

## 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 ( $9.82 \pm 6.77$  vs  $8.29 \pm 6.18$ ,  $p < 0.001$ , 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 ( $p < 0.001$ ,  $\phi^2 = 0.226$ ). Patients with worsened language (18.7%) had higher preoperative language scores ( $p < 0.001$ ,  $\phi^2 = 0.058$ ). Patients with worsened memory (15.1%) had higher BAI scores preoperatively ( $p = 0.002$ ,  $\phi^2 = 0.079$ ). 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.

<https://thejns.org/doi/abs/10.3171/2024.11.JNS241990>

**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.

**SUBMITTED** August 14, 2024. **ACCEPTED** November 19, 2024.

**INCLUDE WHEN CITING** Published online March 7, 2025; DOI: 10.3171/2024.11.JNS241990.

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**E**SSENTIAL tremor (ET) impacts approximately 2.2% of the US population<sup>1</sup> and almost 25 million patients worldwide.<sup>2</sup> 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.<sup>3,4</sup> 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.<sup>4–7</sup> 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.<sup>8</sup> Additionally, multivariate analysis of ET patients compared to healthy controls.<sup>7,9</sup> Cognitive impairment can appear before tremor, similarly suggesting that it may be a primary symptom of ET.<sup>10</sup> These neurobehavioral and cognitive changes have been associated with ET 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.<sup>11</sup> While the benefit of DBS on motor symptoms remains poorly understood,<sup>12</sup> 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.<sup>13</sup> These differences may depend on factors such as patient demographics, measurement differences, intraoperative complications, and DBS targeting.<sup>14</sup> A meta-analysis of seven studies found that VIM DBS was associated with improvements in cognitive scores at the group level after VIM DBS, although 46% of individual ET patients exhibited subtle decrements in different cognitive scores compared to normative data.<sup>13</sup> Conversely, a meta-analysis of seven studies found that STN DBS was associated with improvements in depression scores among a pooled sample of ET patients.<sup>15</sup>

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).<sup>16,17</sup> 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.<sup>18,19</sup> Both STN and GPI DBS have been associated with greater rates of cognitive decline than pharmacological treatment in PD.<sup>20,21</sup> 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 65 patients were identified from the Vanderbilt Institutional Review Board 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).<sup>22</sup> 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, general anesthesia, and CT and MRI were performed. The surgical targets and trajectories were then planned, and a 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 effect. 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.<sup>23</sup> 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.<sup>24</sup> 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

Reckgvpv ygtg encuuk tgf cu jcxkpi c enpkpccnn ukipk t-cant 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.<sup>13</sup> Improvement cpf yqtugpkpi qh cpzkgv rquvqrgtcvkxgn ygtg fgtpgf kp c uk o knct o cpggt wukpi DCK ugxgtkv encuuk tcevkqpu cpf change scores.<sup>13</sup>

Individual cognitive test raw scores were converted to standardized norm-referenced z-scores (mean  $\pm$  SD, 0.0  $\pm$  1.0). Individual test z-scores within the same 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 r tqvqemu. uq o g qh v j g urgek t e eq i p k v x g v g u v u e j c p i g f r c t v 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.

Qp cp kpfkxkfwcn rckgvp ngxgn. c ukipk tcepv rquvqrgtcvkxg ejcpig kp c eq i p k v x g v g u v u y c u f g t p g f c u c f g e n k p g or improvement of  $> 1$  SD on that test score. Patients improved or worsened in a domain if their score changed cv ngcu v 3 UF y kv j k p v j c v f q o c k p Reckgvpv ygtg fgtpgf 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.<sup>13</sup> If a patient improved in at least two more domains than the number of domains in which v j g f g e n k p g f. v j g f ygtg encuuk tgf cu k o r t q x g f 0 K h v j g declined in at least two more domains than the number in y j k e j v j g k o r t q x g f. v j g f ygtg encuuk tgf cu yqtugpgf 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 cp f 3 k p f k e c v k p i p q d g p g t v \*Supplementary Table 2).

### Electrode and Stimulation Characteristics

Active electrode contact and stimulation parameters ygtg kfgpvk tgf htq o c t g x k y q h v j g g n g e v t q p k e o g f k e c n 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)<sup>25</sup> 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  $\pm$  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 ukipk tcepv n f k h h g t g p v h q m n y k p i F D U c v i t q w r n g x g n. c 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 cp f r t g q r g t c v k x g x c t k c d n g u u k i p k t c e p v q p k p f k x k f w c n n g x g n ANOVA for that domain. Effect sizes were calculated using phi ( $\sqrt{}$ ) for 2 X 2 chi-square tests, Cramer's V for 2 X 3 chi-square tests, Cohen's  $d$  for t-test comparisons, omega ( $\emptyset^2$ ) for ANOVA comparisons, and rank-biserial correlation for Mann-Whitney U-test comparisons (Supplementary Table 3) Y g f g t p g f c e n k p k e c n n u k i p k t c e p v e j c p i g k p neuropsychological test measures as a z-score change  $> 1.5$  in combination with a medium or larger effect size.<sup>26</sup> As previously described,<sup>13</sup> rckgvpv ygtg encuuk tgf cu jcxkpi c enpkpccnn ukipk tcepv k o r t q x g o g p v k p f g r t g u u k q p r q u v q r e r a t i v e l y i f t h e y m e t t h e f o l l o w i n g c r i t e r i a : 1) i m p r o v e m e n t k p v j g f g r t g u u k q p e c v i q t v q c n g u u u g x g t g e n c u u k t c e v k q p and 2) a BDI-II score decrease by at least 3 points. Statisticecn ukipk tcepeg ycu ugv vq / = 0.05. Bonferroni correction was used to adjust for multiple comparisons. For analyses





