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NEUROPSYCHOLOGICAL FUNCTION BEFORE AND AFTER SUBCALLOSAL CINGULATE DEEP BRAIN STIMULATION IN PATIENTS WITH TREATMENT-RESISTANT DEPRESSION

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Abstract

Background—Treatment-resistant depression (TRD) is a pervasive and difficult to treat condition for which deep brain stimulation (DBS) of the subcallosal cingulate white matter (SCCwm) is an emerging therapeutic option. However, neuropsychological safety data for this novel treatment have only been published for a small number of subjects. Moreover, little is known regarding the neuropsychological profile present in TRD patients at baseline, prior to initiation of DBS therapy. This report describes the neuropsychological effects of TRD and acute and chronic DBS of the SCCwm in patients with unipolar and bipolar TRD.

Methods—Patients with TRD (N =17) were compared to a healthy control group (N = 15) on subtests from the Cambridge Neuropsychological Test Automated Battery and the Stroop Task. Patients were then tested again at subsequent time points of 1 and 6 months following the initiation of chronic DBS of the SCCwm.

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Dr. Kelley has nothing to disclose.

Results—Patients with TRD showed similar levels of performance to healthy controls on most neuropsychological measures, with the exception that the TRD group had slower processing speed. Patients with bipolar TRD, relative to those with unipolar TRD, obtained lower scores on measures of executive function and memory only at baseline. With acute and chronic SCCwm DBS, neuropsychological function improved in multiple domains including processing speed and executive function (planning, set shifting, response inhibition), and memory remained stable.

Conclusions—Patients with TRD show slowed processing speed but otherwise largely preserved neuropsychological functioning. DBS of the SCCwm does not result in worsening of any aspect of neuropsychological function and may improve certain domains. Future research is warranted to better understand the effects of TRD and DBS on neuropsychological function.

Keywords

deep brain stimulation; neuropsychology; subcallosal cingulate; treatment-resistant depression

INTRODUCTION

Major depressive disorder (MDD) is common and often does not respond to multiple-treatment strategies including psychotherapy, pharmacotherapy, and electroconvulsive therapy (ECT)[1–5] As such, treatment-resistant depression (TRD) is a pervasive and debilitating disorder resulting in significant morbidity and mortality.[6] An emerging treatment for TRD is deep brain stimulation (DBS).[7–10]

Multiple studies have reported the efficacy of DBS applied to the subcallosal cingulate white matter (SCCwm).[8, 11, 12] Holtzheimer et al. (2012) described effects of SCCwm DBS in 17 patients with treatment-resistant unipolar or bipolar II depression. After 6 months of active stimulation, three patients achieved remission and seven showed meaningful clinical response (i.e., 50% reduction in symptom severity). With 2 years of chronic stimulation, 58% of patients remitted, and 92% responded. No mania was observed, and patients achieving remission remained well over time.

Neurocognitive safety is an important component of treatment development, especially as other invasive neurosurgical procedures (i.e., ablation) for TRD have resulted in adverse neuropsychological effects.[13, 14] Mc-Neely et al. (2008) studied six patients (efficacy data reported in Mayberg et al. 2005) who received SCCwm DBS and found that treatment resulted in no adverse neuropsychological effects. Importantly, patients showed improved performance relative to impaired baseline neuropsychological function (e.g., verbal learning, object alternation).

DBS at various targets has been associated with cognitive changes. Specifically, there have been differential findings in Parkinson disease with most studies suggesting that neuropsychological performance remains unchanged[15] or improves across time with DBS (applied to the subthalamic nucleus), though one study reported a decrease in phonemic fluency.[16] Decreased verbal fluency secondary to DBS (applied to the anterior limb of the internal capsule) was also reported in a study to treat obsessive compulsive disorder.[17] Interestingly, a recent investigation[18, 19] found that DBS applied to the fornix improved

performance in global cognitive function and memory for patients with Alzheimer's disease. Thus, questions remain regarding the neuropsychological effects of DBS at these various targets.

To date, no study has specifically reported on the baseline neuropsychological profile of individuals with TRD. This is a limitation with prior DBS investigations. MDD has been shown to be associated with inefficient neuropsychological processing speed, variable learning and memory, and poor executive function.[20, 21] Yet, it is unclear whether TRD patients exhibit a similar or divergent neuropsychological profile and whether impairments change with antidepressant treatment.

This study aimed to assess neuropsychological effects of SCCwm DBS in patients with TRD. Specifically, we sought to (1) characterize neuropsychological performance of a homogenous cohort of TRD patients compared with a healthy control group, (2) determine if neuropsychological performance changed with SCCwm DBS, and (3) assess if change in neuropsychological performance was associated with change in depressive state.

