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Lack of neuropsychological effects following short-term subcallosal cingulate gyrus deep brain stimulation in treatment-resistant depression: a randomised crossover study

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ABSTRACT

Background The subcallosal cingulate gyrus (SCG) is integral to cognitive function and mood regulation. Open-label SCG deep brain stimulation (DBS) studies demonstrate improvement or stabilisation of cognitive function in treatment-resistant depression (TRD).

Objective This randomised controlled study aims to evaluate the neuropsychological effects of SCG-DBS.

Methods 35 participants with TRD received active or sham stimulation over two 3-month periods. A neuropsychological battery was administered to assess processing speed, learning and memory, and cognitive flexibility. Composite measures were derived for each domain after Period I. A mixed model for repeated measures analysis was performed for each test, with further analysis of significant measures to determine sustainability after Period II.

Findings No significant differences in changes in depression scores were observed between groups. There were no significant deteriorations in cognitive performance following active SCG-DBS. Category Fluency Test performance improved after 3 months of active SCG-DBS (p=0.002); however, this was non-significant after correcting for multiple comparisons and was not observed after Period II (p=0.615).

Conclusion and implications While no cognitive deterioration was observed following SCG-DBS, significant improvements in cognitive function were not evident. There may be a transient enhancement in processing speed; however, this effect is not fully understood. Future studies should include larger cohorts and extended stimulation periods to explore the long-term effects of SCG-DBS in TRD and the sustainability of improvements in cognitive domains.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The subcallosal cingulate gyrus (SCG) is the most widely used target for deep brain stimulation (DBS) in treatment-resistant depression (TRD). SCG-DBS is generally well tolerated, with no adverse effects on neuropsychological function and improvements in multiple cognitive skills; however, this result is limited by open-label designs and small sample sizes.

WHAT THIS STUDY ADDS

⇒ Our randomised, sham-controlled, double-blind crossover trial reveals that, over a 3-month period, SCG-DBS does not significantly change measures of cognitive performance compared with sham treatment.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study provides evidence that SCG-DBS does not change cognitive function in the short term. Results support the need for further investigation into the long-term cognitive effects of SCG-DBS in TRD.

BACKGROUND

Finding effective treatments for major depressive disorder (MDD) remains a challenge, with one-third of patients not showing an adequate therapeutic response to conventional treatment methods. Several cognitive processes contribute to the development, maintenance and recurrence of depression and might be associated with the emotional aspects of the disorder.[1] Improvement in cognitive functioning and depressive symptoms plays a crucial role in the treatment outcomes for MDD, due to their associations with psychosocial functioning. Many studies have shown that cognitive dysfunction is a powerful predictor of functional impairments in MDD and presents a significant challenge in treating treatment-resistant depression (TRD).[1]

Deep brain stimulation (DBS) represents one neuromodulation technique with reports of effectiveness stemming from open-label clinical trials and case-control studies for TRD.[2] Although both short-term and long-term DBS have effectively alleviated the symptoms of negative mood and affect,[3] findings concerning the neuropsychological effects of DBS remain inconsistent.[4] For instance, Malone *et al*[5] reported no significant improvement in cognitive

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functioning after ventral striatum-DBS. In contrast, McNeely *et al*[6] reported a slight cognitive improvement following subgenual cingulate gyrus-DBS, although psychomotor retardation was also present. Moreover, Grubert *et al*[7] reported significant improvement on tests of attention, learning and memory, executive function, and visual perception following nucleus accumbens-DBS, with no adverse effects on neuropsychological functioning. A review of studies published prior to 2013,[8] based largely on open-label designs and small samples, concluded that DBS did not negatively impact cognitive functioning. Some studies indicated enhancement following treatment, which appeared to be independent of the improvement in mood, suggesting distinct impacts of DBS on mood and cognition.[7] A more recent systematic review and meta-analysis,[9] with a few studies including sham conditions, found no evidence of cognitive change with up to 6 months of DBS but some improvements in memory, attention/processing speed and executive functioning after 6–18 months. Thus, questions remain regarding the specific effects of DBS on various neuropsychological domains.

The subcallosal cingulate gyrus (SCG)—a critical modulator of cognitive and emotional network hubs—is the most widely used target for DBS in TRD.[10] Patients with TRD show elevated activity in the SCG.[11] Targeting the SCG by DBS (SCG-DBS) appears to improve cognitive functioning in multiple domains, including processing speed[12] and executive function[12 13] and has demonstrated a stabilising effect on memory.[12] SCG-DBS seems to be well tolerated by patients with TRD who typically experience no adverse effects on neuropsychological function.[4] In addition, improvements have been reported in general cognitive function, verbal learning, object alternation[6] and memory[4 14] following SCG-DBS in TRD. Bogod *et al*[14] conducted the first known set of multiyear follow-ups to assess the long-term effects of SCG-DBS in TRD. They monitored neuropsychological function up to 42 months after the surgery and showed general stability and improvement in cognitive abilities over time, specifically in short-term memory deficits, paraphrasing errors of speech and word-finding difficulties. Further investigation is needed to justify whether these results are independent of practice effects.