TABLE 2. Neuropsychological changes following DBS surgery

Test	No.	Preop Score	No.	Postop Score	p Value	Effect Size: Cohen's <i>d</i>	No. Improved	No. Stable	No. Worsened
Depression: BDI-II	126	9.82 ± 6.77	126	8.92 ± 6.18	<b>&lt;0.001</b>	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	Φ0.596	135	Φ0.671	0.249	0.100	29 (21.5)	78 (57.8)	28 (20.7)
Speeded color naming	123	Φ0.750	132	Φ0.817			18		20
Speeded word reading	121	Φ0.736	133	Φ0.828			12		15
Speeded visuomotor sequencing	125	Φ0.539	122	Φ0.302			19		13
Attention span & working memory	132	Φ0.302	138	Φ0.531			4		20
Executive function (z-score)	139	Φ0.350	139	Φ0.460	0.028	0.188	15 (10.8)	95 (68.3)	29 (20.9)
Speeded visuomotor set-shifting	123	Φ0.554	119	Φ0.623			12		15
Speeded response inhibition/set-shifting	123	Φ0.573	131	Φ0.811			10		27
Language (z-score)	139	Φ0.204	139	Φ0.328	<b>0.003</b>	0.259	20 (14.4)	93 (66.9)	26 (18.7)
Confrontation naming	128	0.121	121	0.344			13		9
Semantic Fluency	130	Φ0.563	137	Φ0.563			6		20
Phonemic Fluency	133	Φ0.667	136	Φ0.865			11		14
Memory (z-score)	139	Φ0.115	139	Φ0.452	<b>&lt;0.001</b>	0.336	25 (18.0)	93 (66.9)	21 (15.1)
Word list learning	130	Φ0.401	129	Φ0.439			14		7
Word list recall	133	0.098	134	Φ0.387			11		37
Story learning	122	Φ0.010	122	Φ0.173			14		9
Story recall	132	Φ0.037	130	Φ0.318			11		16
Visuospatial function (z-score)	131	0.059	131	Φ0.033	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	Φ0.038			16		22
Overall cognition (z-score)	139	Φ0.244	139	Φ0.387	<b>&lt;0.001</b>	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 language scores (mean ± standard deviation, 16.67 ± 8.29 vs 5.67 ± 6.66 vs 6.60 ± 6.11, respectively,  $F = 6.928$ ,  $p = 0.002$ ,  $\eta^2 = 0.079$ ; 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 ( $r = -0.573$ ,  $p < 0.001$ ; Table 5).

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

Twenty patients had improved memory following VIM DBS, 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,  $F = 6.928$ ,  $p = 0.002$ ,  $\eta^2 = 0.079$ ; Table 6). Patients with improved memory domain scores had lower preoperative memory scores than those in the patients with stable and worsened memory

scores (mean ± standard deviation, 16.67 ± 8.29 vs 5.67 ± 6.66 vs 6.60 ± 6.11, respectively,  $F = 6.928$ ,  $p = 0.002$ ,  $\eta^2 = 0.079$ ; Table 6). Conversely, multivariable regression revealed that preoperative memory scores were positively correlated with a change in memory score postoperatively ( $r = 0.727$ ,  $p < 0.001$ ; Table 6).

### 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 for visual spatial function (mean ± standard deviation, 16.67 ± 8.29 vs 5.67 ± 6.66 vs 6.60 ± 6.11, respectively,  $F = 6.928$ ,  $p = 0.002$ ,  $\eta^2 = 0.079$ ; 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 that overall cognition improved following VIM DBS, with 15 (10.8%) patients showing improvement, 100 (71.9%) showing stability, and 24 (17.3%) showing worsening. This finding is consistent with previous studies showing that VIM DBS can improve overall cognition in ET patients.