METHODS

STUDY OVERVIEW

This study was part of an investigation assessing safety and efficacy of SCCwm DBS for unipolar and bipolar II TRD.[12] Patients underwent a single-blind sham 4-weeks lead-in period, followed by 24-weeks of open-label stimulation. Patients then entered a naturalistic follow-up phase extending up to 2 years of active stimulation. The primary outcome was reduction in depression severity after 24 weeks of open-label stimulation. Written informed consent was obtained from each participant.[22] This study was approved by the Emory University Institutional Review Board.

PARTICIPANTS

Controls—The healthy control (HC) group consisted of 15 age-and gender-matched healthy volunteers who were recruited via advertisements and referral sources. Participants were excluded if they had a history of neuropsychiatric illness based on the Structured Clinical Interview for DSM-IV diagnoses[23] Additional exclusion criteria included a Mini Mental State Examination[24] score ≤ 27 to rule out global cognitive impairment, and a Beck Depression Inventory II score ≥ 13.[25]

Patients—The TRD group consisted of 17 patients with severe unipolar (UP; $N = 10$) or bipolar II (BP; $N = 7$) TRD who were enrolled in a clinical trial that explored the safety, efficacy, and potential mechanisms of DBS of the SCCwm as a treatment for TRD.[12] Patients were recruited by self- or provider-referral from the international community—no paid advertising was used. Inclusion criteria consisted of a current major depressive episode ≥2 years duration. Treatment resistance was defined as no response to a minimum of four antidepressant treatments (i.e., medications, evidenced-based psychotherapy), and lifetime failure or intolerance to an adequate course of ECT. Baseline 17-item Hamilton Rating Scale for Depression ($HRSD_{17}$)[26] score ≥ 20 and Global Assessment of Function[27] score ≤ 50 was required. Patients were excluded if they had a comorbid medical or psychiatric disorder

that was clinically significant and impacted the presence or severity of their mood disorder.[12]

Fifteen of the 17 patients were currently taking psychotropic medications, including antidepressants (N =13) plus at least one augmentation strategy (N = 11). Both of the patients taking no medications had UP TRD. Of the seven BP TRD patients, four were taking mood stabilizers. Current medication dosage remained fixed for the four weeks prior to baseline assessment and throughout the 4-week sham lead-in period and 6-months of active DBS. Thus, medication dosage was stable across the three neuropsychological testing time points. No new treatments or medication dose changes were allowed from four weeks prior to surgery until six months of active DBS.

DEEP BRAIN STIMULATION

The DBS surgery and treatment protocol are described in Holtzheimer et al., 2012. Briefly, following a 1-month lead-in period of sham stimulation, DBS was delivered continuously at 130 Hz, 91 μs pulse width, and 6–8 mA current applied to the SCCwm (see Fig. 1). The stimulator remained on during neuropsychological testing.

NEUROPSYCHOLOGICAL TESTING

Neuropsychological testing occurred in a distraction free room in the Woodruff Memorial Research Building of Emory University. Computer-based tests were administered on a Dell Latitude D520 laptop computer (Dell, Inc., Round Rock, TX) using the Cambridge Neuropsychological Test Automated Battery (CANTAB) Eclipse standard administration software (version 3.0; Cambridge Cognition Ltd., Bottisham, Cambridge, UK). Participants responded to task cues using either the software's included press pad or an accessory Magic Touch transparent touchscreen (Keytec, Inc., Garland, TX) that was placed over the laptop screen. Trained and certified research personnel administered the neuropsychological battery. Prior to each subtest, the experimenter provided the respective standard test instructions and ensured that participants understood the test requirements. HC subjects completed the neuropsychological battery only at baseline, whereas patients completed the battery at baseline and follow-up time points after 1 and 6 months of active DBS. Time of day was not prospectively controlled for across the three testing time points; however, a chi-square analysis revealed no significant difference in number of morning versus afternoon test administrations between time points (X^2 (2, N = 49) = 3.3 0; P = . 19). For the healthy participants only, we provided monetary compensation ($50) for completion of the neuropsychological battery.

The neuropsychological battery included the Stroop task and subtests from the CANTAB (Cambridge Cognition Ltd., Bottisham, Cambridge, UK): Affective Go/No-Go, Cambridge Gambling Task, Graded Naming Test, Intra/Extra Dimensional Set Shift, Stockings of Cambridge, Verbal Recognition Memory. The North American Adult Reading Test was used to estimate intelligence quotient (IQ).

The CANTAB is a widely used and well-validated computer-based standardized neuropsychological battery,[28] which is sensitive to depression, and assesses cognitive

functions relevant to SCCwm neural circuitry.[29] The subtests used were selected because they are sensitive to dysfunction of brain regions identified as particularly vulnerable to disruption by SCCwm DBS based on white matter connectivity analyses suggesting strong connections between those regions and the SCCwm,[30, 31] The following provides a brief description of the respective subtests and proposed neuroanatomical mediators:

Affective Go/No-Go—The Affective Go/No-Go (AGN) test measures psychomotor speed to affective cues and involves activity of the dorsal anterior cingulate.[32] The participant is shown a series of rapidly appearing words on a computer screen and is instructed to respond as quickly as possible when the current word is the target emotional valence (e.g., happy, sad) and to ignore words of other valence (distracters).

