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CLINICAL ARTICLE

Effect of deep brain stimulation on nonmotor symptoms in essential tremor

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OBJECTIVE Essential tremor (ET) is a prevalent movement disorder that also includes nonmotor symptoms such as anxiety, depression, and cognitive impairment. Deep brain stimulation (DBS) is an established treatment for ET, yet its impact on nonmotor symptoms remains unclear. This study aims to describe neuropsychological outcomes following ventral intermediate nucleus (VIM) DBS in a large cohort of patients with ET and identify factors associated with changes in depression and cognitive function.

METHODS A retrospective cohort study of patients who had undergone VIM DBS was performed. Inclusion criteria were ET diagnosis, surgery between October 2007 and March 2020, and available pre- and post-DBS neuropsychological testing results. Neuropsychological measures included the Beck Depression Inventory–II (BDI-II), Beck Anxiety Inventory (BAI), and cognitive measures assessing attention, executive function, language, memory, and visuospatial function. Post-DBS tremor improvement was graded, and active electrode coordinates and stimulation parameters were identified. Statistical analyses included descriptive statistics, t-tests to compare pre- and postoperative scores at the group level, and one-way analysis of variance to compare variables among patients who improved, were stable, or worsened in psychiatric and cognitive characteristics after DBS.

RESULTS One hundred thirty-nine patients met the study inclusion criteria. BDI-II scores significantly decreased postoperatively (9.82 ± 6.77 vs 8.29 ± 6.18, $p < 0.001$, Cohen's $d = 0.176$), whereas BAI scores remained unchanged. Both language ($p = 0.003$, Cohen's $d = 0.259$) and memory ($p < 0.001$, Cohen's $d = 0.336$) domains showed statistically significant small-magnitude declines following surgery, whereas attention, executive function, and visuospatial function were unchanged. Patients with improved depression (14.3%) following VIM DBS had significantly higher BDI-II scores preoperatively ($p < 0.001$, $\omega^2 = 0.226$). Patients with worsened language (18.7%) had higher preoperative language scores ($p < 0.001$, $\omega^2 = 0.058$). Patients with worsened memory (15.1%) had higher BAI scores preoperatively ($p = 0.002$, $\omega^2 = 0.079$). Preoperative scores were similar between patients with improved and worsened overall cognition postsurgery. Patients with improved overall cognition had improvements in attention, language, and visuospatial function.

CONCLUSIONS VIM DBS for ET did not result in large-magnitude neuropsychological changes. There were statistically significant, though likely not clinically meaningful, small-magnitude improvements in depression and worsening in language and memory scores. Associations were found between multiple preoperative mood and cognitive scores and post-DBS neuropsychological changes. These findings can help inform clinical decision-making and patient counseling for DBS.

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KEYWORDS essential tremor; deep brain stimulation; nonmotor symptoms; depression; anxiety; cognitive function; functional neurosurgery

ABBREVIATIONS AC-PC = anterior commissure–posterior commissure; BAI = Beck Anxiety Inventory; BDI-II = Beck Depression Inventory–II; DBS = deep brain stimulation; ET = essential tremor; PD = Parkinson's disease; STN = subthalamic nucleus; VIM = ventral intermediate nucleus.

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Essential tremor (ET) impacts approximately 2.2% of the US population[1] and almost 25 million patients worldwide.[2] While ET was initially believed to be a purely motor disorder characterized by action and/or postural tremor, it is now understood that patients also experience nonmotor symptoms such as anxiety, depression, cognitive impairment, and sensory disturbances.[3,4] How these nonmotor symptoms respond to deep brain stimulation (DBS) is not well understood.

Anxiety and depression are especially common in ET, with up to 71% of patients experiencing anxiety and 30%–54% experiencing depression, greater percentages than those for healthy controls.[4–7] One study found that higher self-reported depression was associated with the future development of ET, suggesting that depression may be a primary symptom of the disorder.[8] Additionally, multiple studies have found cognitive deficits in ET patients compared to healthy controls.[7,9] Cognitive impairment can appear before tremor, similarly suggesting that it may be a primary symptom of ET.[10] These neurobehavioral and cognitive symptoms can have a significant negative impact on quality of life. Therefore, it is critical to understand these symptoms and their response to standard treatments.

DBS is an effective treatment for ET.[11] While the benefit of DBS for ET is well established, its impact on nonmotor symptoms remains poorly understood.[12] Small studies have reported various impacts of ventral intermediate nucleus (VIM) DBS on cognition, anxiety, and depression in ET patients, with some reporting improvements and others reporting declines.[13] These differences may depend on factors such as patient demographics, measurement differences, intraoperative complications, and DBS targeting.[14] One study found no significant cognitive or neurobehavioral changes at the group level after VIM DBS, although 46% of individual ET patients exhibited subtle decrements in different cognitive scores compared to normative data.[13] Conversely, a meta-analysis of seven studies found that VIM DBS was associated with significantly improved depression scores among a pooled sample of ET patients.[15]

While our understanding of nonmotor outcomes following VIM DBS for ET is limited, there is substantial literature describing psychiatric and cognitive outcomes following DBS for Parkinson's disease (PD).[16,17] In particular, subthalamic nucleus (STN) DBS may negatively impact mood and cognition in some patients. Several studies have found that STN DBS is associated with greater worsening of cognitive function and depression symptoms compared to globus pallidus internus (GPI) DBS in patients with PD.[18,19] Both STN and GPI DBS have been associated with greater rates of cognitive decline than pharmacological treatment in PD.[20,21] Whether VIM DBS similarly impacts nonmotor symptoms is not well understood.

The objective in the present study was to evaluate change in nonmotor symptoms following VIM DBS in a large cohort of patients with ET and identify factors associated with favorable versus unfavorable neuropsychological outcomes.

Methods

Study Design and Patients

We performed a retrospective cohort study of individuals with ET who had undergone VIM DBS at our institution between October 2007 and March 2020. A total of 438 patients with ET were identified from an institutional database. The study was approved by the Vanderbilt Institutional Review Board. All subjects signed written informed consent. All data were obtained from electronic medical records. This article adheres to the reporting guidelines outlined by Strengthening the Reporting of Observational Studies in Epidemiology (STROBE).[22] Inclusion criteria were an ET diagnosis as determined by a fellowship-trained movement disorder neurologist, having undergone VIM DBS during the study period, and having neuropsychological testing results from both before and after DBS surgery. At our center, all patients undergo preoperative neuropsychological testing to help determine DBS surgical candidacy. Patients are advised to undergo postoperative neuropsychological testing but may not complete this due to time, distance, transportation, or other reasons.

DBS Surgery and Postoperative Programming

All patients underwent DBS surgery using STarFix (FHC, Inc.) in a three-stage procedure. During stage 1, four bone fiducials were placed with the patient under general anesthesia, and CT and MRI were performed. The surgical targets and trajectories were then planned, and a patient-specific 3D-printed frame was produced. Stage 2 involved awake microelectrode-guided placement of VIM leads using the custom frame. Microelectrode recording was performed in 1–3 tracts followed by intraoperative stimulation testing using the macrocontact of the microelectrode, to determine the location of optimal clinical efficacy and minimal stimulation-related side effects. Once the optimal location had been determined, the DBS electrode was placed at this location. In stage 3, the implantable pulse generator was placed under general anesthesia. The DBS system was turned on during an initial programming session performed by a movement disorder neurologist approximately 4–6 weeks postoperatively. During this session, the neurologist generally performs a monopolar review to determine optimal initial stimulation contact and settings to maximize tremor suppression while minimizing side effects. Follow-up programming sessions were conducted as needed.