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	Ø² = 0.023
Female sex	15 (83.3)	52 (53.1)	7 (70.0)	Ø² = 6.059	0.048	V = 0.227
Race						
White	16 (88.9)	96 (98.0)	10 (100.0)	Ø² = 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	Ø² = 0.010
Preop BDI-II score	19.44 ± 4.46*†	7.73 ± 5.63	11.50 ± 4.60	F = 35.521	<0.001	Ø² = 0.226
Change in BDI-II score	Φ10.3 ± 6.04*†	Φ0.15 ± 4.25	7.2 ± 3.70*	F = 56.325	<0.001	Ø² = 0.319
Preop BAI score	12.13 ± 10.15	6.00 ± 5.07	6.50 ± 5.32	F = 6.209	0.004	Ø² = 0.086
Change in BAI score	Φ10.2 ± 9.36	Φ0.67 ± 5.98	2.03 ± 4.32	F = 3.856	0.040	Ø² = 0.120
Preop attention score	Φ0.77 ± 0.84	Φ0.49 ± 0.70	Φ0.34 ± 0.55	F = 1.228	0.297	Ø² = 0.002
Change in attention score	Φ0.08 ± 0.65	Φ0.05 ± 0.62	Φ0.45 ± 0.38	F = 1.427	0.244	Ø² = 0.004
Preop executive function score	Φ0.42 ± 0.63	Φ0.32 ± 0.60	Φ0.20 ± 0.51	F = 0.355	0.702	Ø² = Φ0.005
Change in executive function score	Φ0.15 ± 0.56	Φ0.24 ± 0.67	Φ0.33 ± 0.78	F = 0.253	0.777	Ø² = Φ0.006
Preop language score	Φ0.25 ± 0.56	Φ0.17 ± 0.61	Φ0.13 ± 0.71	F = 0.401	0.671	Ø² = Φ0.005
Change in language score	Φ0.13 ± 0.72	Φ0.12 ± 0.62	Φ0.29 ± 0.64	F = 0.241	0.786	Ø² = Φ0.007
Preop memory score	Φ0.24 ± 0.80	Φ0.06 ± 1.04	Φ0.06 ± 0.87	F = 0.292	0.748	Ø² = Φ0.006
Change in memory score	Φ0.18 ± 0.52	Φ0.09 ± 0.74	Φ0.42 ± 0.69	F = 1.151	0.320	Ø² = 0.001
Preop visuospatial score	Φ0.01 ± 0.83	0.14 ± 0.78	0.01 ± 0.82	F = 0.282	0.755	Ø² = Φ0.006
Change in visuospatial score	Φ0.15 ± 0.99	Φ0.10 ± 0.74	Φ0.80 ± 0.99	F = 3.206	0.044	Ø² = 0.020
Motor scores						
FTM						
Total	50.25 ± 16.47	50.43 ± 13.45	57.67 ± 11.68	F = 0.888	0.418	Ø² = Φ0.002
Lt	12.88 ± 4.09	15.05 ± 5.02	14.00 ± 6.56	F = 0.553	0.579	Ø² = Φ0.019
Rt	14.13 ± 6.94	15.87 ± 4.56	21.00 ± 4.58	F = 1.543	0.225	Ø² = 0.011
WHIGET						
Total	27.63 ± 12.72	29.17 ± 7.54	24.00 ± 6.53	F = 1.033	0.362	Ø² = 0.001
Lt	12.25 ± 7.42	13.28 ± 5.29	12.14 ± 3.98	F = 0.106	0.900	Ø² = Φ0.015
Rt	15.38 ± 5.83	15.89 ± 3.40	11.86 ± 3.02	F = 3.396	0.040	Ø² = 0.038
TIR	3.56 ± 0.68	3.50 ± 0.49	3.75 ± 0.35	F = 0.225	0.978	Ø² = Φ0.008
Electrode characteristics						
Laterality						
Bilat	15 (83.3)	86 (87.8)	10 (100.0)	Ø² = 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	Ø² = Φ0.012
Rt	2.79 ± 1.34	2.04 ± 0.99	2.45 ± 0.67	F = 2.229	0.115	Ø² = 0.017
Current (mA)						
Lt	1.73 ± 0.53	2.33 ± 1.13	3.23 ± 0.45	F = 1.739	0.191	Ø² = 0.020
Rt	2.35 ± 0.51	2.21 ± 1.00	2.73 ± 1.14	F = 0.394	0.677	Ø² = Φ0.018
Frequency (Hz)						
Lt	134.64 ± 30.16	130.91 ± 8.54	146.25 ± 23.26	F = 4.182	0.018	Ø² = 0.030
Rt	130.83 ± 28.75	128.68 ± 15.88	141.43 ± 20.35	F = 1.564	0.215	Ø² = 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 ( <i>continued</i> )						
Pulse width (μsec)						
Lt	98.57 ± 23.16	82.26 ± 20.44	90.00 ± 27.77	F = 3.731	0.027	Ø <sup>2</sup> = 0.025
Rt	89.17 ± 28.43	78.11 ± 21.50	81.43 ± 14.64	F = 1.315	0.274	Ø <sup>2</sup> = 0.003
Position						
X						
Lt	15.22 ± 1.03	14.76 ± 5.13	17.21 ± 0.88	F = 0.355	0.704	Ø <sup>2</sup> = Ø0.015
Rt	Ø15.00 ± 0.52	Ø14.67 ± 5.67	Ø16.93 ± 0.15	F = 0.161	0.852	Ø <sup>2</sup> = Ø0.024
Y						
Lt	4.66 ± 4.08	4.22 ± 1.81	3.54 ± 0.53	F = 0.256	0.776	Ø <sup>2</sup> = Ø0.018
Rt	2.94 ± 2.77	3.03 ± 1.96	2.80 ± 1.16	F = 0.014	0.986	Ø <sup>2</sup> = Ø0.028
Z						
Lt	0.12 ± 5.80	4.03 ± 2.90	6.14 ± 6.86	F = 2.622	0.085	Ø <sup>2</sup> = 0.036
Rt	4.22 ± 5.04	5.96 ± 3.48	5.54 ± 3.19	F = 0.236	0.978	Ø <sup>2</sup> = Ø0.022