Cambridge Gambling Task—The Cambridge Gambling Task (CGT) measures aspects of risk taking and is sensitive to dysfunction of the orbitofrontal cortex. Participants are shown a row of 10 boxes on the screen, some red and some blue in varying proportions, and informed that one unspecified box contains a yellow token. The subject must guess whether the token is hidden under a red or blue box, and then bet a portion of their current point total based on confidence in their decision. The test is designed to discern impulsiveness from impatience in the context of risk taking.

Graded Naming Test—The Graded Naming Test (GNT) measures confrontation naming by asking participants to name objects depicted in a series of line drawings. This test has been used to screen for early signs of dementia.[33]

Intra/Extra-Dimensional Set Shift—The Intra/Extra-Dimensional Set Shift (IED) test assesses set shifting and involves function of the dorsolateral prefrontal cortex (DLPFC), similar to the Wisconsin Card Sorting Test.[34] Participants must learn through trial and error the rules to identify correct stimuli among presented shapes. After several sequential correct identifications, the computer shifts to a new set of stimuli; the process iterates several times.

Stockings of Cambridge—The Stockings of Cambridge (SOC) test measures spatial planning and involves the DLPFC and caudate.[35] The subject matches a row of colored balls to the display arrangement, using the minimum number of moves possible (ranging from 2 to 5). Subjects are instructed to plan out their spatial sequence before moving the balls.

Verbal Recognition Memory—The Verbal Recognition Memory (VRM) task measures verbal episodic memory, a domain that correlates with hippocampal atrophy in elderly samples.[36] The subject is instructed to remember a series of words presented sequentially. Free recall and recognition are then assessed.

Stroop Color-Word Task—The Stroop Color Word task[37] has been well validated and relies on performance of the anterior and dorsal cingulate.[38] The first (word) and second (color) conditions of the test measure verbal processing speed, whereas the third condition (color– word) assesses response inhibition.

DATA ANALYSIS

Data analysis was performed using the Statistical Package for Social Sciences Version 18 (SPSS, Chicago, IL). Demographic and neuropsychological data were compared between the HC and TRD groups using *t*-tests, with nonparametric tests used as indicated by the data. Longitudinal data were analyzed using available-case linear mixed modeling for each measure of interest, with time as an independent factor. Customized hypothesis tests of model parameters were used to test for changes over time and differences between UP and BP TRD patients at each time point. To determine if depression severity confounded neuropsychological performance over time, HRSD17 was added as a covariate. To account for the large number of analyses performed, a more stringent threshold of $P < 0.01$ was used to assess for statistical significance. Results with $0.01 < P < 0.05$ are reported as trends.

RESULTS

SOCIODEMOGRAPHIC AND CLINICAL CHARACTERISTICS

Table 1 shows the sociodemographic and clinical characteristics of HC and TRD cohorts; no significant differences were found between groups on sociodemographic variables. As expected, the TRD group showed higher depression severity, more impaired global functional capacity, and resistance to multiple antidepressant treatments. Patients with BP relative to UP TRD showed a shorter duration of current depressive episode ($t(9.5) = 3.7$, $P = .005$).

BASELINE PERFORMANCE ON NEUROPSYCHOLOGICAL MEASURES

Processing Speed—Relative to the HC cohort, the TRD group showed a trend toward poorer performance on the Stroop task Conditions 1 (word; $t(30) = -2.48$, $P = .02$) and 2 (color; $t(30) = -1.93$, $P = .06$). Also, the TRD group was markedly slower to identify both positive ($t(30) = 4.9$, $P < .001$) and negative ($t(30) = 3.6$, $P = .001$) emotional valence targets on the AGN. However, both groups showed similar response inhibition (omissions and commissions) on the AGN (see Table 2).

Executive Function—The HC and TRD cohorts showed similar levels of performance on the Stroop task Condition 3 (color–word; ($t(30) = -1.83$, $P = .08$). Moreover, both groups showed equivalent performance on the SOC, IED, and CGT tasks (see Table 2).

Confrontation Naming and Memory—The HC and TRD cohorts identified an equal number of exemplars on the GNT (see Table 2). Additionally, the two groups recalled or recognized a similar number of words on the VRM test (see Table 2).