Despite the fact that previous studies have assessed the effects of SCG-DBS on neuropsychological functioning in TRD, the data have been acquired using uncontrolled or open-label designs.[4] Due to the complexity of the DBS procedure, controlled studies are still in great need to elucidate whether the neuropsychological effects of DBS are indeed attributed to active stimulation and not placebo-nocebo effects.[2]

OBJECTIVE

This study is a retrospective secondary analysis of a historical dataset from a randomised, sham-controlled, double-blind crossover trial that was conducted in 2010–2017 (ClinicalTrials.gov identifier: NCT01801319) where participants were treated with active SCG-DBS (On) or sham (Off) stimulation over two 3-month periods (ie, On-Off, On-On, Off-On or Off-Off). This secondary analysis aimed to compare (1) the cognitive performance of patients with TRD who received active versus sham SCG-DBS after 3 months of intervention according to their Period I allocation: On versus Off and (2) the cognitive performance of patients with TRD after 6 months of intervention to determine whether a significant treatment effect could be sustained beyond 3 months in treatment groups (ie, On-On, On-Off, Off-On and Off-Off).

METHODS

Participants

The study enrolled 39 adult Diagnostic and Statistical Manual of Mental Disorders Text Revision Fourth Edition (DSM-IV-TR)-diagnosed participants with MDD experiencing a major depressive episode (MDE) for at least 12 months at intake and with resistance to a minimum of four adequate antidepressant treatments from at least three different categories. Additionally, participants had to have a score of ≥3 on the Antidepressant Treatment History Form amended criteria to meet the treatment resistance cut-off. Enrolled participants had moderate-to-severe depression, with a 17-item Hamilton Depression Rating Scale (HDRS-17) score of >20 as determined from three separate baseline visits, with no improvement of ≥25% between visits. Participants were required to remain on a stable antidepressant medication regimen for at least 4 weeks before surgery and throughout the trial. Participants were excluded if they had a diagnosis of bipolarity, psychotic disorders or current MDE with psychotic features; obsessive-compulsive disorder, post-traumatic stress disorder, panic disorder, bulimia or anorexia nervosa active within the past 6 months; borderline or antisocial personality disorders or substance use disorder active within the past 12 months or substantial suicide risk. Participants were also excluded if diagnosed with any central nervous system disease impairing cognitive, motor or sensory function. The full eligibility criteria are provided in online supplemental table 1). Recruitment began in July 2010 and was completed by March 2017.

This study is a secondary analysis of data from a larger trial approved by the University Health Network's Research Ethics Board (Protocol Number: 08–0110-B). The original aim was to enrol 40 participants to achieve 80% power for the primary outcome. However, recruitment was concluded at 39 participants due to challenges in securing the final participant within the study's funding and timeline constraints. For the current analysis, data from 35 participants who completed at least 3 months of DBS were included. The sample size for this secondary analysis was not specifically calculated to detect non-superiority or to assess subtle group differences.

Design overview

Using a computer-generated randomisation sequence code, participants were randomised to one of four treatment sequences (ie, On-Off, On-On, Off-On or Off-Off). For the first 3 months (ie, Period I), participants were treated with either active SCG-DBS or sham stimulation. The crossover occurred at the end of the first 3-month period, and participants were subsequently treated for an additional 3 months (ie, Period II) with either active SCG-DBS or sham stimulation, according to their allocation (online supplemental figure 1). Block randomisation with a block size of four was used to ensure balanced allocation to the four treatment sequences. The treatment phase started 14 days postimplantation when all participants were assessed by a blinded attending psychiatrist. Patients in both groups received equivalent evaluations. The primary clinical outcome was the HDRS-17 administered at three baseline visits prior to device implantation, weekly in the first month of each period and biweekly for the following 2 months of each treatment period (Kennedy *et al* in ACNP[15]). Participants completed a battery of neuropsychological measures at the second baseline visit, the end of Period I and the end of Period II. Written informed consent was obtained from each participant.

Experimental procedure

Psychiatric assessment and neurosurgical procedures took place at the University Health Network's Toronto Western Hospital and Toronto General Hospital.

The DBS system consists of an Implantable Pulse Generator (IPG) designed to be connected to four or eight electrode leads and extensions. The IPG receives radio frequency programming signals using the external programmer and delivers stimulation pulses to a selected combination of output electrodes on the lead. The first 31 participants received a St Jude Medical/Abbott Libra device, while the last four received a Medtronic Activa device; the two devices provided similar stimulation.[16] Using MRI guidance, DBS electrodes were implanted in SCG white matter (Cg25WM) under local anaesthesia. After the implantation of DBS electrodes, short-term stimulation effects were used to confirm the placement of the eight DBS electrodes within the Cg25WM bilaterally as targeted. Participants were discharged from the hospital with stimulation Off.

All DBS-related procedures, including device programming, initialisation of DBS stimulation, adjustments and fine-tuning of stimulation settings, were conducted by the unblinded psychiatrist, who was not involved in the evaluation of clinical outcomes. Adjustments to chronic DBS stimulation were made based on four possibilities involving two pairs of contacts (the mid- and low-level pairs) and two levels of electrical current (3.5 mA and 5 mA). The response to stimulation was recorded at each setting, with the patient blinded to the stimulator settings or changes. The changes in electrode contact selection and the electrical current levels were made according to improvements in the HDRS-17.

