SHORT REPORT

Cognitive outcome after ventral capsule/ventral striatum stimulation for treatment-resistant major depression


ABSTRACT

Background We report the neuropsychological outcome of 25 patients with treatment-resistant major depressive disorder (TRD) who participated in an Institutional Review Board (IRB)-approved randomised double-blind trial comparing active to sham deep brain stimulation (DBS) in the anterior limb of the ventral capsule/ventral striatum (VC/VS).

Methods Participants were randomised to active (n=12) versus sham (n=13) DBS for 16 weeks. Data were analysed at the individual and group levels. Group differences were analysed using repeated measures ANOVAs. Relationships between depression severity and cognition were examined using partial correlations. The false discovery rate method controlled for multiple analyses.

Results No significant interactions comparing active versus sham stimulation over time were evident. Change in depression was unrelated to change in neuropsychological measures. Twenty patients declined by ≥1 SD on at least one measure (41.3% of declines occurred in active group participants; 63.0% in older participants regardless of stimulation status). Twenty-two patients exhibited improvements >1 SD on neuropsychological measures (47.7% in the active group; 63.1% in younger participants).

Conclusions These data suggest that VC/VS DBS in patients with TRD does not significantly affect neuropsychological function. Age at surgery, regardless of stimulation status, may be related to cognitive outcome at the individual patient level.

Trial registration number NCT00837486; Results.

INTRODUCTION

Early treatment-resistant major depressive disorder (TRD) deep brain stimulation (DBS) open-label studies yielded promising results with respect to psychiatric outcome with no indications of significant cognitive morbidity. Indeed, the data suggested that cognitive improvements occur irrespective of changes in depression.\textsuperscript{4,5} Subsequently, a randomised double-blind controlled trial was initiated comparing active to sham stimulation at the VC/VS target. No significant differences in response rates on the Montgomery-Asberg Depression Rating Scale (MADRS) were evident between the active and sham groups following the 16-week controlled phase. We report the neuropsychological outcomes in this trial examining DBS in the VC/VS for the treatment of TRD.

METHODS AND MATERIALS

Participants

Inclusion/exclusion criteria, demographic and baseline psychiatric data are reported in the primary manuscript.\textsuperscript{7} Four of the original 30 participants required removal of their DBS system before postoperative neuropsychological testing (infection, n=3; incorrect lead placement, n=1). New devices were later implanted. Nonetheless, these data were excluded due to potential neuropsychological risks following additional neurosurgery/anaesthesia and longer test–retest intervals. One other participant was noncompliant with the protocol requirements; consequently, our study included 25 participants.

Measures

Participants completed neuropsychological testing before implantation and after 16 weeks of active or sham stimulation. The protocol emphasised executive cognitive, attention and memory abilities given their association with depression,\textsuperscript{8} prior TRD DBS reports\textsuperscript{6,8} and the functional neuroanatomy of the VC/VS region.\textsuperscript{9} General intellectual abilities were also assessed. The same versions of the tests were administered at both time points. Baseline assessments occurred within 1 month prior to implantation, and the blinded phase of the study started ~4 weeks after surgery. The average test–retest interval was 22 weeks.

Surgical technique and stimulation parameters

The surgical target was the ventral striatum and the ventral aspect of the anterior limb of the internal capsule. Specifics regarding bilateral electrode placement and stimulation parameters are reported elsewhere.\textsuperscript{7} Stimulation parameters and medications were unchanged throughout the 16-week blinded phase.

Data analyses

Group differences on demographic and disease variables were examined using Wilcoxon’s or Fisher’s exact statistics. Repeated measures ANOVAs were used to examine the
neuropsychological data with the group×time interaction effects being the primary statistics of interest. The effect of stimulation on general cognitive function was evaluated using full-scale IQ with an α level of 0.05. The false discovery rate (FDR) procedure controlled for multiple comparisons. Relationships between the MADRS and neuropsychological tests were examined using Spearman’s partial rank-order ρ.

Neuropsychological change scores were computed for every participant. Clinically significant changes were defined as change scores >1 SD per normative data. Fisher’s exact statistic was used to examine differences between the groups in the number of clinically significant change scores.

Post hoc analyses examined the role of age at the time of surgery given preliminary review of the data, and Parkinson’s disease DBS reports identifying age as a risk factor for decline. The sample was divided based on median age into younger (<50 years, n = 12) and older (>50 years, n = 13) groups.