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	†	t	p Value
Change in BDI-II					
Age	Ø0.022	0.051	Ø0.035	Ø0.425	0.672
Gender	Ø1.588	1.028	Ø0.124	Ø1.544	0.125
FU duration	0.001	0.001	0.041	0.509	0.611
Preop BDI-II	Ø0.465	0.076	Ø0.504	Ø6.116	<0.001
Change in language					
Age	Ø0.001	0.005	Ø0.019	Ø0.223	0.824
Gender	Ø0.023	0.104	Ø0.018	Ø0.217	0.828
FU duration	0.000	0.000	Ø0.081	Ø0.965	0.336
Preop language	Ø0.369	0.089	Ø0.351	Ø4.130	<0.001
Change in memory					
Age	Ø0.012	0.009	Ø0.163	Ø1.369	0.177
Gender	0.029	0.180	0.019	0.163	0.871
FU duration	0.000	0.000	Ø0.151	Ø1.289	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	Ø0.001	0.000	Ø0.015	Ø0.174	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	Ø² = Φ0.004
Female sex	11 (55.0)	53 (57.0)	11 (42.3)	∂² = 1.773	0.412	V = 0.113
Race						
White	20 (100.0)	91 (97.8)	24 (92.3)	∂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	Ø² = 0.001
Preop BDI-II score	9.72 ± 7.76	9.91 ± 6.98	10.16 ± 6.26	F = 0.022	0.978	Ø² = Φ0.008
Change in BDI-II score	Φ1.78 ± 7.99	Φ0.65 ± 5.95	Φ2.13 ± 6.18	F = 0.602	0.549	Ø² = Φ0.003
Preop BAI score	9.00 ± 12.45	7.60 ± 6.43	3.25 ± 4.56	F = 0.746	0.479	Ø² = Φ0.005
Change in BAI score	Φ6.25 ± 13.59	Φ2.13 ± 6.32	Φ2.32 ± 3.35	F = 0.489	0.621	Ø² = Φ0.025
Preop attention score	Φ0.62 ± 0.76	Φ0.69 ± 0.69	Φ0.25 ± 0.69	F = 3.995	0.021	Ø² = 0.022
Change in attention score	0.04 ± 0.71	0.01 ± 0.62	Φ0.35 ± 0.41	F = 3.925	0.022	Ø² = 0.021
Preop executive function score	Φ0.51 ± 0.69	Φ0.35 ± 0.58	Φ0.24 ± 0.51	F = 1.212	0.301	Ø² = 0.002
Change in executive function score	Φ0.05 ± 0.53	Φ0.32 ± 0.69	Φ0.18 ± 0.72	F = 1.471	0.233	Ø² = 0.003
Preop language score	Φ0.53 ± 0.45*	Φ0.24 ± 0.58	0.18 ± 0.56†	F = 9.566	<0.001	Ø² = 0.058
Change in language score	0.62 ± 0.39*†	Φ0.13 ± 0.56	Φ0.66 ± 0.41†	F = 35.344	<0.001	Ø² = 0.205
Preop memory score	Φ0.35 ± 1.12	0.01 ± 0.95	Φ0.38 ± 0.89	F = 2.201	0.115	Ø² = 0.009
Change in memory score	0.02 ± 0.59	Φ0.21 ± 0.80	Φ0.28 ± 0.58	F = 1.000	0.371	Ø² = 0.000
Preop visuospatial score	0.18 ± 0.77	0.02 ± 0.78	0.11 ± 0.78	F = 0.441	0.644	Ø² = Φ0.004
Change in visuospatial score	Φ0.06 ± 0.80	Φ0.14 ± 0.89	Φ0.19 ± 0.74	F = 0.134	0.874	Ø² = Φ0.007
Motor scores						
FTM						
Total	46.50 ± 10.94	52.81 ± 15.67	50.11 ± 12.50	F = 0.876	0.422	Ø² = Φ0.002
Lt	13.25 ± 4.73	16.08 ± 5.74	14.06 ± 4.87	F = 1.419	0.251	Ø² = 0.008
Rt	13.58 ± 4.44	16.38 ± 5.90	15.67 ± 5.24	F = 1.081	0.347	Ø² = 0.001
WHIGET						
Total	26.50 ± 7.09	28.66 ± 8.30	33.25 ± 8.50	F = 1.489	0.232	Ø² = 0.006
Lt	11.88 ± 5.62	13.03 ± 5.16	16.00 ± 3.85	F = 1.507	0.228	Ø² = 0.007
Rt	14.63 ± 3.89	15.63 ± 4.28	17.25 ± 5.39	F = 0.757	0.473	Ø² = Φ0.003
TIR	3.65 ± 0.63	3.57 ± 0.47	3.20 ± 0.63	F = 2.188	0.124	Ø² = 0.009
Electrode characteristics						
Laterality						
Bilat	19 (95.0)	77 (82.8)	25 (96.2)	∂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	Ø² = 0.004
Rt	2.01 ± 0.99	2.34 ± 0.96	1.98 ± 1.28	F = 1.077	0.345	Ø² = 0.001
Current (mA)						
Lt	1.55 ± 0.36	2.44 ± 1.23	3.24 ± 1.09	F = 4.594	0.016	Ø² = 0.077
Rt	2.25 ± 0.75	2.11 ± 0.99	2.84 ± 0.84	F = 1.901	0.163	Ø² = 0.021
Frequency (Hz)						
Lt	134.25 ± 14.07	132.37 ± 14.87	135.91 ± 18.43	F = 0.492	0.613	Ø² = Φ0.004
Rt	134.44 ± 14.94	133.31 ± 16.73	124.47 ± 29.10	F = 1.768	0.176	Ø² = 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 ( <i>continued</i> )						
Pulse width ( $\mu$ sec)						
Lt	84.50 $\pm$ 17.61	85.31 $\pm$ 23.98	88.18 $\pm$ 21.30	F = 0.173	0.842	$\varnothing^2 = \Phi 0.007$
Rt	78.89 $\pm$ 15.68	82.60 $\pm$ 24.10	74.21 $\pm$ 15.39	F = 1.193	0.307	$\varnothing^2 = 0.002$
Position						
X						
Lt	15.51 $\pm$ 2.01	15.07 $\pm$ 4.83	15.51 $\pm$ 1.06	F = 0.046	0.955	$\varnothing^2 = \Phi 0.018$
Rt	$\Phi 15.69 \pm 1.00$	$\Phi 14.88 \pm 5.54$	$\Phi 15.28 \pm 1.85$	F = 0.078	0.925	$\varnothing^2 = \Phi 0.020$
Y						
Lt	5.03 $\pm$ 2.36	4.08 $\pm$ 1.66	4.18 $\pm$ 2.26	F = 0.820	0.446	$\varnothing^2 = \Phi 0.003$
Rt	2.83 $\pm$ 1.13	3.00 $\pm$ 2.09	3.11 $\pm$ 1.94	F = 0.030	0.971	$\varnothing^2 = \Phi 0.022$
Z						
Lt	2.04 $\pm$ 3.34	4.17 $\pm$ 3.40	2.96 $\pm$ 3.26	F = 1.356	0.267	$\varnothing^2 = 0.007$
Rt	4.86 $\pm$ 2.66	6.18 $\pm$ 3.06	3.77 $\pm$ 3.92	F = 1.759	0.184	$\varnothing^2 = 0.016$