Neuropsychological Testing

All patients underwent both preoperative and postoperative neuropsychological testing with a licensed clinical neuropsychologist. The Beck Depression Inventory–II (BDI-II) was used to quantify depression symptoms.[23] BDI-II scores range from 0 to 63, with scores 0–13 indicating minimal depression symptoms; 14–19, mild symptoms; 20–28, moderate symptoms; and 29–63, severe symptoms. The Beck Anxiety Inventory (BAI) was used to quantify anxiety symptoms.[24] Total scores on the BAI also range from 0 to 63, with scores 0–7 indicating minimal anxiety symptoms; 8–15, mild symptoms; 16–25, moderate symptoms; and 26–63, severe symptoms. Detailed cognitive testing was also performed using a number of cognitive tests within the domains of attention,

executive function, language, memory, and visuospatial function (Supplementary Table 1).

Neuropsychological Changes After DBS

Patients were classified as having a clinically significant change in depression postoperatively if they met the following criteria: 1) change in depression category (minimal/mild/moderate/severe) and 2) change in BDI-II score of at least 3 points, as previously described.[13] Improvement and worsening of anxiety postoperatively were defined in a similar manner using BAI severity classifications and change scores.[13]

Individual cognitive test raw scores were converted to standardized norm-referenced z-scores (mean ± SD, 0.0 ± 1.0). Individual test z-scores within the same cognitive domain were averaged to create five compositive cognitive domain scores: attention, executive function, language, memory, and visuospatial function. The cognitive domain scores were averaged to create an overall cognition score. Due to changes in institutional neuropsychological testing protocols, some of the specific cognitive tests changed part way through the study period. Because of this, a subset of patients had different neuropsychological tests in preoperative and postoperative testing. Supplementary Table 1 shows the tests in each cognitive domain.

On an individual patient level, a significant postoperative change in a cognitive test was defined as a decline or improvement of > 1 SD on that test score. Patients improved or worsened in a domain if their score changed at least 1 SD within that domain. Patients were defined as having worsened or improved overall cognition if they worsened or improved (> 1 SD change), respectively, on at least two tests across different cognitive domains, as described elsewhere.[13] If a patient improved in at least two more domains than the number of domains in which they declined, they were classified as improved. If they declined in at least two more domains than the number in which they improved, they were classified as worsened. Patients who did not meet any of these criteria were considered stable. If a patient both improved and worsened on different subtests within the same cognitive domain, they were excluded from this analysis due to potentially unreliable testing.

Motor Symptom Improvement

Changes in tremor after surgery were determined by a review of records from the neurology clinic visit closest in time to the patient's postoperative neuropsychological testing. Tremor improvement was graded on a scale from 1 to 4 in 0.5 increments, with 4 indicating optimal tremor control and 1 indicating no benefit (Supplementary Table 2).

Electrode and Stimulation Characteristics

Active electrode contact and stimulation parameters were identified from a review of the electronic medical record. The position of the active contact was determined relative to the anterior commissure–posterior commissure (AC-PC) plane midpoint in the atlas space. CranialVault Explorer (CRAVE)[25] software was used to merge each person's postoperative CT scans while electrodes were in place with their preoperative CT and MRI scans. The coordinates of the centroid of each contact were obtained in the preoperative CT and/or MRI patient space. A reference MRI atlas was registered to the preoperative MRI scans with a combination of rigid and nonrigid transformations. These transformations were used to project points from the patient to the atlas. The active contact coordinates were then converted to AC-PC coordinates in the atlas space. If patients had multiple active electrode contacts on one side, the positions of these were averaged to generate a single set of active electrode coordinates for each patient and laterality.

Statistical Analysis

Descriptive statistics were performed for demographic characteristics, motor scores, and neuropsychological test scores. Frequencies were calculated for categorical variables, and means ± standard deviations were computed for continuous variables. Normality of variable distribution was assessed using the Shapiro-Wilk test. Independent samples t-tests were used to compare continuous clinical and demographic variables for normally distributed data between patient groups, and the Mann-Whitney U-test was used for nonnormally distributed variables because of this test's ability to compare nonnormally distributed data and resistance to outliers. Chi-square tests were used to compare categorical variables. As all neuropsychological scores were normally distributed for subjects who had undergone both pre- and postoperative neuropsychological testing, paired sample t-tests were performed to compare pre- and postoperative continuous variables at the group level. Since the preoperative neuropsychological scores of patients who had not undergone postoperative neuropsychological testing were nonnormally distributed, Mann-Whitney U-tests were used to compare preoperative scores between patients who did and those who did not complete follow-up testing. For variables that were significantly different following DBS at a group level, a one-way ANOVA was used to compare data among the three categories of improved, stable, and worsened for this measure at the individual subject level, followed by Tukey's post hoc analysis to identify differences between pairs of categories. Multivariable linear regressions were also utilized to evaluate the relationship between change in domain scores and age, gender, follow-up duration, and any preoperative variables significant on individual-level ANOVA for that domain. Effect sizes were calculated using phi (ϕ) for 2 × 2 chi-square tests, Cramer's V for 2 × 3 chi-square tests, Cohen's *d* for t-test comparisons, omega (ω^2) for ANOVA comparisons, and rank-biserial correlation for Mann-Whitney U-test comparisons (Supplementary Table 3). We defined a clinically significant change in neuropsychological test measures as a z-score change > 1.5 in combination with a medium or larger effect size.[26] As previously described,[13] patients were classified as having a clinically significant improvement in depression postoperatively if they met the following criteria: 1) improvement in the depression category to a less severe classification and 2) a BDI-II score decrease by at least 3 points. Statistical significance was set to $\alpha = 0.05$. Bonferroni correction was used to adjust for multiple comparisons. For analyses

TABLE 1. Demographic and clinical characteristics of 139 ET patients who underwent DBS

Variable	Value
Demographics	
Age in yrs	66.63 ± 10.22
Female	74 (53.2)
Race	
White	135 (97.1)
Black	4 (2.9)
FU in days (range)	389.76 ± 383.45 (183–1533)
Motor Scores	
Preop FTM (n = 57)	
Total	50.58 ± 13.76
Lt	14.78 ± 5.29
Rt	15.52 ± 5.40
Preop WHIGET (n = 75)	
Total	28.92 ± 8.27
Lt	13.23 ± 5.13
Rt	15.69 ± 4.35
Postop TIR (n = 131)	3.51 ± 0.55
Electrode characteristics	
Laterality	
Bilat	121 (87.1)
Lt	14 (10.1)
Rt	4 (2.9)
Stimulation parameters	
Voltage (V)	
Lt	2.64 ± 0.94
Rt	2.23 ± 1.01
Current (mA)	
Lt	2.46 ± 1.20
Rt	2.27 ± 0.95
Frequency (Hz)	
Lt	133.33 ± 15.38
Rt	131.93 ± 19.34
Pulse width (μsec)	
Lt	86.59 ± 22.47
Rt	80.55 ± 21.71
Electrode AC-PC coordinates	
X	
Lt	15.17 ± 4.31
Rt	–15.04 ± 4.81
Y	
Lt	4.22 ± 1.80
Rt	2.99 ± 1.94
Z	
Lt	3.78 ± 3.41
Rt	5.69 ± 3.18

FTM = Fahn-Tolosa-Marin; FU = follow-up; TIR = tremor improvement rating; WHIGET = Washington Heights–Inwood Genetic Study of ET.
Values are expressed as mean ± standard deviation or number (%), unless indicated otherwise.

comparing preoperative to postoperative scores, we set significance at $p < 0.006$ to control for 8 primary neuropsychological outcome measures. For analyses comparing variables among subjects who were improved, unchanged, and worsened on neuropsychological outcome measures following DBS, we used a threshold of $p < 0.003$ to control for 14 demographic and clinical outcome measures. Analyses were performed using IBM SPSS Statistics 27 (IBM Corp.).