At the start of the study (week 0), DBS stimulation was initiated using the mid pairs of contact closest to the target, with the current set to 3.5 mA. If the HDRS-17 did not improve by at least 20% from baseline at weeks 2 and 4, the current would be raised by 1.5 mA. Changes in settings were not made during the subsequent 4-week period. If at week 8, the HDRS-17 improvement remained below 20%, the current would be increased by 1.5 mA or a second pair of contacts could be added to the initial pair, maintaining the same current if two increases had already been made. No further changes in settings were made for the next 4 weeks. The Off group received 0.0 mA for the duration of the study. A postoperative follow-up visit occurred approximately 2 weeks after implantation for wound care, including suture removal and wound evaluation.

Clinical and neuropsychological measures

Depression severity was assessed with the HDRS-17. The battery of neuropsychological tests took approximately 2.5 hours to complete, with brief breaks between tasks. The complete neuropsychological battery included the Wechsler Adult Reading Test, the two-element Wechsler Abbreviated Scale of Intelligence, five subtests of the Delis-Kaplan Executive Function System (D-KEFS) battery (including Category Fluency, Letter Fluency, Category Switching Accuracy, and Trail-Making Tests A and B), the California Verbal Learning Test-II (CVLT-II), the Cambridge Neuropsychological Test Automated Battery Delayed Match to Sample, the Working Memory Reward Task, the Grooved Pegboard Test (GPT) and the Iowa Gambling Test (IGT).

The current report selected specific tests from the battery to assess three cognitive domains of interest in line with those used in previous research,[17] including processing speed, learning and memory and cognitive flexibility. Although many tasks assess multiple domains, as is typical with standardised measures, the alignment of the tasks to the three domains was based on clinical neuropsychological literature. As such, the tests for evaluating processing speed consisted of the GPT (dominant hand) and the Category Fluency and Trail-Making Test-A from the D-KEFS battery. The learning and memory domain in this study consisted of six measures from the CVLT-II related to immediate recall, delayed recall and total recognition discriminability. The cognitive flexibility domain consisted of measures from the Verbal Fluency subtests, including Letter Fluency and Category Switching Accuracy, of the D-KEFS, Trail-making Test B from the D-KEFS and the IGT. In addition to the individual measures, three composite measures of performance were derived by taking the average of the individual test scores within each cognitive domain (ie, processing speed, learning and memory and cognitive flexibility).

Statistical analysis

Participants' scores from the aforementioned neuropsychological measures were transformed into z-scores using age- and sex-matched normative data to derive population-normed domain scores for processing speed, learning and memory, and cognitive flexibility. These normed test scores were used in all analyses, with higher scores reflecting better cognitive performance. Baseline characteristics and cognitive performance were summarised and compared between the On and Off groups using t-tests and χ^2/Fisher's tests. HDRS-17 scores were averaged across the three baseline visits for each participant. The differences in total HDRS-17 scores between Period I and baseline, as well as between Period II and baseline, were calculated. A one-way analysis of variance was applied to test for differences among the groups, followed by Tukey's honestly significant difference test for pairwise comparisons.

To examine differences in cognitive performance after the first 3 months of SCG-DBS, participants were categorised into two groups according to their allocation during Period I: On (ie, On-On and On-Off) versus Off (ie, Off-On and Off-Off). Mixed Model Repeated Measures (MMRM) were conducted with each neuropsychological test score as the dependent variable. A time (categorical) × treatment group interaction term was included to examine whether the On and Off groups differed in their change in test scores over time. The baseline test score was included as the covariate. For each MMRM, there were three planned comparisons that examined treatment group differences in (1) mean test scores at baseline, (2) mean test scores at 3 months and (3) mean change in test scores after 3 months (interaction). All MMRMs allowed for the intercept to vary randomly between participants. Multiple testing within each cognitive domain was corrected using Benjamini-Hochberg's False Discovery Rate (FDR) method.[18]

Follow-up analyses for the neuropsychological measures that showed a significant difference between the On and Off groups at 3 months further examined whether these differences would hold by conducting within-group comparisons in the treatment periods; specifically, baseline versus 3 months for the On-Off group, 3 months versus 6 months for the Off-On group and baseline versus 3 months/6 months for the On-On group. All within-group comparisons were conducted using paired t-tests. In addition, between-group t-test comparisons were performed by comparing the test scores of the On-On and Off-Off groups at 6 months to assess whether a significant treatment effect could be sustained beyond 3 months.