Values are expressed as the mean  $\pm$  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. Y j kng" v j g u g" l p f k p i u" u w i i g u v" v j c v" X K O" F D U" o c { " j c x g" limited impact on neuropsychological function on average, individual variability and the potential for clinically u k i p k l e c p v" e j c p i g u" k p" u q o g" r c v k g p v u" u j q w n f" d g" e q p u k f g t g f" when assessing the overall neuropsychological implications of this procedure.

### Effect of VIM DBS on Depression and Anxiety

Y g" h q w p f" c" u v c v k u v k e c n { " u k i p k l e c p v" f g e t g c u g" k p" D F K / K K" scores at the group level following DBS, with 14.3% of patients showing clinically meaningful improvement. These l p f k p i u" c n k i p" y k v j" r t g x k q w u" t g u g t e j" u w i i g u v k p i" k o r t q x g m e n t in depression following VIM DBS for ET.<sup>13,27</sup> One prospective multicenter study of 118 ET patients found a u k i p k l e c p v" f g e t g c u g" k p" D F K / K K" u e q t g u" h t q o" : 0 : " v q" 80 : " h q n l o w i n g u n i l a t e r a l V I M D B S.<sup>27</sup> Similarly, a retrospective study of 71 patients showed a 2.25-point decrease in BDI-II scores postoperatively.<sup>28</sup> Several studies have also reported p q p u k i p k l e c p v" f g e t g c u g" k p" D F K / K K" u e q t g u" Q p g" u w w f { " t g r q t v g f" c" p q p u k i p k l e c p v" f g e n k p g" k p" D F K / K K" u e q t g u" h t q o" 9 / 74" to 6.62 in 50 patients.<sup>13</sup> Another reported a BDI-II score decline from 6.14 to 5.61 in 40 patients 1 year following VIM DBS.<sup>29</sup> While some studies have found statistically u k i p k l e c p v" f g e t g c u g" k p" f g r t g u u k q p" u e q t g u" c h v g t" X K O" F D U." v j g" o c l q t k v { " q h" v j g u g" l p f k p i u" o c { " p q v" j c x g" d g g p" e n k p k e c n { " meaningful due to the small magnitude.<sup>13,27,29</sup> A 3-point reduction in the BDI-II score has been found to be the

minimal clinically important difference.<sup>30</sup> Similarly, our l p f k p i u" f k f" p q v" o g g v" v j k u" v j t g u j q n f" h q t" e n k p k e c n" o g c p i n g f u l n e s s. 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.<sup>31</sup> Interestingly, we found that patients who had improvement k p" f g r t g u u k q p" r q u v q r g t c v k x g n { " j c f" u k i p k l e c p v n { " j k i j g t" r t g o p e r a t i v e d e p r e s s i o n s c o r e s. 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.