Results

ET Patient Demographics

A total of 438 patients underwent VIM DBS during the study period. Of these, 282 were excluded because they had not undergone postoperative neuropsychological testing. An additional 17 patients had undergone postoperative neuropsychological testing but did not have complete reports available and thus were also excluded. Overall, 139 patients met the study inclusion criteria. The mean age of these patients was 66.63 ± 10.22 years, and a majority of patients were female (n = 74, 53.2%) and White (n = 132, 97.1%; Table 1). The mean follow-up duration was 389.76 ± 383.45 days (range 183–1533 days). Postoperative tremor rating was available for 131 patients, and the mean tremor improvement rating was 3.51 ± 0.55. There were no differences in any demographic or clinical measures between patients who did and those who did not undergo follow-up neuropsychological testing (Supplementary Table 4).

Effect of DBS on Mood and Cognition

Among the 126 patients for whom data were available, postoperative BDI-II scores were significantly lower than preoperative scores (8.29 ± 6.18 vs 9.82 ± 6.77, respectively, $p < 0.001$, Cohen's $d = 0.176$; Table 2). There was no significant change in BAI scores postoperatively. There were statistically significant small-magnitude declines in language (–0.20 preoperatively vs –0.33 postoperatively, $p = 0.003$, Cohen's $d = 0.259$) and memory (–0.12 vs –0.45, respectively, $p < 0.001$, Cohen's $d = 0.336$) domain scores following VIM DBS, as well as in overall cognition (–0.24 vs –0.39, respectively, $p < 0.001$, Cohen's $d = 0.345$). No changes were observed in the domains of executive function, attention, or visuospatial function.

Factors Associated With a Change in Depression After VIM DBS

Eighteen (14.3%) patients had improved depression following VIM DBS, 98 (77.8%) had stable depression, and 10 (7.9%) experienced worsened depression (Table 3). The patients with improved postoperative depression had significantly higher depression scores preoperatively (19.44 ± 4.46, mild to moderate elevation) relative to those in both the stable (7.73 ± 5.63) and worsened (11.50 ± 4.60) depression groups ($p < 0.001$, $\omega^2 = 0.226$). No other demographic or clinical variables were different among depression change groups. Multivariable linear regression revealed that preoperative BDI-II scores were inversely correlated with the change in BDI-II scores ($\beta = -0.504$, $p < 0.001$; Table 4).

TABLE 2. Neuropsychological changes following DBS surgery

Test	No.	Preop Score	No.	Postop Score	p Value	Effect Size: Cohen's *d*	No. Improved	No. Stable	No. Worsened
Depression: BDI-II	126	9.82 ± 6.77	126	8.92 ± 6.18	**<0.001**	0.176	18 (14.3)	98 (77.8)	10 (7.9)
Anxiety: BAI	25	7.53 ± 6.93	25	7.60 ± 5.06	0.152	0.360	8 (32.0)	14 (56.0)	3 (12.0)
Attention (z-score)	135	−0.596	135	−0.671	0.249	0.100	29 (21.5)	78 (57.8)	28 (20.7)
Speeded color naming	123	−0.750	132	−0.817			18		20
Speeded word reading	121	−0.736	133	−0.828			12		15
Speeded visuomotor sequencing	125	−0.539	122	−0.302			19		13
Attention span & working memory	132	−0.302	138	−0.531			4		20
Executive function (z-score)	139	−0.350	139	−0.460	0.028	0.188	15 (10.8)	95 (68.3)	29 (20.9)
Speeded visuomotor set-shifting	123	−0.554	119	−0.623			12		15
Speeded response inhibition/set-shifting	123	−0.573	131	−0.811			10		27
Language (z-score)	139	−0.204	139	−0.328	**0.003**	0.259	20 (14.4)	93 (66.9)	26 (18.7)
Confrontation naming	128	0.121	121	0.344			13		9
Semantic fluency	130	−0.563	137	−0.563			6		20
Phonemic fluency	133	−0.667	136	−0.865			11		14
Memory (z-score)	139	−0.115	139	−0.452	**<0.001**	0.336	25 (18.0)	93 (66.9)	21 (15.1)
Word list learning	130	−0.401	129	−0.439			14		7
Word list recall	133	0.098	134	−0.387			11		37
Story learning	122	−0.010	122	−0.173			14		9
Story recall	132	−0.037	130	−0.318			11		16
Visuospatial function (z-score)	131	0.059	131	−0.033	0.092	0.152	11 (8.4)	96 (73.3)	24 (18.3)
Visual angle estimation	129	0.087	128	0.001			4		12
Visual detail perception	132	0.050	131	−0.038			16		22
Overall cognition (z-score)	139	−0.244	139	−0.387	**<0.001**	0.345	15 (10.8)	100 (71.9)	24 (17.3)

Values are expressed as mean ± standard deviation or number (%), unless indicated otherwise. Participants were included in the overall domain score if they completed at least one test within the domain, resulting in a larger sample size for the domain compared to individual test components. Boldface type indicates statistical significance. Significance set at $p < 0.006$ (8 comparisons) to adjust for multiple comparisons.

Factors Associated With a Change in Language Domain Function After VIM DBS

Twenty patients had improved language following VIM DBS, 93 had stable language, and 26 had worsened language. Those with worsened function had higher preoperative language scores than the scores for patients with improved or stable function (0.18 ± 0.56 vs −0.53 ± 0.45 vs −0.24 ± 0.58, respectively, $F = 9.566$, $p < 0.001$, $\omega^2 = 0.058$; Table 5). There were no differences in other clinical or demographic variables between groups. Multivariable linear regression revealed that the preoperative language domain score was inversely correlated with a change in language score ($\beta = -0.351$, $p < 0.001$; Table 4)

Factors Associated With a Change in Memory Domain Function After VIM DBS

Twenty-five patients had improved memory domain scores, 93 had stable scores, and 21 had worsened scores following VIM DBS. The patients with a worsened memory had higher preoperative BAI scores than those in patients with an improved or stable memory (16.67 ± 8.29 vs 5.67 ± 6.66 vs 6.60 ± 6.11, respectively, $F = 6.928$, $p = 0.002$, $\omega^2 = 0.079$; Table 6). Patients with improved memory domain scores had lower preoperative memory scores than those in the patients with stable and worsened memory (−0.90 ± 0.89 vs 0.10 ± 0.93 vs −0.05 ± 0.78, respectively, $F = 11.950$, $p < 0.001$, $\omega^2 = 0.078$). Conversely, multivariable regression revealed that preoperative memory scores were positively correlated with a change in memory score postoperatively ($\beta = 0.505$, $p < 0.001$; Table 4).

Factors Associated With Overall Cognitive Change After VIM DBS

Fifteen patients had improved overall cognition following VIM DBS, 100 were stable, and 24 had worsened overall cognition. The patients with improved overall cognition had a greater improvement in scores across all domains except executive function and memory (attention: $p < 0.001$, $\omega^2 = 0.102$; language: $p < 0.001$, $\omega^2 = 0.050$; visuospatial: $p < 0.001$, $\omega^2 = 0.055$; Table 7). There were no differences in other clinical or demographic characteristics among groups. No factors were associated with a change in overall cognition on multivariable regression (Table 4).