RESULTS
The mean scores on all of the cognitive measures were within the average range, per normative data. Participants were similarly represented in the two stimulation groups (active = 12, sham = 13). There were no significant group differences on demographic or disease variables (mean age: active = 47.1 ±14.0, sham = 49.9 ±8.4; %male: active = 41.7%, sham = 69.2%; % college graduates: active = 58.3%, sham = 53.8%; baseline MADRS: active = 38.1 ±4.8, sham = 36.5 ±3.4; pos-top MADRS: active = 29.5 ±13.7, sham = 29.1 ±8.7). The only difference between the two age groups was a higher rate of self-reported cardiovascular disease risk factors in the older group (p = 0.047).

There was no significant interaction effect of stimulation status over time on full-scale IQ (F(1,23) =0.2, p =0.66). Only one of the remaining interactions had a p value of <0.05, which did not meet the FDR criteria for significance. Thus, participants’ scores did not differ significantly as a function of stimulation status over time (all Fs ≤6.0, p values ≥0.02) (Table 1). A large effect size was evident on a test assessing mental flexibility and response inhibition; the active group declined, whereas the sham groups’ scores improved slightly. None of the correlations examining the relationships between change in depression severity and change in neuropsychological measures were significant per FDR (all |r| <0.50, p >0.02).

Twenty participants exhibited a decline on ≥1 of the neuropsychological measures. Forty-six declines (7.5% of the total possible measures) were evident (41.3% of those declines involved participants in the active group vs 58.7% in the sham group; 63.0% in the older group vs 37.0% in the younger group). Twenty-two participants demonstrated an improvement on ≥1 of the neuropsychological measures for a total of 65 improvements (47.7% in the active group vs 52.3% in sham group; 63.1% in the younger group vs 36.9% in the older group). A greater number of older patients declined on a story memory test following DBS, whereas several younger patients demonstrated improvements (p =0.05). This was the only group comparison with a p value of <0.05 but was not significant as per the FDR.

Individual declines were observed most frequently on tests assessing category word fluency (n =4), category switching fluency (n =3), processing speed and mental flexibility (n =5), delayed recall of visual designs (n =5) and delayed recall of a word list (n =4). Individual improvements were more common on tests examining visual working memory (n =5), immediate recall of short stories (n =4), recognition memory for faces (immediate n =7, delayed n =6), visual design learning (n =5), decision-making (n =5) and perseverative responses (n =5).

The analyses were repeated including the four participants who were originally excluded; the results were unchanged.

DISCUSSION
The few studies that examined neuropsychological outcome following DBS for TRD involved open-label studies with different targets. Except for one study showing transient motor slowing early after DBS in Area 25 (n =6), all other studies reported improvements in processing speed, memory or executive cognitive abilities (Area 25, n =17, 8 nucleus accumbens, n =10; VC/VS n =21 mixed group of TRD and OCD). The cognitive improvements were unrelated to improvements in psychiatric symptoms.

We compared neuropsychological outcome in 25 participants who had 16 weeks of either active or sham stimulation of the VC/VS region for TRD. Our data failed to reveal significant differences in neuropsychological outcome based on stimulation status. Review of the associated effect sizes revealed a large effect size for a measure assessing mental flexibility and response inhibition. This finding was reported in the primary outcome paper as part of the preliminary neuropsychological analyses. In that publication, we questioned the clinical significance of this finding due to Type I error concerns, particularly since the absolute magnitude of the change was relatively small. The individual change scores from this test revealed that only two