PERFORMANCE ON NEUROPSYCHOLOGICAL MEASURES AFTER DEEP BRAIN STIMULATION

Processing Speed—After 1 month of DBS, a trend toward improved performance was observed for Condition 2 (color) of the Stroop Task ($Z = -2.2$, $P = .04$), and after 6 months performance improved significantly on Condition 1 (word) ($Z = -3.5$, $P = .002$). No changes were observed in the AGN response latencies for positive or negative words (see

Table 2). However, the number of omissions of positive words did show a trend decrease after six months of DBS ($Z = 2.5$, $P = .02$).

Executive Function—A trend increase in the number of correctly solved SOC problems was observed at 1 month ($Z = -2.5$, $P = .02$), which became significant at 6 months ($Z = 2.7$, $P = .01$). A corresponding significant improvement was observed in subsequent thinking time ($Z = 3.3$, $P = .003$). Total adjusted errors on the IED showed a trend decrease by 6 months ($Z = 2.5$, $P = .02$). This may have been due to a decrease in errors committed prior to the extra-dimensional shift (EDS) stage ($Z = 1.7$, $P = .09$). The number of IED stages completed also showed a near-trend improvement at the 6-month time point ($Z = -1.9$, $P = .06$). Response inhibition (Stroop Condition 3) showed a trend improvement at 1-month ($Z = -2.3$, $P = .03$), which became significant by the 6-month time point ($Z = 3.4$, $P = .002$). Risk adjustment and deliberation time on the CGT showed trend improvement at six-months ($Z = 2.4$, $P = .02$ and $Z = 2.3$, $P = .03$, respectively). Overall risk taking and proportion bet did not change, nor did delay aversion (see Table 3).

Memory—In TRD patients, the number of correct words recalled on the VRM showed no change from baseline to 1 month, but performance improved between 1 and 6 months ($Z = -2.6$, $P = .01$). Number of correct items recognized on the VRM was consistent across the three testing time points, and the number of false-positive (incorrect) recognitions trended toward a decrease at 1 month ($Z = 2.1$, $P = .04$), but was not maintained at 6 months ($Z = 1.5$, $P > .10$).

ASSOCIATION BETWEEN CHANGES IN MOOD AND NEUROPSYCHOLOGICAL FUNCTION

In the mixed model analyses, statistical differences remained when the HRSD17 was included as a covariate. This suggested no association between change in depression severity and change in neuropsychological function across time.

DIFFERENCES BETWEEN UNIPOLAR AND BIPOLAR PATIENTS

At baseline, patients with BP relative to those with UP obtained lower scores on measures of executive function and verbal memory. Specifically, BP patients had a trend toward longer deliberation time ($Z = 2.0$, $P = .05$) on the GCT, and completed fewer stages ($Z = -2.8$, $P = .007$) and committed more errors (adjusted for number of stages completed; $Z = 3.1$, $P = .003$) particularly on the stages prior to the extra-dimensional set shift ($Z = 2.5$, $P = .02$) of the IED. Further, BP patients showed a trend toward fewer words recalled ($Z = -2.0$, $P = .05$) and more false-positive recognition errors ($Z = 2.6$, $P = .01$) on the VRM. At follow-up time points, BP patients performed comparably to UP patients on all measures with the exception of a trend toward making more total errors on the IED (unadjusted) at 1 month ($Z = 2.2$, $P = .04$).

DISCUSSION

This study systematically examined neuropsychological function in patients with TRD (compared to healthy controls), and assessed change in neuropsychological function over time with SCCwm DBS. Patients with TRD and healthy controls showed similar levels of

performance on most neuropsychological measures, with the exception that the TRD group had slower processing speed. Regarding effects of DBS to the SCCwm, neuropsychological functioning in multiple domains including processing speed, executive function (planning, set shifting, response inhibition), and memory remained stable or slightly improved with stimulation. The change in neuropsychological performance over time appeared unrelated to change in depression severity.

Our finding that patients with TRD showed no significant cognitive impairments beyond poor processing speed was in contrast to prior investigations that suggested depression is associated with widespread neuropsychological impairments including poor attention, memory, and executive dysfunction.[39–42] Not all studies though suggest that depression is necessarily associated with neuropsychological impairment.[43–45] One potential reason for the limited impairment observed in our TRD cohort could be the nature of the neuropsychological battery performed. Our battery was designed to include tests sensitive to dysfunction in regions connected to the SCCwm, rather than tests previously reported to be impaired in MDD per se. Moreover, pure measures of certain fundamental cognitive domains such as attention and working memory were not included. Another factor due to the small cohort is statistical power. While sample size of this study was small, it is consistent with that of other DBS studies of depression. Importantly, a strength of this sample was the homogeneous composition in terms of illness characteristics, chronicity of disorder, and limited comorbidities. This may explain the inconsistent findings compared with studies of heterogeneous[46] or acute[47] samples. Furthermore, most patients in the study had extensive exposure (past and present) to many psychotropic medications and ECT. The neuropsychological effects of medication in our sample are unclear and could have contributed to worse performance (e.g., slowed processing speed),[48, 49] or to better performance (e.g., preserved function in other neuropsychological domains).[50, 51] Thus, due to all of these factors, the present data preclude definitive conclusions regarding the relationship between TRD and neuropsychological function. A more comprehensive neuropsychological battery performed in larger cohorts is therefore needed to fully characterize the neuropsychological phenotype of TRD, as well as any relationship with comorbid conditions or medication exposure.