Discussion

In this retrospective cohort study, we examined neuropsychological outcomes following VIM DBS in a large sample of 139 ET patients. At the group level, we found statistically significant improvement in depression and

TABLE 3. Individual-level depression changes after DBS in 126 patients

Variable	Depression Improved (n = 18)	Depression Stable (n = 98)	Depression Worsened (n = 10)	Statistic	p Value	Effect Size
Demographics						
Age in yrs	62.04 ± 11.62	68.00 ± 9.82	63.23 ± 7.48	F = 3.752	0.026	ω^2 = 0.023
Female sex	15 (83.3)	52 (53.1)	7 (70.0)	χ^2 = 6.059	0.048	V = 0.227
Race						
White	16 (88.9)	96 (98.0)	10 (100.0)	χ^2 = 3.987	0.136	V = 0.184
Black	2 (11.1)	2 (2.0)	—			
Neuropsychological evaluation						
FU in days	528.67 ± 495.58	428.19 ± 382.44	670.50 ± 517.36	F = 2.149	0.121	ω^2 = 0.010
Preop BDI-II score	19.44 ± 4.46*†	7.73 ± 5.63	11.50 ± 4.60	F = 35.521	**<0.001**	ω^2 = 0.226
Change in BDI-II score	−10.3 ± 6.04*†	−0.15 ± 4.25	7.2 ± 3.70*	F = 56.325	**<0.001**	ω^2 = 0.319
Preop BAI score	12.13 ± 10.15	6.00 ± 5.07	6.50 ± 5.32	F = 6.209	0.004	ω^2 = 0.086
Change in BAI score	−10.2 ± 9.36	−0.67 ± 5.98	2.03 ± 4.32	F = 3.856	0.040	ω^2 = 0.120
Preop attention score	−0.77 ± 0.84	−0.49 ± 0.70	−0.34 ± 0.55	F = 1.228	0.297	ω^2 = 0.002
Change in attention score	−0.08 ± 0.65	−0.05 ± 0.62	−0.45 ± 0.38	F = 1.427	0.244	ω^2 = 0.004
Preop executive function score	−0.42 ± 0.63	−0.32 ± 0.60	−0.20 ± 0.51	F = 0.355	0.702	ω^2 = −0.005
Change in executive function score	−0.15 ± 0.56	−0.24 ± 0.67	−0.33 ± 0.78	F = 0.253	0.777	ω^2 = −0.006
Preop language score	−0.25 ± 0.56	−0.17 ± 0.61	−0.13 ±0.71	F = 0.401	0.671	ω^2 = −0.005
Change in language score	−0.13 ± 0.72	−0.12 ± 0.62	−0.29 ± 0.64	F = 0.241	0.786	ω^2 = −0.007
Preop memory score	−0.24 ± 0.80	−0.06 ± 1.04	−0.06 ± 0.87	F = 0.292	0.748	ω^2 = −0.006
Change in memory score	−0.18 ± 0.52	−0.09 ± 0.74	−0.42 ± 0.69	F = 1.151	0.320	ω^2 = 0.001
Preop visuospatial score	−0.01 ± 0.83	0.14 ± 0.78	0.01 ± 0.82	F = 0.282	0.755	ω^2 = −0.006
Change in visuospatial score	−0.15 ± 0.99	−0.10 ± 0.74	−0.80 ± 0.99	F = 3.206	0.044	ω^2 = 0.020
Motor scores						
FTM						
Total	50.25 ± 16.47	50.43 ± 13.45	57.67 ± 11.68	F = 0.888	0.418	ω^2 = −0.002
Lt	12.88 ± 4.09	15.05 ± 5.02	14.00 ± 6.56	F = 0.553	0.579	ω^2 = −0.019
Rt	14.13 ± 6.94	15.87 ± 4.56	21.00 ± 4.58	F = 1.543	0.225	ω^2 = 0.011
WHIGET						
Total	27.63 ± 12.72	29.17 ± 7.54	24.00 ± 6.53	F = 1.033	0.362	ω^2 = 0.001
Lt	12.25 ± 7.42	13.28 ± 5.29	12.14 ± 3.98	F = 0.106	0.900	ω^2 = −0.015
Rt	15.38 ± 5.83	15.89 ± 3.40	11.86 ± 3.02	F = 3.396	0.040	ω^2 = 0.038
TIR	3.56 ± 0.68	3.50 ± 0.49	3.75 ± 0.35	F = 0.225	0.978	ω^2 = −0.008
Electrode characteristics						
Laterality						
Bilat	15 (83.3)	86 (87.8)	10 (100.0)	χ^2 = 7.257	0.509	V = 0.175
Unilat lt	2 (11.1)	9 (9.2)	—			
Unilat rt	1 (5.6)	3 (3.1)	—			
Stimulation parameters						
Voltage (V)						
Lt	2.58 ± 0.74	2.64 ± 1.01	2.68 ± 0.66	F = 0.021	0.978	ω^2 = −0.012
Rt	2.79 ± 1.34	2.04 ± 0.99	2.45 ± 0.67	F = 2.229	0.115	ω^2 = 0.017
Current (mA)						
Lt	1.73 ± 0.53	2.33 ± 1.13	3.23 ± 0.45	F = 1.739	0.191	ω^2 = 0.020
Rt	2.35 ± 0.51	2.21 ± 1.00	2.73 ± 1.14	F = 0.394	0.677	ω^2 = −0.018
Frequency (Hz)						
Lt	134.64 ± 30.16	130.91 ± 8.54	146.25 ± 23.26	F = 4.182	0.018	ω^2 = 0.030
Rt	130.83 ± 28.75	128.68 ± 15.88	141.43 ± 20.35	F = 1.564	0.215	ω^2 = 0.006

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TABLE 3. Individual-level depression changes after DBS in 126 patients

Variable	Depression Improved (n = 18)	Depression Stable (n = 98)	Depression Worsened (n = 10)	Statistic	p Value	Effect Size
Stimulation parameters (*continued*)						
Pulse width (μsec)						
Lt	98.57 ± 23.16	82.26 ± 20.44	90.00 ± 27.77	F = 3.731	0.027	ω^2 = 0.025
Rt	89.17 ± 28.43	78.11 ± 21.50	81.43 ± 14.64	F = 1.315	0.274	ω^2 = 0.003
Position						
X						
Lt	15.22 ± 1.03	14.76 ± 5.13	17.21 ± 0.88	F = 0.355	0.704	ω^2 = –0.015
Rt	–15.00 ± 0.52	–14.67 ± 5.67	–16.93 ± 0.15	F = 0.161	0.852	ω^2 = –0.024
Y						
Lt	4.66 ± 4.08	4.22 ± 1.81	3.54 ± 0.53	F = 0.256	0.776	ω^2 = –0.018
Rt	2.94 ± 2.77	3.03 ± 1.96	2.80 ± 1.16	F = 0.014	0.986	ω^2 = –0.028
Z						
Lt	0.12 ± 5.80	4.03 ± 2.90	6.14 ± 6.86	F = 2.622	0.085	ω^2 = 0.036
Rt	4.22 ± 5.04	5.96 ± 3.48	5.54 ± 3.19	F = 0.236	0.978	ω^2 = –0.022

Values are expressed as the mean ± standard deviation or number (%), unless indicated otherwise. Boldface type indicates statistical significance. Significance set at p < 0.003 (14 comparisons) to adjust for multiple comparisons.
* Different from stable group.
† Different from worsened group.

TABLE 4. Multivariable linear regressions predicting changes in depression, language, memory, and overall cognition

Variable	B	SE	*β*	t	p Value
Change in BDI-II					
Age	–0.022	0.051	–0.035	–0.425	0.672
Gender	–1.588	1.028	–0.124	–1.544	0.125
FU duration	0.001	0.001	0.041	0.509	0.611
Preop BDI-II	–0.465	0.076	–0.504	–6.116	**<0.001**
Change in language					
Age	–0.001	0.005	–0.019	–0.223	0.824
Gender	–0.023	0.104	–0.018	–0.217	0.828
FU duration	0.000	0.000	–0.081	–0.965	0.336
Preop language	–0.369	0.089	–0.351	–4.130	**<0.001**
Change in memory					
Age	–0.012	0.009	–0.163	–1.369	0.177
Gender	0.029	0.180	0.019	0.163	0.871
FU duration	0.000	0.000	–0.151	–1.289	0.203
Preop BAI	0.009	0.013	0.087	0.741	0.462
Preop memory	0.475	0.112	0.505	4.244	**<0.001**
Change in overall cognition					
Age	0.008	0.004	0.147	1.717	0.088
Gender	0.122	0.089	0.117	1.379	0.170
FU duration	–0.001	0.000	–0.015	–0.174	0.862

SE = standard error.
Boldface type indicates statistical significance. Significance set at p < 0.01 (4 comparisons) to adjust for multiple comparisons.