### Table 1
<table>
<thead>
<tr>
<th>Test</th>
<th>F</th>
<th>df</th>
<th>p Value</th>
<th>d</th>
</tr>
</thead>
<tbody>
<tr>
<td>WASI full-scale IQ</td>
<td>0.20</td>
<td>1, 23</td>
<td>0.66</td>
<td>0.19</td>
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<tr>
<td>WMS-III: digit span</td>
<td>0.03</td>
<td>1, 23</td>
<td>0.85</td>
<td>0.07</td>
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<tr>
<td>WMS-III: letter number sequencing</td>
<td>0.44</td>
<td>1, 23</td>
<td>0.51</td>
<td>0.28</td>
</tr>
<tr>
<td>WMS-III: spatial span</td>
<td>2.30</td>
<td>1, 23</td>
<td>0.14</td>
<td>0.63*</td>
</tr>
<tr>
<td>WMS-III: logical memory, immediate recall</td>
<td>0.27</td>
<td>1, 23</td>
<td>0.61</td>
<td>0.22</td>
</tr>
<tr>
<td>WMS-III: logical memory, delayed recall</td>
<td>0.47</td>
<td>1, 23</td>
<td>0.50</td>
<td>0.29</td>
</tr>
<tr>
<td>WMS-III: faces memory, immediate memory</td>
<td>2.60</td>
<td>1, 23</td>
<td>0.12</td>
<td>0.67*</td>
</tr>
<tr>
<td>WMS-III: faces memory, delayed memory</td>
<td>2.23</td>
<td>1, 23</td>
<td>0.15</td>
<td>0.62*</td>
</tr>
<tr>
<td>WAIS-III: processing speed index</td>
<td>0.44</td>
<td>1, 21</td>
<td>0.51</td>
<td>0.29</td>
</tr>
<tr>
<td>BVRT, total recall</td>
<td>0.17</td>
<td>1, 22</td>
<td>0.69</td>
<td>0.18</td>
</tr>
<tr>
<td>BVRT, delayed recall</td>
<td>0.01</td>
<td>1, 22</td>
<td>0.93</td>
<td>0.04</td>
</tr>
<tr>
<td>DKEFS, letter fluency</td>
<td>0.18</td>
<td>1, 23</td>
<td>0.67</td>
<td>0.18</td>
</tr>
<tr>
<td>DKEFS, category fluency</td>
<td>0.20</td>
<td>1, 23</td>
<td>0.66</td>
<td>0.19</td>
</tr>
<tr>
<td>DKEFS, category fluency switch correct</td>
<td>1.43</td>
<td>1, 23</td>
<td>0.24</td>
<td>0.50*</td>
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<tr>
<td>DKEFS, category fluency switch accuracy</td>
<td>1.75</td>
<td>1, 23</td>
<td>0.20</td>
<td>0.55*</td>
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<td>DKEFS, trials number letter</td>
<td>0.15</td>
<td>1, 23</td>
<td>0.70</td>
<td>0.16</td>
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<tr>
<td>DKEFS, colour word inhibition</td>
<td>0.06</td>
<td>1, 21</td>
<td>0.81</td>
<td>0.11</td>
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<tr>
<td>DKEFS, colour word inhibition switching</td>
<td>6.00</td>
<td>1, 21</td>
<td>0.02</td>
<td>1.07*</td>
</tr>
<tr>
<td>Iowa gambling test, net total</td>
<td>0.01</td>
<td>1, 22</td>
<td>0.93</td>
<td>0.04</td>
</tr>
<tr>
<td>WCST, perseverative responses</td>
<td>0.18</td>
<td>1, 22</td>
<td>0.68</td>
<td>0.18</td>
</tr>
<tr>
<td>CVLT, total learning</td>
<td>0.90</td>
<td>1, 23</td>
<td>0.35</td>
<td>0.40</td>
</tr>
<tr>
<td>CVLT, short-delay free recall</td>
<td>2.22</td>
<td>1, 23</td>
<td>0.15</td>
<td>0.62*</td>
</tr>
<tr>
<td>CVLT, long-delay free recall</td>
<td>0.53</td>
<td>1, 23</td>
<td>0.47</td>
<td>0.30</td>
</tr>
</tbody>
</table>

F, p and d values for the interaction effects. *Large effect size (d>0.8).BVMT, brief visual memory test; CVLT, California verbal learning test; DKEFS, Delis–Kaplan executive function system; WAIS-III, Wechsler adult intelligence scale, third edition; WASI, Wechsler abbreviated intelligence scale; WCST, Wisconsin card-sorting test; WMS-III, Wechsler memory scale, third edition.
participants’ scores declined (both in the active group, one older) and one participant’s score improved (sham group, younger). These data suggest that relatively few changes were evident at the individual level on this measure, further raising questions regarding clinical meaningfulness.

Similar to previous studies, our data suggest that changes in depression severity and neuropsychological function are unrelated following DBS. Although cognitive and mood symptoms are common in depression, there is a considerable amount of variance that is not shared which might explain these results.13–14

All of the available findings suggest that there is little cognitive morbidity at the group level associated with DBS for TRD. Unlike the open-label studies, we did not observe significant improvements on cognitive measures at the group level following stimulation. This discrepancy may reflect differences in anatomical targets, stimulation parameters, study design or patient characteristics.