The more severe baseline impairment in executive function and memory observed in patients with BP relative to UP is consistent with a large body of literature that investigated the differential neuropsychological impact of these distinct mood disorders.[52] Although the effect of diagnosis was not the primary aim of this study, it is notable that differences in neuropsychological function were present, but became less significant following DBS. The emergence of a greater number of EDS errors on the IED in the BP patients at one month may be related to lower completion of the EDS stages at the baseline assessment in BP patients. Thus, BP patients may have had less opportunity to benefit from practice effects resulting from repeated exposure to later task stages.

This study provides evidence, consistent with prior research,[29] that neuropsychological function remains stable or may improve with SCCwm DBS in patients with TRD. Additionally, this study both replicates and expands on the initial findings of McNeely et al. (2008), who used a neuropsychological battery comprised of tasks sensitive to the frontal

lobes and showed that SCCwm DBS caused no brain dysfunction. Here, we show safety in tasks mediated by both frontal and more distal cortical regions with clear strong connections to the SCCwm. Evidence of preserved and/or improved neuropsychological function is also in line with other investigations of DBS for the treatment of TRD, albeit at other cortical sites including the nucleus accumbens[53] and ventral capsule/ventral striatum.[7] As DBS is an invasive neurosurgical procedure, it is critical that detailed neuropsychological safety be assessed in future studies. For instance, increased risk taking (e.g., gambling) is a potential side effect of DBS of the basal ganglia for movement disorders.[47] Our study found no disinhibition or impulsivity as a result of DBS, rather the trend improvements seen on the CGT (increased "risk adjustment" and decreased "deliberation time") suggest an increased willingness to engage in and more efficient processing of the task.

The most notable improvements found in this study were in the domain of processing speed measured on the Stroop task Conditions 1 and 2. Interestingly, however, there was no change in response speed on the AGN. One possible explanation is that the latter task required a motoric response. Many of the patients experienced mild-to-moderate residual depressive symptoms, including psychomotor retardation at the 6-month testing time point, which may have contributed to a slowed motoric response.

Some of the improvements observed in the TRD cohort were in neuropsychological abilities that were intact at baseline. The most prominent of these was executive function as assessed by the SOC and IED tests. Importantly, there are no alternate forms available for the SOC. Similarly, although multiple forms exist for the IED, the fundamental strategy learned during first exposure to the task remains consistent across subsequent administrations. These two strategy-based tests are thus highly susceptible to practice effects. Because the comparison group in our study did not undergo testing at subsequent time points, we are unable to rule out the possibility of practice effects contributing to the results observed.[54]

Practice effects are a major concern whenever a test–retest design is employed.[55] However, we took steps to mitigate this confound. Following McNeely et al. (2008), we spaced the assessment time points such that a small portion of the active DBS stimulation period occurred between assessment time points one and two, where we expected the impact of practice effects to be greatest.[56] Many significant results did not emerge until the 6-month time point, and thus are unlikely to be due primarily to practice effects because of the large interval (5 months) between follow-up assessments.

Another consideration is the impact of time of day of testing,[57] which was not prospectively controlled across time points. However, the proportion of morning versus afternoon test administrations remained consistent over time, suggesting that changes in neuropsychological function were unrelated to variation in test administration time.

CONCLUSION

In summary, this study found that patients with severe TRD have relatively few neuropsychological impairments compared to healthy controls. Further, it was demonstrated that neuropsychological function in TRD patients either remained stable or improved with

acute and chronic SCCwm DBS. Future work will include a comprehensive neuropsychological battery to improve sensitivity to detect abnormalities specific to TRD, as well as better inform the effects of SCCwm DBS on neuropsychological function.