Table 1 Baseline sociodemographic and clinical characteristics

	Total sample (n=35)	DBS On during Period I (n=18)	DBS Off during Period I (n=17)	P value (On vs Off)
Age, mean (SD)	45.0 (9.3)	45.7 (10.6)	44.2 (8.0)	0.631*
Sex, male (%)	13 (37.1)	8 (44.4)	5 (29.4)	0.569†
Education (years), mean (SD)	20.9 (7.4)	21.8 (7.6)	20.06 (7.3)	0.495*
MDE duration (months), mean (SD)	79.6 (65.0)	93.6 (81.3)	64.8 (39.0)	0.195*
Total number of MDEs, mean (SD)	5.6 (4.9)	4.8 (3.8)	6.5 (5.8)	0.309*
HDRS-17, mean (SD)	25.6 (2.2)	25.4 (1.9)	25.8 (2.5)	0.578‡
Marital status (%)				0.154‡
Divorced	3 (8.6)	3 (16.7)	0 (0.00)	
Married	15 (42.9)	5 (27.8)	10 (58.8)	
Separated	3 (8.6)	2 (11.1)	1 (5.9)	
Single	14 (40.0)	8 (44.4)	6 (35.3)	

Off refers to sham stimulation group. On refers to active subcallosal cingulate gyrus DBS group. Period I refers to first 3 months.
*χ^2 test.
†Fisher's exact test.
‡Independent t-test.
DBS, deep brain stimulation; HDRS-17, Hamilton Depression Rating Scale, 17-item; MDE, major depressive episode.

Missing data were accounted for using an available case analysis. Sensitivity analysis provided similar results after removing extreme observations using the IQR method (1.5 IQR below and above the first and third quartiles). All analyses were conducted at a 0.05 significance level using R software.

FINDINGS

Clinical outcomes

35 participants who received DBS for at least 3 months were included in the current analysis (Online supplemental figure 2). After grouping participants according to their Period I allocation, there were 18 and 17 participants in the active (On) and sham (Off) groups, respectively. 31 participants completed the neuropsychological protocol. Scores for individual tests were missing for four participants (online supplemental material).

The mean age of the sample was 45 (SD=9.3), and 62.9% of participants were female. There were no significant differences in baseline characteristics between the On and Off groups (table 1). Average performances on 15 of 16 cognitive measures were within normal limits (ie, 1 SD from normative mean values) at baseline, indicating the sample was not substantially impaired from a neuropsychological perspective.

The mean HDRS-17 total score at baseline was 25.6 (SD=2.2). At the end of Period I, the change in HDRS-17 total scores did not significantly differ between the On (mean change (SD)=−7.7 (5.1)) and Off (mean change (SD)=−9.5 (7.4)) groups (p=0.388). Similarly, by the end of Period II, the change in HDRS-17 total scores did not significantly differ between the Off-Off (mean change (SD)=−13.6 (9.8)) and the On-On (mean change (SD)=−7.9 (7.8); p=0.411), On-Off (mean change (SD)=−6 (7); p=0.207) or Off-On (mean change (SD)=−10.5 (6.1); p=0.857) groups.

Cognitive performance after 3 months of SCG-DBS

For the composite measures of performance, there were no significant treatment group differences at baseline and 3 months, and there were no significant time-by-treatment group interactions for any domain (p>0.050; figure 1 and Online supplemental tables 2 and 3). For the Category Fluency Test, the On group increased, whereas the Off group decreased in score over 3 months (time×treatment group, p=0.032; figure 2 and online supplemental table 3), although the interaction was non-significant after correcting for multiple comparisons (FDR-P=0.097; Online supplemental table 3). However, participants in the On group performed significantly better on the Category Fluency Test than the Off group at 3 months (p=0.002, FDR-P=0.005; Online supplemental table 2). Performance on other tests in the processing speed domain, as well as on individual tests in the learning and memory and cognitive flexibility domains,

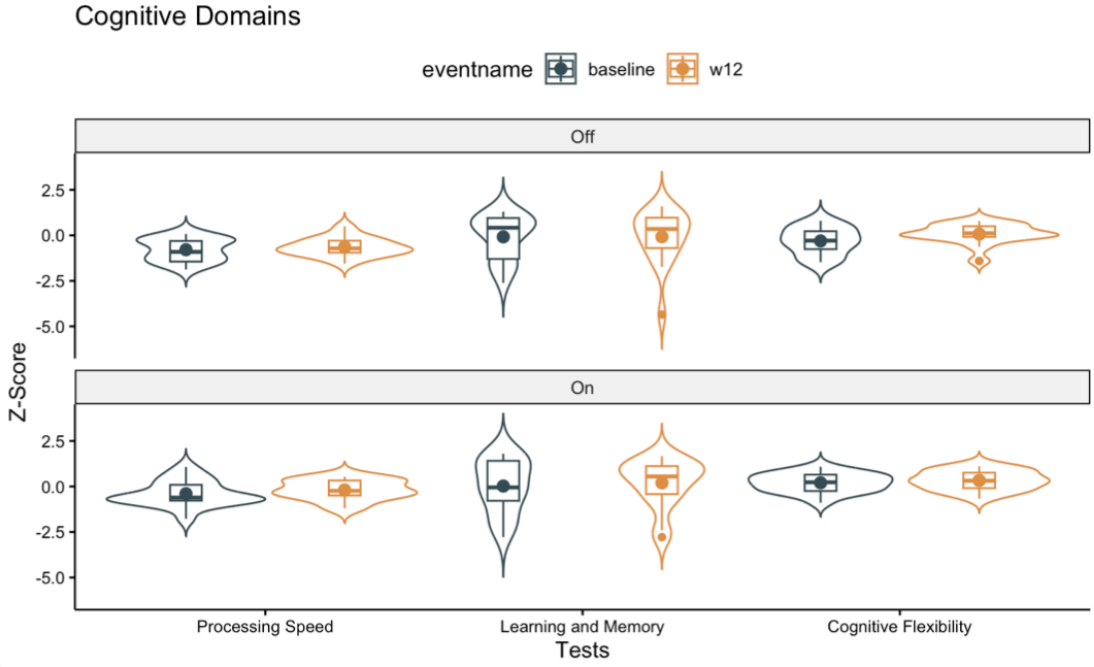

Figure 1 Baseline and 3-month mean test scores for the cognitive domains. Note. The bar represents CIs. Domain scores are obtained by averaging the z-score across individual tests within each domain. W12, week 12.