Our data suggest that older age (>50 years) was more often associated with decline in neuropsychological measures, whereas improvements were more frequent in younger participants regardless of stimulation. It is most likely that the observed improvements reflect practice effects. The proportion of participants who declined was roughly equal in the active and sham groups suggesting that other aspects of the DBS procedure shared by both groups (eg, lead placement, microlesion effects, anaesthesia) may have contributed to a greater number of older patients showing declines on neuropsychological measures with significant mental flexibility, word fluency or memory demands. Given the relatively short test–retest intervals, it is highly unlikely that this observation reflects normal ageing. The observed age differences may have been associated with self-reported cardiovascular disease factors. This observation requires replication in light of our small sample, imprecise assessment of cardiovascular risk, and relationship between age and cardiovascular disease. We caution against using age in and of itself as an exclusion criterion for future DBS trials in TRD. We suspect that age is a marker for some other variable (eg, reduced brain reserve) potentially associated with greater risk of cognitive decline.

Given the small sample size, it is critical that our observations are replicated. Previous open-label TRD DBS studies have documented benefits following longer follow-up intervals that were not apparent in the short term. Consequently, future studies should include long-term follow-up assessments to evaluate potential benefits and risks to psychiatric symptoms and cognition. We encourage future investigators to include consideration of clinically meaningful individual changes in their data analyses. Such detailed studies may reveal important patient characteristics that help elucidate potential risks and benefits related to TRD and DBS in the VC/VS region.

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Contributors CSK involved in literature search, hypothesis generation, study design, data collection, data analysis, data interpretation and writing and figures. TB involved in data analysis, data interpretation, writing and figures. MAB, TD, PM, PMo, and AIT participated in literature search, hypothesis generation, study design, data collection, data analysis, data interpretation and writing. EW participated in writing and figures. GHB, MTB, LLC, DDD, RHH, ARR and DAM participated in data collection and writing.

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Competing interests This study was funded by Medtronic. CSK has received research funding from NIH and has a patent issued (US 8 538 536) for methods of improving neuropsychological function in a patient having a neurocognitive disorder by chemical or electrically modulating a target site(s) in the ventral striatum/ventral capsule (VS/VC) region. TB is an employee and shareholder of Medtronic. TD research has been funded by NIH, NIMH, NARSAD, TSA, IOCDF, Tufts University, DBDAT, Otsuka Pharmaceuticals and Cogito; he has received honoraria, consultation fees and/or royalties from the MGH Psychiatry Academy, BrainCells, Clintara, LLC, Systems Research and Applications Corporation, Boston University, the Catalan Agency for Health Technology Assessment and Research, the National Association of Social Workers Massachusetts, the Massachusetts Medical Society, Tufts University, NIDA, NIH and Oxford University Press; he has also participated in research funded by DARPA, NIH, NIMH, AIA, ARHQ, PCORI, Janssen Pharmaceuticals, The Forest Research Institute, Shire Development, Medtronic, Cyberonics, NorthStar and Takeda. AIT reports the following disclosures: Consultant/Advisory Boards: Medtronic, St Jude Medical, Boston Scientific, Teva, Theravance, Pfizer, Takeda; and Grants/Stipends from: Michael J Fox Foundation, Barrow Neurological Foundation; Royalties: Oxford University Press. EW is an employee and shareholder of Medtronic. MTB reports research support from Medtronic, Cyberonics, Neosync, Asta Zenergan, and Janssen. LLC discloses research support from Neuronetics, Cervel and Neosyn; she serves as a consultant to Mag Stim. DDD reports research support and honoraria from Medtronic, research support from Cyberonics, research support and travel expenses from Roche, and honoraria from Insys and Johnson and Johnson. RHH reports research support from Medtronic, Neosync, Otsuka, Janssen and NIMH. ARR reports Ownership equity, Consultant and Board of Directors of Autonomic Technologies; and Issued patent (US 8 538 536) for methods of improving neuropsychological function in a patient having a neurocognitive disorder by chemical or electrically modulating a target site(s) in the VS/VC region. DAM reports research funding from Medtronic and NIH.

Ethics approval All study sites’ IRB committees approved this study.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement There is data sharing across the study sites with Medtronic serving as a central repository. A Publications Committee permits release of data as justified. Additional unpublished data are limited to long-term outcome data examining psychiatric and neuropsychological function.

REFERENCES
|---|---|
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