patients recover from depression. This has been seen in studies of patients with cyclic illness patterns (e.g., Seasonal Affective Disorder) (126,127) and medication trials (128-130), though some level of residual cognitive impairment may persist (131-133). Correlations between individuals' changes in neurocognitive performance and their changes in mood can help clarify whether any recovery of neurocognitive function was more likely to have been a direct effect of antidepressant therapy or a secondary effect of response to treatment. Such analyses suggested that improvements in test performance were likely attributable to improvements in mood in the VNS for TRD study, but not in the rTMS, tDCS, or DBS studies.

Lastly, many of the reported neurocognitive findings could be due, in part, to the substantial methodological variations between studies. Differences in study cohorts, treatment parameters, antidepressant effects, and testing conditions have important implications and must be controlled or accounted for when comparing multiple studies. For example, cohort and treatment parameter differences may account for the inconsistency in the tDCS literature regarding a possible improvement in working memory. Similarly, differences in testing conditions and neurocognitive batteries used may be the source of the large variability in reported neurocognitive improvements following rTMS. Future investigations should further characterize the basis of observed neurocognitive changes through improved methodological rigor.

Cognitive safety of emerging neuromodulation techniques: a summary

With the above caveats in mind, the reviewed literature suggests that many of the neuromodulation treatments currently under investigation have a lower risk of adverse neurocognitive side effects compared to ECT. Specifically, two of these novel treatments (MST and rTMS) have been directly compared to ECT and demonstrated greater neurocognitive safety (64,73). For rTMS, multiple studies have confirmed the lack of significant adverse cognitive effects allowing one to conclude that these treatments are neuropsychologically benign. A smaller database supports the cognitive safety of tDCS. While VNS in general appears to have no concerning neuropsychological adverse effects, data specific to TRD are more limited. Finally, preliminary data for three DBS targets for TRD (SCCwm, VC/VS, and NAc) have not shown any neurocognitive adverse effects associated with treatment; however, more research is clearly needed to confirm this.

Conclusion

Much progress is being made in the search for TRD treatments that can match or exceed the antidepressant efficacy of ECT and ablative surgeries while minimizing adverse neurocognitive effects. Evaluation of cognitive safety has therefore been and continues to be an important component of this effort. As development of these and other therapies moves forward, careful, comprehensive assessment of neurocognitive outcomes should continue – especially for more invasive approaches (such as DBS) where potential benefit must be weighed very carefully against possible adverse effects. Specific to DBS – where multiple potential targets exist – comprehensive neuropsychological assessment insures that comparable data will be obtained across studies.

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Figure 1.
Timeline of Major Milestones for Established and Emerging Neuromodulation Techniques. DBS=deep brain stimulation, ECT=electroconvulsive therapy, FDA= United States Food and Drug Administration, MST=magnetic seizure therapy, OCD=Obsessive Compulsive Disorder, rTMS=repetitive transcranial magnetic stimulation, tDCS=transcranial direct current stimulation, VNS=vagus nerve stimulation

Table 1

Neurocognitive Effects of Established and Emerging Neuromodulation Techniques

Neuromodulation Technique	Neurocognitive Effects
Electroconvulsive Therapy	Retrograde amnesia, anterograde amnesia, postictal disorientation
Ablative Surgery	
Anterior Capsulotomy	Possible impairment in emotion recognition, set shifting, verbal fluency, and working memory
Anterior Cingulotomy	Mixed reports, with some studies showing impairments in executive functioning, and others reporting improvements in executive functioning
Stereotactic Subcaudate Tractotomy	Possible transient wide spread frontal impairment (potentially associated with post-operative edema)
Limbic Leucotomy	No neurocognitive impairment on the WAIS; possible improvements in WAIS Verbal, Performance, and Full Scale IQ Scores (potentially associated with practice effects)
Repetitive Transcranial Magnetic Stimulation	Mixed reports, with most studies reporting no impairments, but some studies finding mild reductions in sustained attention, spatial planning, and verbal retention; possible improvements in global cognitive awareness, manual motor speed, simple reaction time, verbal learning, attention, processing speed, verbal fluency, autobiographical memory, visual learning, working memory, and executive functioning
Magnetic Seizure Therapy	Minimal retrograde amnesia, minimal anterograde amnesia, rapid postictal reorientation
Transcranial Direct Current Stimulation	No neurocognitive impairment in psychomotor speed, working memory, attention, recognition memory, or executive functioning; possible improvement in working memory
Vagus Nerve Stimulation	No neurocognitive impairment in attention, psychomotor speed, verbal fluency, memory, or executive functioning; possible improvement in psychomotor speed, language, and executive functioning (potentially associated with mood improvement)
Deep Brain Stimulation	
Subcallosal cingulate white matter (SCCwm)	No neurocognitive impairment in verbal IQ, attention, psychomotor speed, risk taking, memory, or executive functioning; possible improvement in verbal and visual memory, manual motor speed, and verbal learning in patients performing below average at baseline (not apparently associated with mood improvement)
Ventral capsule/ventral striatum (VC/VS)	No neurocognitive impairment in general intellectual ability, language, processing speed, executive functioning, learning, or memory; possible improvement in verbal learning (not apparently associated with mood improvement)
Nucleus Accumbens (NAc)	No neurocognitive impairment in general intellectual ability, language, processing speed, executive functioning, learning, or memory
Inferior thalamic peduncle (ITP)	No changes in visual attention, visuoconstructive perception, verbal fluency or abstraction; possible improvements in manual praxis and verbal/nonverbal memory
Lateral Habenula (LHb)	No data available