TABLE 5. Individual-level language domain changes after DBS among 139 patients

Variable	Language Improved (n = 20)	Language Stable (n = 93)	Language Worsened (n = 26)	Statistic	p Value	Effect Size
Demographics						
Age in yrs	67.72 ± 10.42	66.06 ± 9.79	67.83 ± 11.74	F = 0.434	0.649	$\omega^2 = -0.004$
Female sex	11 (55.0)	53 (57.0)	11 (42.3)	$\chi^2 = 1.773$	0.412	V = 0.113
Race						
White	20 (100.0)	91 (97.8)	24 (92.3)	$\chi^2 = 2.925$	0.232	V = 0.145
Black	—	2 (2.2)	2 (7.7)			
Neuropsychological evaluation						
FU in days	464.65 ± 552.35	505.57 ± 480.89	349.00 ± 294.25	F = 1.160	0.316	$\omega^2 = 0.001$
Preop BDI-II score	9.72 ± 7.76	9.91 ± 6.98	10.16 ± 6.26	F = 0.022	0.978	$\omega^2 = -0.008$
Change in BDI-II score	–1.78 ± 7.99	–0.65 ± 5.95	–2.13 ± 6.18	F = 0.602	0.549	$\omega^2 = -0.003$
Preop BAI score	9.00 ± 12.45	7.60 ± 6.43	3.25 ± 4.56	F = 0.746	0.479	$\omega^2 = -0.005$
Change in BAI score	–6.25 ± 13.59	–2.13 ± 6.32	–2.32 ± 3.35	F = 0.489	0.621	$\omega^2 = -0.025$
Preop attention score	–0.62 ± 0.76	–0.69 ± 0.69	–0.25 ± 0.69	F = 3.995	0.021	$\omega^2 = 0.022$
Change in attention score	0.04 ± 0.71	0.01 ± 0.62	–0.35 ± 0.41	F = 3.925	0.022	$\omega^2 = 0.021$
Preop executive function score	–0.51 ± 0.69	–0.35 ± 0.58	–0.24 ± 0.51	F = 1.212	0.301	$\omega^2 = 0.002$
Change in executive function score	–0.05 ± 0.53	–0.32 ± 0.69	–0.18 ± 0.72	F = 1.471	0.233	$\omega^2 = 0.003$
Preop language score	–0.53 ± 0.45*	–0.24 ± 0.58	0.18 ± 0.56†	F = 9.566	**<0.001**	$\omega^2 = 0.058$
Change in language score	0.62 ± 0.39*†	–0.13 ± 0.56	–0.66 ± 0.41†	F = 35.344	**<0.001**	$\omega^2 = 0.205$
Preop memory score	–0.35 ± 1.12	0.01 ± 0.95	–0.38 ± 0.89	F = 2.201	0.115	$\omega^2 = 0.009$
Change in memory score	0.02 ± 0.59	–0.21 ± 0.80	–0.28 ± 0.58	F = 1.000	0.371	$\omega^2 = 0.000$
Preop visuospatial score	0.18 ± 0.77	0.02 ± 0.78	0.11 ± 0.78	F = 0.441	0.644	$\omega^2 = -0.004$
Change in visuospatial score	–0.06 ± 0.80	–0.14 ± 0.89	–0.19 ± 0.74	F = 0.134	0.874	$\omega^2 = -0.007$
Motor scores						
FTM						
Total	46.50 ± 10.94	52.81 ± 15.67	50.11 ± 12.50	F = 0.876	0.422	$\omega^2 = -0.002$
Lt	13.25 ± 4.73	16.08 ± 5.74	14.06 ± 4.87	F = 1.419	0.251	$\omega^2 = 0.008$
Rt	13.58 ± 4.44	16.38 ± 5.90	15.67 ± 5.24	F = 1.081	0.347	$\omega^2 = 0.001$
WHIGET						
Total	26.50 ± 7.09	28.66 ± 8.30	33.25 ± 8.50	F = 1.489	0.232	$\omega^2 = 0.006$
Lt	11.88 ± 5.62	13.03 ± 5.16	16.00 ± 3.85	F = 1.507	0.228	$\omega^2 = 0.007$
Rt	14.63 ± 3.89	15.63 ± 4.28	17.25 ± 5.39	F = 0.757	0.473	$\omega^2 = -0.003$
TIR	3.65 ± 0.63	3.57 ± 0.47	3.20 ± 0.63	F = 2.188	0.124	$\omega^2 = 0.009$
Electrode characteristics						
Laterality						
Bilat	19 (95.0)	77 (82.8)	25 (96.2)	$\chi^2 = 14.794$	0.063	V = 0.231
Unilat lt	1 (5.0)	12 (12.9)	1 (3.8)			
Unilat rt	—	4 (4.3)	—			
Stimulation parameters						
Voltage (V)						
Lt	2.35 ± 0.97	2.74 ± 0.90	2.49 ± 1.03	F = 1.430	0.244	$\omega^2 = 0.004$
Rt	2.01 ± 0.99	2.34 ± 0.96	1.98 ± 1.28	F = 1.077	0.345	$\omega^2 = 0.001$
Current (mA)						
Lt	1.55 ± 0.36	2.44 ± 1.23	3.24 ± 1.09	F = 4.594	0.016	$\omega^2 = 0.077$
Rt	2.25 ± 0.75	2.11 ± 0.99	2.84 ± 0.84	F = 1.901	0.163	$\omega^2 = 0.021$
Frequency (Hz)						
Lt	134.25 ± 14.07	132.37 ± 14.87	135.91 ± 18.43	F = 0.492	0.613	$\omega^2 = -0.004$
Rt	134.44 ± 14.94	133.31 ± 16.73	124.47 ± 29.10	F = 1.768	0.176	$\omega^2 = 0.007$

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TABLE 5. Individual-level language domain changes after DBS among 139 patients

Variable	Language Improved (n = 20)	Language Stable (n = 93)	Language Worsened (n = 26)	Statistic	p Value	Effect Size
Stimulation parameters (*continued*)						
Pulse width (μsec)						
Lt	84.50 ± 17.61	85.31 ± 23.98	88.18 ± 21.30	F = 0.173	0.842	ω^2 = –0.007
Rt	78.89 ± 15.68	82.60 ± 24.10	74.21 ± 15.39	F = 1.193	0.307	ω^2 = 0.002
Position						
X						
Lt	15.51 ± 2.01	15.07 ± 4.83	15.51 ± 1.06	F = 0.046	0.955	ω^2 = –0.018
Rt	–15.69 ± 1.00	–14.88 ± 5.54	–15.28 ± 1.85	F = 0.078	0.925	ω^2 = –0.020
Y						
Lt	5.03 ± 2.36	4.08 ± 1.66	4.18 ± 2.26	F = 0.820	0.446	ω^2 = –0.003
Rt	2.83 ± 1.13	3.00 ± 2.09	3.11 ± 1.94	F = 0.030	0.971	ω^2 = –0.022
Z						
Lt	2.04 ± 3.34	4.17 ± 3.40	2.96 ± 3.26	F = 1.356	0.267	ω^2 = 0.007
Rt	4.86 ± 2.66	6.18 ± 3.06	3.77 ± 3.92	F = 1.759	0.184	ω^2 = 0.016

Values are expressed as the mean ± standard deviation or number (%), unless indicated otherwise. Boldface type indicates statistical significance. Significance set at p < 0.003 (14 comparisons) to adjust for multiple comparisons.

* Different from worsened group.