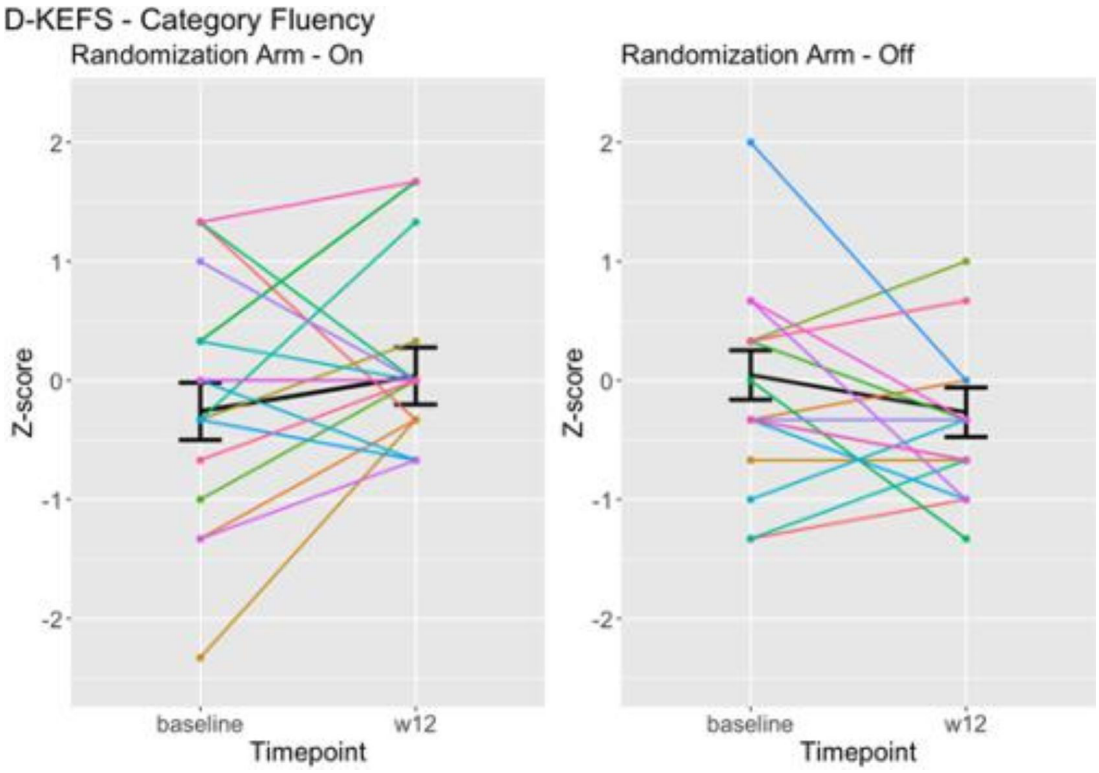

Figure 2 Baseline and 3-month mean D-KEFS Category Fluency Test scores. Note. The bolded black line represents the mean Z-score. The bar represents CIs. Coloured lines represent individual changes in z-score, with each colour indicating a unique participant. D-KEFS, Delis-Kaplan Executive Function System; W12, week 12.

remained stable over time in both groups (online supplemental figure 3 and Online supplemental table 2).

Within- and between-group comparisons after 3 and 6 months of SCG-DBS

For the follow-up analyses related to the Category Fluency Test, there were no significant differences in the performance of the On-Off group between baseline versus 3 months (p=0.413) and in the performance of the Off-On group between 3 months versus 6 months (p=0.652; figure 3). Likewise, there were no significant differences in the performance of the On-On group between baseline versus 3 months (p=0.446) and baseline versus 6 months (p=0.615). At 6 months, no significant differences in the performance were observed between the On-On and Off-Off groups (p=0.805).

DISCUSSION

The current study used data from a randomised, sham-controlled, double-blind crossover trial to investigate the neuropsychological effects of active versus sham SCG-DBS over two 3-month periods in TRD. No significant differences in changes in depression or composite measures of cognitive domains were observed between active and sham SCG-DBS. Individual neuropsychological measures showed no deterioration. While Category Fluency Test performance, a measure of processing speed, improved after 3 months, this effect became non-significant after correcting for multiple comparisons and was not maintained after the crossover period. The absence of significant and sustained changes underscores the need for cautious interpretation and might reflect our small sample rather than the absence of true group differences.