Y g" f k f" p q v" l p f" c" e j c p i g" k p" c p z k g v { " u e q t g u" h q n n q y k p i" VIM DBS. One study of 50 ET patients found that 34% had an improvement in anxiety following VIM DBS,<sup>13</sup> 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 v j g" R t q l i n g" q h" O q q f" U v c v g u." y c u" u k i p k l e c p v n { " k o r t q x g f" k p" 40 ET patients who had undergone unilateral VIM DBS.<sup>29</sup> It has been suggested that anxiety may be a primary symptom of ET and not necessarily occur secondary to tremor.<sup>4</sup> 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,<sup>29</sup> suggesting a p g g f" h q t" h w t v j g t" k p x g u v k i c v k q p" V j g u g" l p f k p i u" j k i j n k i j v" v j g" 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	Ø <sup>2</sup> = 0.000
Female sex	7 (28.0)	55 (59.1)	13 (61.9)	∂ <sup>2</sup> = 8.320	0.016	V = 0.245
Race						
White	25 (100)	90 (96.8)	20 (95.2)	∂ <sup>2</sup> = 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	Ø <sup>2</sup> = 0.004
Preop BDI-II score	8.61 ± 7.40	9.64 ± 6.44	12.57 ± 7.85	F = 2.066	0.131	Ø <sup>2</sup> = 0.008
Change in BDI-II score	0.17 ± 5.61	∅0.57 ± 5.95	∅4.43 ± 7.41	F = 3.826	0.025	Ø <sup>2</sup> = 0.023
Preop BAI score	5.67 ± 6.66*	6.60 ± 6.11	16.67 ± 8.29†	F = 6.928	<b>0.002</b>	Ø <sup>2</sup> = 0.079
Change in BAI score	0.56 ± 3.61	0.12 ± 6.24	∅9.83 ± 8.35	F = 4.646	0.024	Ø <sup>2</sup> = 0.148
Preop attention score	∅0.55 ± 0.75	∅0.61 ± 0.72	∅0.59 ± 0.68	F = 0.057	0.945	Ø <sup>2</sup> = ∅0.007
Change in attention score	∅0.01 ± 0.58	∅0.07 ± 0.64	∅0.03 ± 0.57	F = 0.113	0.894	Ø <sup>2</sup> = ∅0.007
Preop executive function score	∅0.40 ± 0.69	∅0.33 ± 0.56	∅0.38 ± 0.62	F = 0.173	0.841	Ø <sup>2</sup> = ∅0.006
Change in executive function score	∅0.21 ± 0.66	∅0.25 ± 0.68	∅0.33 ± 0.69	F = 0.192	0.825	Ø <sup>2</sup> = ∅0.006
Preop language score	∅0.13 ± 0.63	∅0.19 ± 0.57	∅0.36 ± 0.65	F = 0.920	0.401	Ø <sup>2</sup> = ∅0.001
Change in language score	∅0.08 ± 0.52	∅0.16 ± 0.62	∅0.01 ± 0.77	F = 0.576	0.564	Ø <sup>2</sup> = ∅0.003
Preop memory score	∅0.90 ± 0.89*†	0.10 ± 0.93	∅0.05 ± 0.78	F = 11.950	<b>&lt;0.001</b>	Ø <sup>2</sup> = 0.078
Change in memory score	0.31 ± 0.47*†	∅0.28 ± 0.79	∅0.46 ± 0.48	F = 8.664	<b>&lt;0.001</b>	Ø <sup>2</sup> = 0.056
Preop visuospatial score	0.11 ± 0.92	0.06 ± 0.69	∅0.03 ± 0.93	F = 0.188	0.829	Ø <sup>2</sup> = ∅0.006
Change in visuospatial score	∅0.02 ± 0.57	∅0.21 ± 0.97	∅0.01 ± 0.51	F = 0.828	0.439	Ø <sup>2</sup> = ∅0.001
Motor scores						
Preop FTM						
Total	49.67 ± 12.41	47.64 ± 13.26	57.00 ± 15.09	F = 2.228	0.118	Ø <sup>2</sup> = 0.021
Lt	14.06 ± 4.10	13.74 ± 5.90	17.36 ± 5.00	F = 2.379	0.103	Ø <sup>2</sup> = 0.025
Rt	15.35 ± 4.87	15.00 ± 6.02	16.57 ± 5.19	F = 0.371	0.692	Ø <sup>2</sup> = ∅0.012
Preop WHIGET						
Total	25.00 ± 10.39	29.22 ± 8.09	28.43 ± 9.52	F = 0.497	0.610	Ø <sup>2</sup> = ∅0.007
Lt	10.50 ± 5.80	13.63 ± 5.01	11.14 ± 5.76	F = 1.347	0.267	Ø <sup>2</sup> = 0.005
Rt	14.50 ± 5.07	15.59 ± 4.26	17.29 ± 5.06	F = 0.631	0.535	Ø <sup>2</sup> = ∅0.005
TIR	3.60 ± 0.66	3.46 ± 0.54	3.55 ± 0.52	F = 0.247	0.782	Ø <sup>2</sup> = ∅0.001
Electrode characteristics						
Laterality						
Bilat	24 (96.0)	78 (83.9)	19 (90.5)	∂ <sup>2</sup> = 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	Ø <sup>2</sup> = 0.009
Rt	1.88 ± 1.00	2.23 ± 0.98	2.36 ± 0.96	F = 2.107	0.128	Ø <sup>2</sup> = 0.013
Current (mA)						
Lt	1.92 ± 0.71	2.66 ± 1.33	2.63 ± 1.25	F = 1.559	0.223	Ø <sup>2</sup> = 0.013
Rt	1.73 ± 0.62	2.48 ± 1.00	2.36 ± 0.96	F = 2.391	0.105	Ø <sup>2</sup> = 0.033
Frequency (Hz)						
Lt	138.86 ± 20.58	131.25 ± 13.42	135.83 ± 15.17	F = 2.451	0.091	Ø <sup>2</sup> = 0.012
Rt	123.68 ± 28.28	132.81 ± 16.54	137.81 ± 16.22	F = 2.618	0.078	Ø <sup>2</sup> = 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 ( <i>continued</i> )						
Pulse width (μsec)						
Lt	84.78 ± 18.80	83.90 ± 22.04	95.00 ± 27.28	F = 1.848	0.162	Ø <sup>2</sup> = 0.007
Rt	83.00 ± 13.80	78.78 ± 21.64	85.63 ± 29.20	F = 0.807	0.449	Ø <sup>2</sup> = Ø0.002
Position						
X						
Lt	15.99 ± 1.76	15.00 ± 4.79	15.66 ± 0.99	F = 0.155	0.857	Ø <sup>2</sup> = Ø0.016
Rt	Ø14.09 ± 1.57	Ø15.11 ± 5.32	Ø15.46 ± 1.24	F = 0.114	0.893	Ø <sup>2</sup> = Ø0.020
Y						
Lt	3.23 ± 1.00	4.38 ± 1.69	3.88 ± 2.87	F = 1.031	0.364	Ø <sup>2</sup> = 0.001
Rt	2.68 ± 1.94	2.99 ± 1.84	3.36 ± 3.23	F = 0.134	0.875	Ø <sup>2</sup> = Ø0.019
Z						
Lt	2.51 ± 4.51	4.03 ± 3.25	3.06 ± 3.89	F = 0.583	0.562	Ø <sup>2</sup> = Ø0.008
Rt	2.48 ± 3.57	5.90 ± 2.65	7.79 ± 5.17	F = 3.951	0.027	Ø <sup>2</sup> = 0.060