† Different from stable group.

worsening in language, memory, and overall cognition scores following VIM DBS. However, the magnitude of these changes was small and did not reach the threshold for clinical meaningfulness. On individual-level analysis, an inverse relationship between preoperative function and post-DBS change was observed for mood and language. While these findings suggest that VIM DBS may have limited impact on neuropsychological function on average, individual variability and the potential for clinically significant changes in some patients should be considered when assessing the overall neuropsychological implications of this procedure.

Effect of VIM DBS on Depression and Anxiety

We found a statistically significant decrease in BDI-II scores at the group level following DBS, with 14.3% of patients showing clinically meaningful improvement. These findings align with previous research suggesting improvement in depression following VIM DBS for ET.[13,27] One prospective multicenter study of 118 ET patients found a significant decrease in BDI-II scores from 8.8 to 6.8 following unilateral VIM DBS.[27] Similarly, a retrospective study of 71 patients showed a 2.25-point decrease in BDI-II scores postoperatively.[28] Several studies have also reported nonsignificant decreases in BDI-II scores. One study reported a nonsignificant decline in BDI-II scores from 7.52 to 6.62 in 50 patients.[13] Another reported a BDI-II score decline from 6.14 to 5.61 in 40 patients 1 year following VIM DBS.[29] While some studies have found statistically significant decreases in depression scores after VIM DBS, the majority of these findings may not have been clinically meaningful due to the small magnitude.[13,27,29] A 3-point reduction in the BDI-II score has been found to be the minimal clinically important difference.[30] Similarly, our findings did not meet this threshold for clinical meaningfulness. Our results also suggest that the relationship between preoperative depression and post-DBS outcomes may be more complex than previously thought. Currently, severe depression is considered a contraindication for DBS due to concerns that surgery may exacerbate depression.[31] Interestingly, we found that patients who had improvement in depression postoperatively had significantly higher preoperative depression scores. However, a limitation of our study is that patients, on average, had relatively low preoperative depression scores. Further study is needed in prospective cohorts with more severe depression symptoms to better understand this relationship.

We did not find a change in anxiety scores following VIM DBS. One study of 50 ET patients found that 34% had an improvement in anxiety following VIM DBS,[13] but when BAI was adjusted to remove items that could be accounted for by tremor symptoms (hand trembling and shakiness), the improvement in anxiety no longer occurred. Another study found that anxiety, as measured by the Profile of Mood States, was significantly improved in 40 ET patients who had undergone unilateral VIM DBS.[29] It has been suggested that anxiety may be a primary symptom of ET and not necessarily occur secondary to tremor.[4] The absence of improvement in anxiety following DBS surgery or the correlation between tremor improvement and a change in anxiety scores adds support for this theory. However, previous studies have documented associations among changes in mood, anxiety, and self-reported (but not clinician-rated) tremor severity,[29] suggesting a need for further investigation. These findings highlight the importance of addressing anxiety as a distinct component in the management of ET patients undergoing DBS. Fur-

TABLE 6. Individual-level memory changes after DBS among 139 patients

Variable	Memory Improved (n = 25)	Memory Stable (n = 93)	Memory Worsened (n = 21)	Statistic	p Value	Effect Size
Demographics						
Age in yrs	68.24 ± 11.65	66.78 ± 9.30	64.06 ± 12.23	F = 0.982	0.377	ω^2 = 0.000
Female sex	7 (28.0)	55 (59.1)	13 (61.9)	χ^2 = 8.320	0.016	V = 0.245
Race						
White	25 (100)	90 (96.8)	20 (95.2)	χ^2 = 1.048	0.592	V = 0.087
Black	—	3 (3.2)	1 (4.8)			
Neuropsychological evaluation						
FU in days	341.56 ± 204.41	516.80 ± 539.40	418.29 ± 254.26	F = 1.573	0.211	ω^2 = 0.004
Preop BDI-II score	8.61 ± 7.40	9.64 ± 6.44	12.57 ± 7.85	F = 2.066	0.131	ω^2 = 0.008
Change in BDI-II score	0.17 ± 5.61	−0.57 ± 5.95	−4.43 ± 7.41	F = 3.826	0.025	ω^2 = 0.023
Preop BAI score	5.67 ± 6.66*	6.60 ± 6.11	16.67 ± 8.29†	F = 6.928	**0.002**	ω^2 = 0.079
Change in BAI score	0.56 ± 3.61	0.12 ± 6.24	−9.83 ± 8.35	F = 4.646	0.024	ω^2 =0.148
Preop attention score	−0.55 ± 0.75	−0.61 ± 0.72	−0.59 ± 0.68	F = 0.057	0.945	ω^2 = −0.007
Change in attention score	−0.01 ± 0.58	−0.07 ± 0.64	−0.03 ± 0.57	F = 0.113	0.894	ω^2 = −0.007
Preop executive function score	−0.40 ± 0.69	−0.33 ± 0.56	−0.38 ± 0.62	F = 0.173	0.841	ω^2 = −0.006
Change in executive function score	−0.21 ± 0.66	−0.25 ± 0.68	−0.33 ± 0.69	F = 0.192	0.825	ω^2 = −0.006
Preop language score	−0.13 ± 0.63	−0.19 ± 0.57	−0.36 ± 0.65	F = 0.920	0.401	ω^2 = −0.001
Change in language score	−0.08 ± 0.52	−0.16 ± 0.62	−0.01 ± 0.77	F = 0.576	0.564	ω^2 = −0.003
Preop memory score	−0.90 ± 0.89*†	0.10 ± 0.93	−0.05 ± 0.78	F = 11.950	**<0.001**	ω^2 = 0.078
Change in memory score	0.31 ± 0.47*†	−0.28 ± 0.79	−0.46 ± 0.48	F = 8.664	**<0.001**	ω^2 = 0.056
Preop visuospatial score	0.11 ± 0.92	0.06 ± 0.69	−0.03 ± 0.93	F = 0.188	0.829	ω^2 = −0.006
Change in visuospatial score	−0.02 ± 0.57	−0.21 ± 0.97	−0.01 ± 0.51	F = 0.828	0.439	ω^2 = −0.001
Motor scores						
Preop FTM						
Total	49.67 ± 12.41	47.64 ± 13.26	57.00 ± 15.09	F = 2.228	0.118	ω^2 = 0.021
Lt	14.06 ± 4.10	13.74 ± 5.90	17.36 ± 5.00	F = 2.379	0.103	ω^2 = 0.025
Rt	15.35 ± 4.87	15.00 ± 6.02	16.57 ± 5.19	F = 0.371	0.692	ω^2 = −0.012
Preop WHIGET						
Total	25.00 ± 10.39	29.22 ± 8.09	28.43 ± 9.52	F = 0.497	0.610	ω^2 = −0.007
Lt	10.50 ± 5.80	13.63 ± 5.01	11.14 ± 5.76	F = 1.347	0.267	ω^2 = 0.005
Rt	14.50 ± 5.07	15.59 ± 4.26	17.29 ± 5.06	F = 0.631	0.535	ω^2 = −0.005
TIR	3.60 ± 0.66	3.46 ± 0.54	3.55 ± 0.52	F = 0.247	0.782	ω^2 = −0.001
Electrode characteristics						
Laterality						
Bilat	24 (96.0)	78 (83.9)	19 (90.5)	χ^2 = 14.824	0.063	V = 0.231
Unilat lt	1 (4.0)	11 (11.8)	2 (9.5)			
Unilat rt	—	4 (4.3)	—			
Stimulation parameters						
Voltage (V)						
Lt	2.25 ± 1.10	2.69 ± 0.85	2.83 ± 1.07	F = 1.920	0.152	ω^2 = 0.009
Rt	1.88 ± 1.00	2.23 ± 0.98	2.36 ± 0.96	F = 2.107	0.128	ω^2 = 0.013
Current (mA)						
Lt	1.92 ± 0.71	2.66 ± 1.33	2.63 ± 1.25	F = 1.559	0.223	ω^2 = 0.013
Rt	1.73 ± 0.62	2.48 ± 1.00	2.36 ± 0.96	F = 2.391	0.105	ω^2 = 0.033
Frequency (Hz)						
Lt	138.86 ± 20.58	131.25 ± 13.42	135.83 ± 15.17	F = 2.451	0.091	ω^2 = 0.012
Rt	123.68 ± 28.28	132.81 ± 16.54	137.81 ± 16.22	F = 2.618	0.078	ω^2 = 0.015