Structural and functional brain alterations in TRD are associated with a higher risk of cognitive decline and its negative outcomes on functionality in this population. The SCG is a key target for DBS in treating TRD, primarily influencing mood through a top-down mechanism that enhances emotional regulation and alleviates depressive symptoms.[10] SCG-DBS has demonstrated the ability to preserve cognitive functioning in TRD.[6 12 19] In contrast, the ventral capsule (VC), another common target for DBS, operates via a bottom-up mechanism that directly activates motivational circuits and reward processing.[20] Evidence indicates that while both targets aim to alleviate TRD symptoms, their cognitive impacts diverge significantly, with SCG stimulation being less likely to disrupt cognitive processes compared with VC stimulation.[20] Consistent with our findings, studies that targeted the SCG in smaller samples found no deterioration in executive function, language, processing speed, attention or verbal fluency 12 months post-DBS surgery.[13 19]

The Category Fluency Test was the only assessment that demonstrated a short-term response to SCG-DBS at 3 months. However, this became non-significant after correcting for multiple comparisons and was not maintained after 6 months of stimulation. Research has shown that participants with MDD perform significantly worse than those with no psychiatric history on this test,[21] reflecting impairments in processing speed. A small long-term study of open-label SCG-DBS with follow-up to 42 months reported individual variability in performance on the Category Fluency Test.[14] As part of a network that also comprises cortical structures, stimulating the SCG via DBS may cause local and distributed effects.[11 13] While category fluency is typically considered to index functions dependent on the lateral temporal and prefrontal cortex, tasks involving word generation or decisions to semantic cues have been shown to engage non-classical language areas such as the posterior cingulate cortex and adjacent precuneus.[22 23] Functional neuroimaging studies

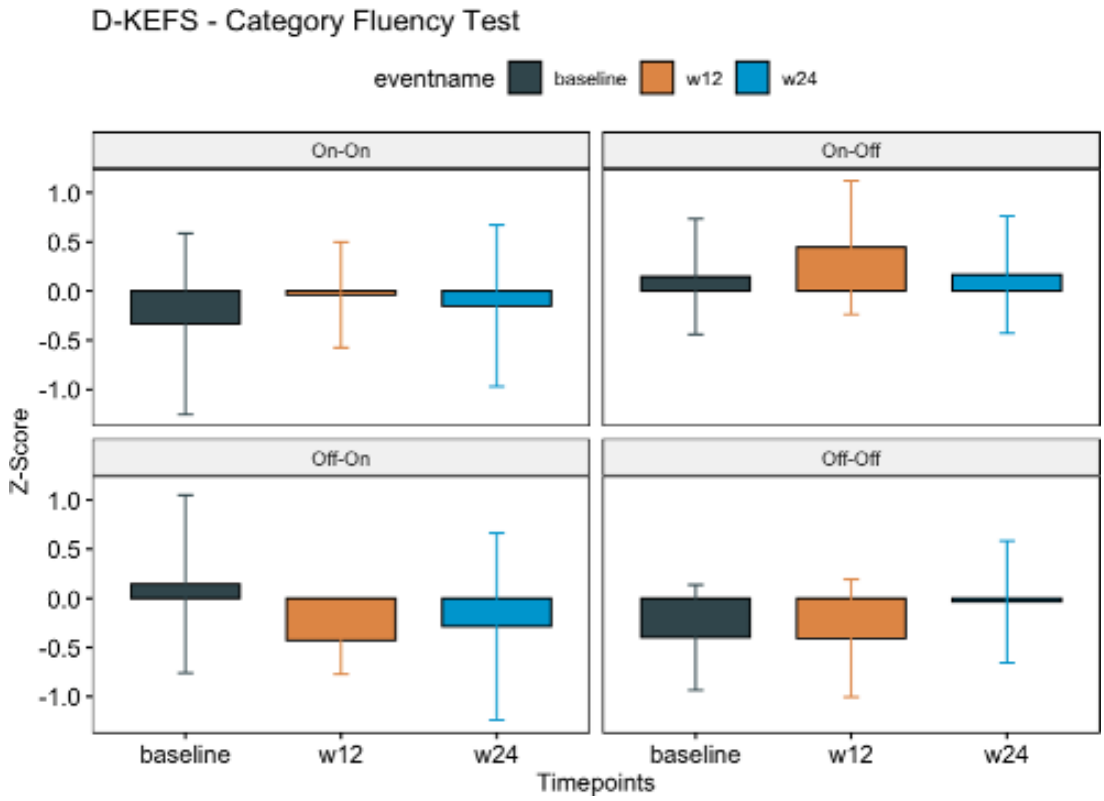

Figure 3 Within-group and between-group Category Fluency Test comparisons. Note: The bar represents CIs. D-KEFS, Delis-Kaplan Executive Function System; W12, week 12; W24, week 24.

of SCG-DBS demonstrate activation in this region with stimulation.[24 25] Therefore, it is possible that DBS altered connectivity to such regions, although transiently, in our cohort.