Values are expressed as the mean  $\pm$  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.

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

Cv" vjg" i tqwr" ngxgn." yg" hqwpf" uvcvkuecnn{" uki pk tēcpv" but small-magnitude declines in overall cognition as well as language and memory domain scores following DBS. Vjgtg" ygtg" pq" uki pk tēcpv" ejcpigu" kp" cvvgpvkqp. "gzgewkxg" function, or visuospatial function scores. Several studies on cognition after VIM DBS for ET have reported mixed tpfkpiu." kpenwfkpi" pq" ejcpig" kp" qxgtcnn" eqi pkvkqp.<sup>32</sup> improvements in visuoperceptual abilities, visuomotor coordination, verbal memory, and confrontation naming,<sup>13,29</sup> and declines in language<sup>29</sup> and working memory.<sup>13</sup> We hqwpf" uvcvkuecnn{" uki pk tēcpv" fgenkpgu" kp" ncpiwcig" cpf" ogoqt{" .urgek tēcnn{" yqtf" nkuv" cpf" uvqt{" ogoqt{" o gcuwtgu" 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 the decline in memory function may be due to cortico-subcortical dysfunction,<sup>33</sup> yjkej" ecp" ngcf" vq" fkh tēwnvkgu" kp" initiating and maintaining complex information processing strategies.<sup>34</sup>

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

kp"cvvgpvkqp"cpf"xluwqurcvkc"hwpevkqkpi"Vjg"lpfkpi"qh" 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.<sup>13</sup> 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