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TABLE 6. Individual-level memory changes after DBS among 139 patients

Variable	Memory Improved (n = 25)	Memory Stable (n = 93)	Memory Worsened (n = 21)	Statistic	p Value	Effect Size
Stimulation parameters (*continued*)						
Pulse width (μsec)						
Lt	84.78 ± 18.80	83.90 ± 22.04	95.00 ± 27.28	F = 1.848	0.162	ω^2 = 0.007
Rt	83.00 ± 13.80	78.78 ± 21.64	85.63 ± 29.20	F = 0.807	0.449	ω^2 = –0.002
Position						
X						
Lt	15.99 ± 1.76	15.00 ± 4.79	15.66 ± 0.99	F = 0.155	0.857	ω^2 = –0.016
Rt	–14.09 ± 1.57	–15.11 ± 5.32	–15.46 ± 1.24	F = 0.114	0.893	ω^2 = –0.020
Y						
Lt	3.23 ± 1.00	4.38 ± 1.69	3.88 ± 2.87	F = 1.031	0.364	ω^2 = 0.001
Rt	2.68 ± 1.94	2.99 ± 1.84	3.36 ± 3.23	F = 0.134	0.875	ω^2 = –0.019
Z						
Lt	2.51 ± 4.51	4.03 ± 3.25	3.06 ± 3.89	F = 0.583	0.562	ω^2 = –0.008
Rt	2.48 ± 3.57	5.90 ± 2.65	7.79 ± 5.17	F = 3.951	0.027	ω^2 = 0.060

Values are expressed as the mean ± standard deviation or number (%), unless indicated otherwise. Boldface type indicates statistical significance. Significance set at p < 0.003 (14 comparisons) to adjust for multiple comparisons.
* Different from worsened group.
† Different from stable group.

thermore, these findings emphasize the need for additional research to elucidate the underlying mechanisms and factors contributing to anxiety in ET, which could lead to more-targeted interventions for symptom relief.

Effect of VIM DBS on Cognition

At the group level, we found statistically significant but small-magnitude declines in overall cognition as well as language and memory domain scores following DBS. There were no significant changes in attention, executive function, or visuospatial function scores. Several studies on cognition after VIM DBS for ET have reported mixed findings, including no change in overall cognition,[32] improvements in visuoperceptual abilities, visuomotor coordination, verbal memory, and confrontation naming,[13,29] and declines in language[29] and working memory.[13] We found statistically significant declines in language and memory, specifically word list and story memory measures assessing encoding and retrieval. However, the effect size was small and not expected to be clinically meaningful. Additionally, a larger number of patients had postoperative improvement rather than a decline in memory function, suggesting that the decline in the mean memory domain score postoperatively may be due to larger declines in a small number of patients. Previous studies have hypothesized that these deficits may stem from cerebello-thalamo-cortical dysfunction,[33] which can lead to difficulties in initiating and maintaining complex information processing strategies.[34]

At the individual level, 14.4% of patients had improved language, whereas 18.7% had worsened language following DBS. Similarly, 18.0% showed improved memory, while 15.1% had worsened memory following DBS. An inverse relationship was observed between preoperative function and post-DBS change in language, such that those with improved language had lower preoperative scores in this domain. For memory, while ANOVA revealed that patients with improved postoperative function had lower preoperative memory scores, multivariable regression showed that preoperative scores positively correlated with postoperative change. This discrepancy may be due to a U-shaped relationship, as patients with unchanged memory scores had higher preoperative scores than those of both the improved and declined patients. Additionally, controlling for other contributing variables including BAI in the multivariate analysis may have impacted the direction of this relationship. Patients with improved overall cognition had greater improvements in attention, language, and visuospatial function compared to those with stable or worsened overall cognition following DBS. Similarly, those who had worsened overall cognition, compared to those who had stable overall cognition, had a greater decline in attention and visuospatial functioning. The finding of worsened overall cognition has been previously observed, with some authors reporting that approximately half of patients showed at least a slight overall cognitive decline following DBS.[13] One limitation of our study is that we were unable to control for the effect of disease progression or potential medication on cognition. Gradual cognitive decline can also be part of the natural progression of ET, limiting the ability to attribute this finding to DBS.[35] Medications commonly used to treat ET, such as propranolol,[36] can also negatively impact cognitive functioning. Following DBS surgery, many patients discontinue these medications. It is possible that medication reductions may positively influence cognition after DBS and may help counteract any surgery-related negative effects. Regardless, the overall