Maintained cognitive functioning on the remaining tests in the domains of processing speed, learning and memory and cognitive flexibility is consistent with prior findings in TRD. Similar to our results, a previous trial of SCG-DBS in TRD reported stable performance on the Trail-making Test A at 1 year post-surgery and no univariate effect of time on the Trail-making Test B.[19] Bogod *et al*[14] also observed stable CVLT-II (Delayed Recall) performance in two participants throughout the study. Most of the extant literature indicates no significant change or, at most, a modest improvement in some cognitive measures.[14 19] A recent meta-analysis suggests that it may take more than 6 months of DBS treatment for significant cognitive gains.[9] While our study was unable to assess the long-term effects of SCG-DBS, supporting evidence also suggests that it may take time for improvements to emerge.[26] Cognitive improvements reported in some open-label studies[6 7] may reflect practice (ie, due to repeated administration of neuropsychological tests) or placebo effects, which are minimised in our crossover sham-controlled design. Moreover, the cohort for our study also performed relatively well at baseline, despite selecting measures from domains previously demonstrated to be impaired in MDD.[1] In our study, only one test score (ie, GPT) was more than one SD below the normative mean value. Thus, the opportunity to observe 'normalisation' on a statistically reliable basis may have been blunted. Future studies should enrol participants with considerable cognitive deficits in addition to TRD to better assess the effects of SCG-DBS on cognitive function.

Moreover, no significant changes in HDRS-17 scores were observed in this study. Cognitive improvements in individuals with MDD are often linked to reductions in depressive symptoms. A systematic review and meta-analysis of 69 studies found that both symptom improvement and the number of prior depressive episodes influenced cognitive changes.[27] Thus, the lack of significant changes in depressive symptoms in our study may have contributed to the absence of cognitive improvement following SCG-DBS. Moreover, the SCG, a key component of the mood-regulating circuit, shows reduced activity following antidepressant treatments and is the primary target for DBS.[28] However, SCG-DBS trials for TRD have yielded inconsistent results regarding efficacy and sustainability. While some studies report significant improvements in depressive symptoms following SCG-DBS,[11 29] a 6-month double-blind, sham-controlled trial found no statistically significant antidepressant effects despite demonstrating the safety and feasibility of SCG-DBS.[30] Additionally, our study demonstrated non-significant changes in depressive symptoms following SCG-DBS, highlighting the need to consider potential placebo effects. Furthermore, the antidepressant effects of DBS may develop in a delayed and progressive manner, with differences between active and sham stimulation potentially not evident until after 1–2 years of treatment, posing significant challenges for sham-controlled studies.

A strength of this study is that the randomised crossover design combined with the double-blinding enhances the robustness. Additionally, employing both active and sham treatment groups mitigated confounding effects arising from repeated neuropsychological testing, such as practice and task familiarity. However, some limitations warrant consideration. The potential for carryover effects, particularly in the absence of a sufficient washout period, remains an important methodological concern. Similarly, the impact of concomitant antidepressant treatments on cognitive performance was not assessed, and the 4-week stable antidepressant regimen prior to the DBS surgery might not have been sufficient to stabilise clinical changes fully.

Another limitation lies in the use of two distinct medical devices (ie, St Jude Medical/Abbott Libra or Medtronic Activa), which could have complicated the results. Furthermore, participants were not matched across groups based on their treatment history, concurrent treatment regimens or depressive symptoms. While including these covariates in MMRMs might have increased model complexity, baseline HDRS-17 scores did not differ significantly between groups, suggesting a limited impact on findings. Given the study's small sample size and the primary aim of detecting differences, the results should be interpreted with caution, as insufficient statistical power may have obscured subtle group differences. Nonetheless, these results contribute valuable insights to the growing body of literature on SCG-DBS and its cognitive effects. Moreover, the relatively short stimulation period might have prevented clinical benefits from emerging. Future studies should enrol larger samples and implement longer stimulation periods to provide a more comprehensive evaluation of SCG-DBS and its effects.

CONCLUSION AND CLINICAL IMPLICATIONS

This study demonstrates that cognitive function remains unaffected following SCG-DBS for TRD in the short term. No significant deteriorations in composite measures of cognitive performance were observed following 3 months of active SCG-DBS compared with sham stimulation. Transient improvement on the Category Fluency Test suggests a potential effect on semantic access; however, this effect should be explored in greater depth in future studies. These findings highlight the need for further research investigating the efficacy of SCG-DBS in enhancing cognitive function and alleviating depressive symptoms in TRD. A larger randomised controlled trial with extended stimulation periods is required to clarify potential neuropsychological effects.