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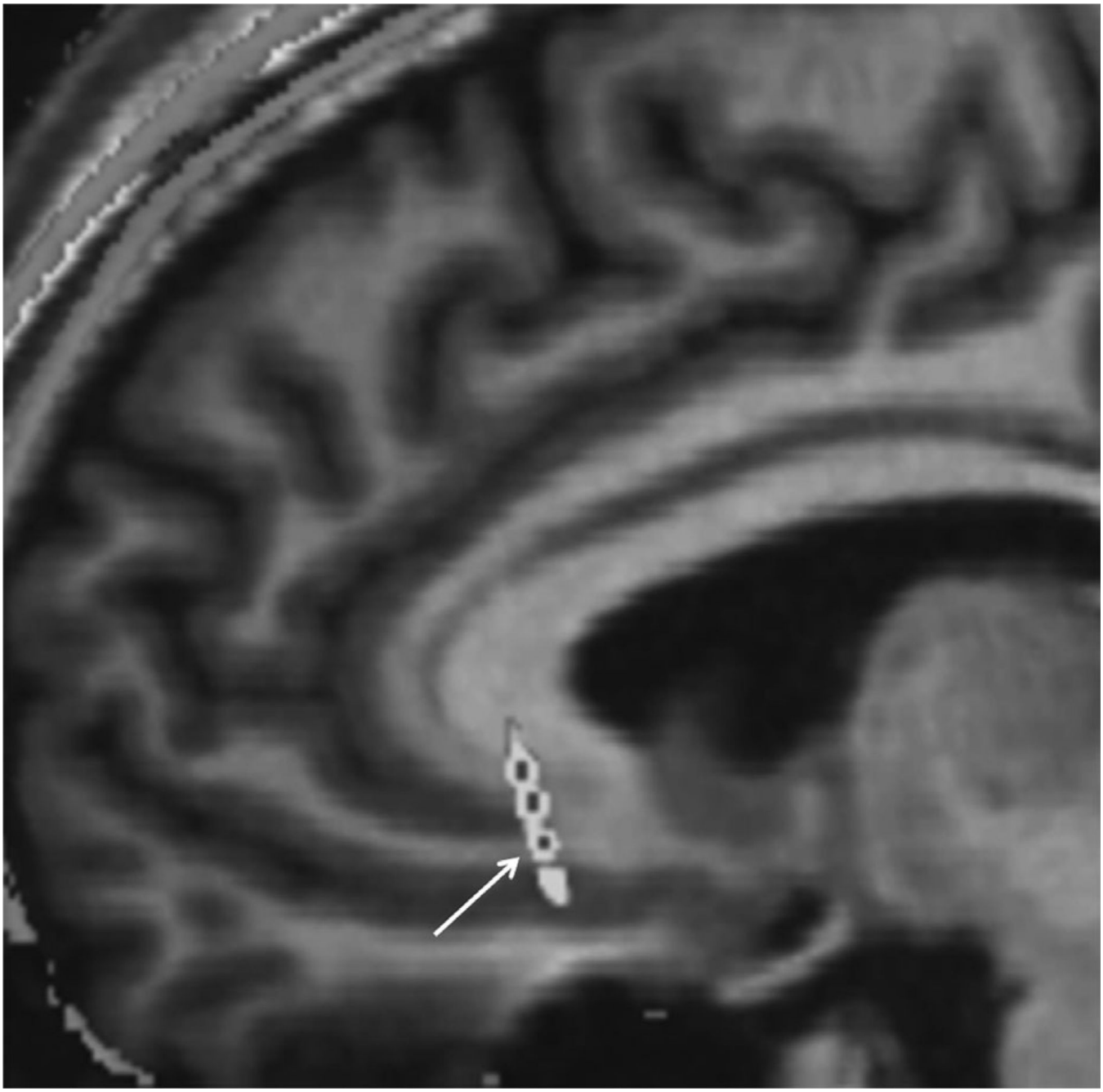

Figure 1.
Subcallosal cingulate white matter deep brain stimulation target. Sagittal view of a representative single patient's preoperative MRI scan coregistered with the post-operative high-resolution computed tomography scan used to visualize electrode lead placement. Arrow indicates the active contact in this patient. Stimulation was delivered at 130 Hz, with a 91 μs pulse width, and 6–8 mA current.

TABLE 1

Demographic and clinical characteristics of the study sample

	TRD	HC
Group N (M, F)	17(7,10)	15 (9, 6)
Age	42.0(8.9)	36.0(10.7)
Years of Education	16.4(2.9)	17.3 (2.2)
NAART FSIQ	113.4(5.9)	112.1(6.1)
Test-Day BDI-H	37.7(11.3)	0.8 (1.4)*
Baseline 17-Item HDRS	23.8(3.2)	-
Age of illness onset	18.6(8.2)	-
Total number of depressive episodes	7.0 (9.2)	-
Duration of present episode (weeks)	280.0(238.6)	-
Duration of illness (years)	23.3(10.8)	-
Lifetime suicide attempts	1.7(3.0)	-
Total mood related hospitalizations	5.2 (5.5)	-

* $P \leq .001$.

BDI-II: Beck Depression Inventory II, HC: Healthy Controls, HDRS: Hamilton Depression Rating Scale, NAART FSIQ: North American Adult Reading Test Full Scale Intelligence Quotient, TRD: Treatment-Resistant Depression.