TABLE 7. Individual-level overall cognition changes after DBS among 139 patients

Variable	Cognition Improved (n = 15)	Cognition Stable (n = 100)	Cognition Worsened (n = 24)	Statistic	p Value	Effect Size
Demographics						
Age in yrs	64.94 ± 6.05	65.97 ± 10.85	70.05 ± 5.41	F = 1.431	0.243	ω^2 = 0.003
Female sex	9 (60.0)	59 (59.0)	15 (62.5)	χ^2 = 1.963	0.375	V = 0.119
Race						
White	15 (100.0)	99 (99.0)	21 (87.5)	χ^2 = 7.349	0.035	V = 0.230
Black	—	1 (1.0)	3 (12.5)			
Neuropsychological evaluation						
FU in days	481.80 ± 274.60	464.98 ± 469.10	506.71 ± 551.01	F = 0.053	0.948	ω^2 = –0.007
Preop BDI-II score	6.93 ± 5.89	9.97 ± 7.03	10.29 ± 6.36	F = 0.384	0.131	ω^2 = –0.005
Change in BDI-II score	0.86 ± 5.00	–0.83 ± 6.62	–2.21 ± 6.01	F = 1.331	0.268	ω^2 = 0.003
Preop BAI score	7.14 ± 4.81	7.84 ± 7.05	11.29 ± 7.10	F = 1.009	0.371	ω^2 = –0.001
Change in BAI score	–1.43 ± 7.63	–2.10 ± 4.90	–3.60 ± 7.37	F = 7.213	0.015	ω^2 = 0.228
Preop attention score	–0.72 ± 0.84	–0.62 ± 0.70	–0.35 ± 0.70	F = 0.671	0.513	ω^2 = –0.002
Change in attention score	0.626 ± 0.51*†	–0.05 ± 0.58	–0.493 ± 0.45*	F = 16.199	**0.001**	ω^2 = 0.102
Preop executive function score	–0.60 ± 0.78	–0.32 ± 0.58	–0.24 ± 0.56	F = 1.883	0.156	ω^2 = 0.006
Change in executive function score	0.34 ± 0.49	–0.28 ± 0.66	–0.47 ± 0.61	F = 5.717	0.004	ω^2 = 0.033
Preop language score	–0.19 ± 0.52	–0.25 ± 0.60	0.08 ± 0.57	F = 2.585	0.079	ω^2 = 0.011
Change in language score	0.45 ± 0.49*†	–0.14 ± 0.61	–0.56 ± 0.54	F = 8.026	**<0.001**	ω^2 = 0.050
Preop memory score	–0.20 ± 0.88	–0.11 ± 1.01	0.16 ± 0.93	F = 0.048	0.953	ω^2 = –0.007
Change in memory score	–0.03 ± 0.53	–0.22 ± 0.77	–0.17 ± 0.58	F = 1.067	0.347	ω^2 = 0.001
Preop visuospatial score	0.09 ± 0.73	0.03 ± 0.80	0.26 ± 0.80	F = 1.598	0.206	ω^2 = 0.004
Change in visuospatial score	0.41 ± 0.49†	–0.10 ± 0.82	–0.65 ± 0.72*	F = 8.266	**<0.001**	ω^2 = 0.055
Motor scores						
FTM						
Total	49.89 ± 12.71	50.74 ± 14.82	50.41 ± 13.42	F = 0.193	0.825	ω^2 = –0.014
Lt	14.75 ± 5.95	14.97 ± 5.63	15.00 ± 4.31	F = 0.195	0.824	ω^2 = –0.015
Rt	15.13 ± 5.06	15.66 ± 5.82	14.50 ± 4.41	F = 0.267	0.767	ω^2 = –0.014
WHIGET						
Total	30.50 ± 13.23	28.84 ± 8.21	29.50 ± 9.09	F = 1.228	0.299	ω^2 = 0.003
Lt	13.50 ± 8.12	13.20 ± 5.19	13.13 ± 5.89	F = 0.701	0.499	ω^2 = –0.004
Rt	17.00 ± 5.25	15.64 ± 4.32	16.38 ± 4.41	F = 1.246	0.294	ω^2 = 0.003
TIR	3.75 ± 0.27	3.54 ± 0.54	3.25 ± 0.63	F = 1.558	0.222	ω^2 = 0.003
Electrode characteristics						
Laterality						
Bilat DBS	14 (93.3)	85 (85.0)	22 (91.7)	χ^2 = 11.685	0.166	V = 0.205
Lt DBS	1 (6.7)	12 (12.0)	1 (4.2)			
Rt DBS	—	3 (3.0)	1 (4.2)			
Stimulation parameters						
Voltage (V)						
Lt	2.77 ± 1.37	2.61 ± 0.89	2.86 ± 1.09	F = 0.327	0.722	ω^2 = –0.007
Rt	2.33 ± 0.63	2.23 ± 1.04	2.09 ± 1.27	F = 0.074	0.929	ω^2 = –0.011
Current (mA)						
Lt	1.62 ± 0.34	2.59 ± 1.35	2.47 ± 0.56	F = 1.443	0.248	ω^2 = 0.010
Rt	1.90 ± 0.82	2.38 ± 1.00	1.98 ± 0.73	F = 0.768	0.471	ω^2 = –0.006
Frequency (Hz)						
Lt	130.00 ± 12.73	133.74 ± 16.04	132.50 ± 16.03	F = 0.260	0.772	ω^2 = –0.006
Rt	129.29 ± 1.89	132.10 ± 20.43	132.27 ± 16.94	F = 0.069	0.933	ω^2 = –0.009

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TABLE 7. Individual-level overall cognition changes after DBS among 139 patients

Variable	Cognition Improved (n = 15)	Cognition Stable (n = 100)	Cognition Worsened (n = 24)	Statistic	p Value	Effect Size
Stimulation parameters (*continued*)						
Pulse width (μsec)						
Lt	82.22 ± 13.02	86.47 ± 23.57	81.67 ± 18.50	F = 0.357	0.700	$\omega^2 = -0.005$
Rt	77.14 ± 16.04	83.15 ± 22.18	60.91 ± 3.02	F = 5.702	0.004	$\omega^2 = 0.041$
Position						
X						
Lt	13.58 ± 7.76	15.19 ± 4.57	15.42 ± 0.93	F = 0.032	0.969	$\omega^2 = -0.018$
Rt	–11.97 ± 9.16	–14.95 ± 5.17	–15.82 ± 1.35	F = 0.072	0.930	$\omega^2 = -0.021$
Y						
Lt	3.86 ± 1.62	4.23 ± 1.82	3.91 ± 2.34	F = 2.087	0.135	$\omega^2 = 0.020$
Rt	2.22 ± 2.07	2.99 ± 2.03	2.45 ± 2.19	F = 0.031	0.970	$\omega^2 = -0.022$
Z						
Lt	3.29 ± 2.20	3.96 ± 3.47	4.21 ± 2.61	F = 0.525	0.595	$\omega^2 = -0.009$
Rt	4.54 ± 3.57	5.80 ± 2.98	6.88 ± 4.08	F = 0.263	0.770	$\omega^2 = -0.016$

Values are expressed as the mean ± standard deviation or number (%), unless indicated otherwise. Boldface type indicates statistical significance. Significance set at $p < 0.003$ (14 comparisons) to adjust for multiple comparisons.

* Different from stable group.

† Different from worsened group.

minimal cognitive changes found in this population suggest that for most patients, DBS is not likely to result in clinically significant negative changes in neuropsychological functions. The inverse relationships observed between baseline scores and changes may represent regression to the mean. Prior studies have identified certain variables like stimulation parameters[13,37] and postoperative complications[13] that are associated with an increased risk of cognitive decline in ET patients undergoing DBS. Continuing to investigate predictive factors is necessary to improve patient selection and counseling for this intervention.

Study Limitations

Our study has several limitations. First, the retrospective design inherently introduces limitations, such as missing or incomplete data. Due to a change in our institution's neuropsychological test battery protocol during the study period, subsets of patients were administered different but overlapping batteries. However, the tests were carefully selected to ensure the measurement of similar cognitive domains across batteries. However, standardized normative data allowed scores from analogous tests to be combined and analyzed together based on the construct being evaluated. Another limitation of this study is the potential for selection bias due to the retrospective design and the fact that only a subset of patients who had undergone DBS chose to complete follow-up neuropsychological testing. However, our analysis revealed no statistically significant differences in preoperative demographic or clinical variables between patients who did and those who did not undergo follow-up testing, suggesting that these populations were similar overall at baseline. Factors such as travel distance, overall satisfaction with the DBS procedure, or socioeconomic status may have influenced patient decisions to return for follow-up, further skewing this sample. It is possible that a change in depression or cognition impacted patient decisions to undergo neuropsychological testing; thus, our study sample may be enriched for patients who had either greater improvements or worsening. Given the retrospective nature of this study and the lack of a control group, we were unable to control for the impact of medication changes, education, test-retest effects, surgical effects, or postoperative complications on neuropsychological changes following DBS. As a result, it is challenging to determine whether the observed changes are primarily due to the natural progression of ET or the effects of DBS surgery or stimulation. ET patients have a higher incidence of depression than healthy controls;[7] therefore, the small-magnitude improvement in postoperative depression scores is less likely to be related to disease progression. Conversely, ET patients experience cognitive impairments that worsen with time;[9] therefore, it is possible that the small-magnitude worsening in language and memory scores that we observed was secondary to disease progression. Additionally, while we used definitions of clinical meaningfulness based on the literature, they may not fully capture real-world functional changes. For example, information about changes in antidepressant medications may provide additional information about the meaningfulness of changes in depression scores; unfortunately, such information was not available in the current study. Further research is needed to better establish clinically meaningful thresholds for neuropsychological outcomes in this context. Lastly, due to postoperative testing protocols, our study focused on short-term outcomes, with a median follow-up of 306.5 days after DBS surgery. Long-term follow-up studies are necessary to evaluate the durability and stability of the observed effects over time. Future pro-

spective studies addressing these limitations will contribute to a more robust understanding of the effects of DBS on nonmotor symptoms and provide additional insights for clinical decision-making.

Conclusions

ET patients had statistically significant but likely clinically insignificant improvement in depression scores and worsening of overall cognition, language, and memory scores after VIM DBS. There were no significant changes in anxiety, executive function, attention, or visuospatial function scores. An inverse relationship between preoperative function and post-DBS change was observed for mood and language.

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Supplemental Information

Online-Only Content

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