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REFERENCES

1 Pan Z, Park C, Brietzke E, *et al*. Cognitive impairment in major depressive disorder. *CNS Spectr* 2019;24:22–9.
2 Puigdemont D, Portella M, Pérez-Egea R, *et al*. A randomized double-blind crossover trial of deep brain stimulation of the subcallosal cingulate gyrus in patients with treatment-resistant depression: a pilot study of relapse prevention. *J Psychiatry Neurosci* 2015;40:224–31.
3 Zhou C, Zhang H, Qin Y, *et al*. A systematic review and meta-analysis of deep brain stimulation in treatment-resistant depression. *Prog Neuropsychopharmacol Biol Psychiatry* 2018;82:224–32.
4 Sullivan CRP, Olsen S, Widge AS. Deep brain stimulation for psychiatric disorders: From focal brain targets to cognitive networks. *Neuroimage* 2021;225.
5 Malone DA Jr, Dougherty DD, Rezai AR, *et al*. Deep brain stimulation of the ventral capsule/ventral striatum for treatment-resistant depression. *Biol Psychiatry* 2009;65:267–75.
6 McNeely HE, Mayberg HS, Lozano AM, *et al*. Neuropsychological impact of Cg25 deep brain stimulation for treatment-resistant depression: preliminary results over 12 months. *J Nerv Ment Dis* 2008;196:405–10.
7 Grubert C, Hurlemann R, Bewernick BH, *et al*. Neuropsychological safety of nucleus accumbens deep brain stimulation for major depression: effects of 12-month stimulation. *World J Biol Psychiatry* 2011;12:516–27.
8 Anderson RJ, Frye MA, Abulseoud OA, *et al*. Deep brain stimulation for treatment-resistant depression: efficacy, safety and mechanisms of action. *Neurosci Biobehav Rev* 2012;36:1920–33.
9 Runia N, Mol GJJ, Hillenius T, *et al*. Effects of deep brain stimulation on cognitive functioning in treatment-resistant depression: a systematic review and meta-analysis. *Mol Psychiatry* 2023;28:4585–93.
10 Ramirez-Mahaluf JP, Perramon J, Otal B, *et al*. Subgenual anterior cingulate cortex controls sadness-induced modulations of cognitive and emotional network hubs. *Sci Rep* 2018;8:8566.
11 Mayberg HS, Lozano AM, Voon V, *et al*. Deep brain stimulation for treatment-resistant depression. *Neuron* 2005;45:651–60.

12 Moreines JL, McClintock SM, Kelley ME, *et al*. Neuropsychological function before and after subcallosal cingulate deep brain stimulation in patients with treatment-resistant depression. *Depress Anxiety* 2014;31:690–8.
13 McInerney SJ, McNeely HE, Geraci J, *et al*. Neurocognitive Predictors of Response in Treatment Resistant Depression to Subcallosal Cingulate Gyrus Deep Brain Stimulation. *Front Hum Neurosci* 2017;11:74.
14 Bogod NM, Sinden M, Woo C, *et al*. Long-term neuropsychological safety of subgenual cingulate gyrus deep brain stimulation for treatment-resistant depression. *J Neuropsychiatry Clin Neurosci* 2014;26:126–33.
15 ACNP 61st Annual Meeting: Poster Abstracts P271-P540. *Neuropsychopharmacol* 2022;47:220–370.
16 Paff M, Loh A, Sarica C, *et al*. Update on Current Technologies for Deep Brain Stimulation in Parkinson's Disease. *J Mov Disord* 2020;13:185–98.
17 Schulze L, Wheeler S, McAndrews MP, *et al*. Cognitive safety of dorsomedial prefrontal repetitive transcranial magnetic stimulation in major depression. *Eur Neuropsychopharmacol* 2016;26:1213–26.
18 Benjamini Y, Hochberg Y. Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. J R Stat Soc Series B 1995;57:289–300.
19 Serra-Blasco M, Vita S, Rodríguez MR, *et al*. Cognitive functioning after deep brain stimulation in subcallosal cingulate gyrus for treatment-resistant depression: An exploratory study. *Psychiatry Res* 2015;225:341–6.
20 Sobstyl M, Kupryjaniuk A, Prokopienko M, *et al*. Subcallosal Cingulate Cortex Deep Brain Stimulation for Treatment-Resistant Depression: A Systematic Review. *Front Neurol* 2022;13:780481.
21 Hammar A, Strand M, Ardal G, *et al*. Testing the cognitive effort hypothesis of cognitive impairment in major depression. *Nord J Psychiatry* 2011;65:74–80.
22 Cho YW, Song H-J, Lee JJ, *et al*. Age-related differences in the brain areas outside the classical language areas among adults using category decision task. *Brain Lang* 2012;120:372–80.
23 Binder JR, Desai RH, Graves WW, *et al*. Where is the semantic system? A critical review and meta-analysis of 120 functional neuroimaging studies. *Cereb Cortex* 2009;19:2767–96.
24 Elias GJB, Germann J, Boutet A, *et al*. Structuro-functional surrogates of response to subcallosal cingulate deep brain stimulation for depression. *Brain (Bacau)* 2022;145:362–77.
25 Cha J, Choi KS, Rajendra JK, *et al*. Whole brain network effects of subcallosal cingulate deep brain stimulation for treatment-resistant depression. *Mol Psychiatry* 2024;29:112–20.
26 Kennedy SH, Giacobbe P, Rizvi SJ, *et al*. Deep brain stimulation for treatment-resistant depression: follow-up after 3 to 6 years. *Am J Psychiatry* 2011;168:502–10.
27 Ahern E, White J, Slattery E. Change in Cognitive Function over the Course of Major Depressive Disorder: A Systematic Review and Meta-analysis. *Neuropsychol Rev* 2024.
28 Figee M, Riva-Posse P, Choi KS, *et al*. Deep Brain Stimulation for Depression. *Neurotherapeutics* 2022;19:1229–45.
29 Lozano AM, Mayberg HS, Giacobbe P, *et al*. Subcallosal cingulate gyrus deep brain stimulation for treatment-resistant depression. *Biol Psychiatry* 2008;64:461–7.
30 Holtzheimer PE, Husain MM, Lisanby SH, *et al*. Subcallosal cingulate deep brain stimulation for treatment-resistant depression: a multisite, randomised, sham-controlled trial. *Lancet Psychiatry* 2017;4:839–49.