TABLE 2

Neuropsychological test results of healthy controls and patients with treatment-resistant depression

	HC	TRD baseline	TRD 1-month DBS	TRD 6-months DBS
Affective Go/No-Go (AGN)				
Mean correct latency–positive (ms)	466.1 (52.8)	586.1 (80.1)**	598.2 (103.8)	578.3 (89.8)
Mean correct latency–negative (ms)	487.8 (60.8)	582.6 (82.8)**	585.7(91.5)	575.1 (91.6)
Total commissions–positive	3.1 (2.5)	3.1(3.2)	2.9(2.9)	2.7(2.7)
Total commissions–negative	2.9(3.1)	2.4(2.9)	2.1(2.7)	1.8(3.3)
Total omissions–positive	1.1(1.2)	1.8(2.4)	1.4(1.5)	0.5 (0.6)#
Total omissions–negative	1.1 (1.4)	1.6(1.5)	1.1(1.2)	1.0(1.0)
Cambridge gambling task (CGT)				
Quality of decision making	0.95 (0.09)	0.93 (0.13)	0.93 (0.12)	0.96 (0.08)
Deliberation time (s)	2.265 (0.859)	3.023 (2.571)	2.510(1.231)	2.114(0.651)#
Risk taking	0.59(0.13)	0.49(0.17)	0.51(0.14)	0.51(0.12)
Risk adjustment	1.7(1.2)	1.6(0.80)	1.6(1.1)	2.0(1.2)#
Delay aversion	0.24 (0.09)	0.18(0.15)	0.2 (0.19)	0.22 (0.18)
Overall proportion bet	0.54(0.14)	0.46(0.17)	0.48(0.14)	0.47(0.11)
Graded naming test (GNT)				
Percent correct	65.1 (12.4)	59.6 (9.5)	-	-
Intra/Extra dimensional shift task (IED)				
Pre-ED errors	8.7 (7.3)	13.8(15.0)	8.2 (3.8)	8.6 (5.3)
EDS errors	6.7(9.1)	3.9(7.2)	4.9 (6.7)	3.9(6.8)
Total errors	18.3(13.5)	21.2(16.3)	16.1(12.4)	13.7(9.1)##
Total errors adjusted	20.0(17.0)	37.4(50.9)	17.7(15.5)	15.3 (14.4)#
Stages completed	8.8 (0.6)	8.1 (2.0)	8.8 (0.54)	8.9 (0.5)
Stockings of Cambridge (SOC)				
Problems solved in minimum moves	9.3 (2.0)	8.1 (2.2)	9.4(2.0)#	9.6(1.5)##
Mean initial thinking time (5-move problems) (s)	11.632(6.419)	15.782 (13.244)	17.062 (16.507)	15.653 (14.852)
Mean subsequent thinking time (5-move problems) (s)	2.263 (4.063)	2.631(3.090)	1.327(1.284)	0.648(1.017)##
Verbal recognition memory (VRM)				
Free recall–total correct (immediate)	8.9 (2.0)	7.6(2.4)	7.4(2.2)	8.8 (2.0)#
Free recall-total novel words (immediate)	0.0 (0.0)	0.24(0.56)	0.31(0.60)	0.19(0.40)
Recognition–total correct (immediate)	23.3(1.5)	22.6(1.2)	22.9(1.2)	23.3(1.1)
Recognition–total false positives (immediate)	0.13(0.35)	0.53 (1.0)	0.06(0.25)#	0.19(0.40)
Stroop task				
Word *t*-score	46.1 (6.6)	39.5 (8.2)*	40.2(11.7)	49.4 (7.8)##
Color *t*-score	47.7 (8.0)	41.2 (10.5)	44.4(11.9)#	52.6(10.1)###
Color-word *t*-score	49.5 (6.9)	43.6(10.6)	50.9 (14.9)#	55.0(15.9)##

Means and (Standard Deviations) presented.

$^{*}P \leq .05$ versus HC,

$^{**}P \leq .001$ versus HC,

$^{\#}P \leq .05$ versus TRD Baseline,

$^{\#\#}P \leq .01$ versus TRD Baseline,

$^{\#\#\#}P \leq .001$ versus TRD Baseline,

DBS: Deep Brain Stimulation, HC: Healthy Controls, TRD: Treatment-Resistant Depression.

TABLE 3

Effect of diagnosis on neuropsychological test results following deep brain stimulation

	Baseline		1-month DBS		6-months DBS	
	UP	**BP**	**UP**	**BP**	**UP**	**BP**
Affective Go/No-Go (AGN)						
Mean correct latency—positive (ms)	592.0(97.8)	577.6(51.2)	576.0 (89.3)	635.0(124.0)	563.2 (75.8)	629.9(124.5)
Mean correct latency—negative (ms)	570.1 (83.8)	600.6 (84.4)	568.4(77.0)	614.7(113.3)	562.4(67.6)	630.7(147.5)
Total commissions—positive	2.5 (2.2)	4.2 (4.5)	2.4(2.2)	3.7(3.8)	2.0(0.9)	3.7(3.8)
Total commissions—negative	1.6(1.6)	3.8(4.2)	1.8(1.4)	2.6(4.1)	1.1(1.4)	3.0 (4.7)
Total omissions—positive	2.3 (2.9)	1.1(1.3)	1.2 (1.6)	1.7(1.5)	0.5 (0.7)	0.9(1.1)
Total omissions—negative	1.8(1.5)	1.3 (1.4)	0.9(1.3)	1.5(1.0)	0.9 (0.9)	1.4(1.4)
Cambridge gambling task (CGT)						
Quality of decision making	0.95 (0.12)	0.91 (0.16)	0.94(0.10)	0.91 (0.14)	0.96 (0.09)	0.95 (0.08)
Deliberation time (s)	2.345 (0.653)	3.993 (3.889)*	2.126(0.535)	3.085 (1.787)	1.969(0.383)	2.532 (0.980)
Risk taking	0.49(0.16)	0.49(0.19)	0.52 (0.14)	0.51(0.16)	0.52(0.10)	0.52 (0.15)
Risk adjustment	1.8(0.7)	1.2 (0.8)	1.7(1.2)	1.4(0.8)	2.3 (1.4)	1.7 (0.8)
Delay aversion	0.17(0.14)	0.19(0.18)	0.24(0.20)	0.15(0.18)	0.22(0.19)	0.23 (0.16)
Overall proportion bet	0.46(0.16)	0.47(0.19)	0.49(0.14)	0.46(0.14)	0.48(0.10)	0.48(0.14)
Graded naming test (GNT)						
Percent correct	59.7(5.3)	59.5 (14.1)	-	-	-	-
Intra/Extra dimensional shift task (IED)						
Pre-ED errors	9.3 (6.7)	21.2(22.1)*	7.6(2.5)	9.0 (5.4)	7.0 (2.7)	13.0(8.4)
EDS errors	5.1 (8.9)	1.8(1.9)	2.3(1.5)	8.7 (9.3)	1.8(1.4)	7.1(9.7)
Total errors	16.1 (9.6)	28.4(21.5)*	11.1(3.6)	24.5(17.4)*	10.0 (3.6)	21.3(12.0)
Total errors adjusted	18.6(16.3)	64.1 (71.3)**	11.1(3.6)	28.7(21.5)	10.0 (3.6)	24.9(19.5)
Stages completed	8.8 (0.6)	7.1 (2.9)**	9.0 (0.0)	8.5 (0.8)	9.0 (0.0)	8.7 (0.8)
Stockings of Cambridge (SOC)						
Problems solved in minimum moves	8.2 (2.1)	8.0(2.5)	9.6(2.4)	9.0(1.3)	10.0(1.7)	8.1(2.0)
Mean initial thinking time	17.544(13.432)	13.263(13.582)	20.030 (20.576)	12.114(2.897)	15.771 (15.497)	14.467 (14.070)

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	Baseline		1-month DBS		6-months DBS	
	UP	**BP**	**UP**	**BP**	**UP**	**BP**
(*5*-move problems) (s)						
Mean subsequent thinking time (*5*-move problems) (s)	2.592 (2.832)	2.686(3.664)	1.284(1.267)	1.400(1.428)	0.937(1.210)	0.571 (1.080)
Verbal recognition memory (VRM)						
Free recall-total correct (immediate)	8.5(2.1)	6.3 (2.4)*	7.8(2.7)	6.7 (0.8)	8.7 (2.2)	8.3 (2.5)
Free recall-total novel words (immediate)	0.3 (0.7)	0.1 (0.4)	0.3 (0.5)	0.3 (0.8)	0.3 (0.5)	0.0 (0.0)
Recognition-total correct (immediate)	22.9(1.2)	22.3(1.3)	22.9(1.3)	23.0(1.1)	23.0(1.2)	23.4(1.1)
Recognition-total false positives (immediate)	0.2 (0.4)	1.0(1.4)**	0.1 (0.3)	0.0 (0.0)	0.2 (0.4)	0.1(0.4)
Stroop task						
Word *t*-score	40.0 (6.7)	38.7(10.5)	43.1 (10.5)	36.4(12.8)	50.9(5.5)	42.4(15.3)
Color *t*-score	44.2 (9.5)	37.0(11.1)	46.4(10.5)	41.7(13.7)	54.9 (9.0)	44.3 (16.0)
Color-word *t*-score	46.2 (10.0)	40.0(11.3)	52.3 (10.5)	49.0 (20.5)	59.3 (17.7)	47.1(9.2)

Mean and (Standard Deviation) presented.

*$P \leq .05$ versus UP at same time point,

**$P \leq 0.01$ versus UP at same time point.

BP: Bipolar Depressed, UP: Unipolar Depressed.