vjg"cdknkv{"vq"cvvtdwvg"vjku"lpfkpi"vq"FDU<sup>35</sup> Medications commonly used to treat ET, such as propranolol,<sup>36</sup> can also negatively impact cognitive functioning. Following DBS surgery, many patients discontinue these medications. It is possible that medication reductions may positively influence 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	Ø <sup>2</sup> = 0.003
Female sex	9 (60.0)	59 (59.0)	15 (62.5)	∂ <sup>2</sup> = 1.963	0.375	V = 0.119
Race						
White	15 (100.0)	99 (99.0)	21 (87.5)	∂ <sup>2</sup> = 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	Ø <sup>2</sup> = 0.007
Preop BDI-II score	6.93 ± 5.89	9.97 ± 7.03	10.29 ± 6.36	F = 0.384	0.131	Ø <sup>2</sup> = 0.005
Change in BDI-II score	0.86 ± 5.00	0.83 ± 6.62	0.21 ± 6.01	F = 1.331	0.268	Ø <sup>2</sup> = 0.003
Preop BAI score	7.14 ± 4.81	7.84 ± 7.05	11.29 ± 7.10	F = 1.009	0.371	Ø <sup>2</sup> = 0.001
Change in BAI score	0.43 ± 7.63	0.10 ± 4.90	0.36 ± 7.37	F = 7.213	0.015	Ø <sup>2</sup> = 0.228
Preop attention score	0.72 ± 0.84	0.62 ± 0.70	0.35 ± 0.70	F = 0.671	0.513	Ø <sup>2</sup> = 0.002
Change in attention score	0.626 ± 0.51*†	0.05 ± 0.58	0.493 ± 0.45*	F = 16.199	0.001	Ø <sup>2</sup> = 0.102
Preop executive function score	0.60 ± 0.78	0.32 ± 0.58	0.24 ± 0.56	F = 1.883	0.156	Ø <sup>2</sup> = 0.006
Change in executive function score	0.34 ± 0.49	0.28 ± 0.66	0.47 ± 0.61	F = 5.717	0.004	Ø <sup>2</sup> = 0.033
Preop language score	0.19 ± 0.52	0.25 ± 0.60	0.08 ± 0.57	F = 2.585	0.079	Ø <sup>2</sup> = 0.011
Change in language score	0.45 ± 0.49*†	0.14 ± 0.61	0.56 ± 0.54	F = 8.026	<0.001	Ø <sup>2</sup> = 0.050
Preop memory score	0.20 ± 0.88	0.11 ± 1.01	0.16 ± 0.93	F = 0.048	0.953	Ø <sup>2</sup> = 0.007
Change in memory score	0.03 ± 0.53	0.22 ± 0.77	0.17 ± 0.58	F = 1.067	0.347	Ø <sup>2</sup> = 0.001
Preop visuospatial score	0.09 ± 0.73	0.03 ± 0.80	0.26 ± 0.80	F = 1.598	0.206	Ø <sup>2</sup> = 0.004
Change in visuospatial score	0.41 ± 0.49†	0.10 ± 0.82	0.65 ± 0.72*	F = 8.266	<0.001	Ø <sup>2</sup> = 0.055
Motor scores						
FTM						
Total	49.89 ± 12.71	50.74 ± 14.82	50.41 ± 13.42	F = 0.193	0.825	Ø <sup>2</sup> = 0.014
Lt	14.75 ± 5.95	14.97 ± 5.63	15.00 ± 4.31	F = 0.195	0.824	Ø <sup>2</sup> = 0.015
Rt	15.13 ± 5.06	15.66 ± 5.82	14.50 ± 4.41	F = 0.267	0.767	Ø <sup>2</sup> = 0.014
WHIGET						
Total	30.50 ± 13.23	28.84 ± 8.21	29.50 ± 9.09	F = 1.228	0.299	Ø <sup>2</sup> = 0.003
Lt	13.50 ± 8.12	13.20 ± 5.19	13.13 ± 5.89	F = 0.701	0.499	Ø <sup>2</sup> = 0.004
Rt	17.00 ± 5.25	15.64 ± 4.32	16.38 ± 4.41	F = 1.246	0.294	Ø <sup>2</sup> = 0.003
TIR	3.75 ± 0.27	3.54 ± 0.54	3.25 ± 0.63	F = 1.558	0.222	Ø <sup>2</sup> = 0.003
Electrode characteristics						
Laterality						
Bilat DBS	14 (93.3)	85 (85.0)	22 (91.7)	∂ <sup>2</sup> = 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	Ø <sup>2</sup> = 0.007
Rt	2.33 ± 0.63	2.23 ± 1.04	2.09 ± 1.27	F = 0.074	0.929	Ø <sup>2</sup> = 0.011
Current (mA)						
Lt	1.62 ± 0.34	2.59 ± 1.35	2.47 ± 0.56	F = 1.443	0.248	Ø <sup>2</sup> = 0.010
Rt	1.90 ± 0.82	2.38 ± 1.00	1.98 ± 0.73	F = 0.768	0.471	Ø <sup>2</sup> = 0.006
Frequency (Hz)						
Lt	130.00 ± 12.73	133.74 ± 16.04	132.50 ± 16.03	F = 0.260	0.772	Ø <sup>2</sup> = 0.006
Rt	129.29 ± 1.89	132.10 ± 20.43	132.27 ± 16.94	F = 0.069	0.933	Ø <sup>2</sup> = 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 ( <i>continued</i> )						
Pulse width ( $\mu$ sec)						
Lt	82.22 $\pm$ 13.02	86.47 $\pm$ 23.57	81.67 $\pm$ 18.50	F = 0.357	0.700	$\phi^2 = \phi 0.005$
Rt	77.14 $\pm$ 16.04	83.15 $\pm$ 22.18	60.91 $\pm$ 3.02	F = 5.702	0.004	$\phi^2 = \phi 0.041$
Position						
X						
Lt	13.58 $\pm$ 7.76	15.19 $\pm$ 4.57	15.42 $\pm$ 0.93	F = 0.032	0.969	$\phi^2 = \phi 0.018$
Rt	$\phi 11.97 \pm 9.16$	$\phi 14.95 \pm 5.17$	$\phi 15.82 \pm 1.35$	F = 0.072	0.930	$\phi^2 = \phi 0.021$
Y						
Lt	3.86 $\pm$ 1.62	4.23 $\pm$ 1.82	3.91 $\pm$ 2.34	F = 2.087	0.135	$\phi^2 = \phi 0.020$
Rt	2.22 $\pm$ 2.07	2.99 $\pm$ 2.03	2.45 $\pm$ 2.19	F = 0.031	0.970	$\phi^2 = \phi 0.022$
Z						
Lt	3.29 $\pm$ 2.20	3.96 $\pm$ 3.47	4.21 $\pm$ 2.61	F = 0.525	0.595	$\phi^2 = \phi 0.009$
Rt	4.54 $\pm$ 3.57	5.80 $\pm$ 2.98	6.88 $\pm$ 4.08	F = 0.263	0.770	$\phi^2 = \phi 0.016$

Values are expressed as the mean  $\pm$  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 enkpkecm{"ukipkfecpv"pgicvixg"ejcpigu"kp"pgwtgru{ejqnqik-cal functions. The inverse relationships observed between baseline scores and changes may represent regression to vjg"ogcp0"Rtkqt"uvwfkgu"jcxg"kfgrpvkfgf"egtvcvp"xtkcdngu" like stimulation parameters<sup>13,37</sup> and postoperative complications<sup>13</sup> 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. Jqygxgt."qwt"cpn{"uku"tgxcngf"pq"uvcvkuvkecm{"uki pkfecpv" 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 soekqgeqpq o ke"uvcvwu" o c{"jcxg"kpEwgpegf"rcvkgpv"fgelukqpu"

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;<sup>7</sup> 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;<sup>9</sup> therefore, it is possible that the small-magnitude worsening in language and memory scores that we observed was secondary to disease progression. i tguukqp0" Cf fkvkqpcnn{"y jkng"yg"wugf"fgtpkvkqpu"qh"enkpical 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

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## Acknowledgments

Data record keeping was funded by the National Center for Advancing Translational Sciences, National Institutes of Health (grant no. UL1 TR000445).

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## Disclosures

Dr. Terry reported grants from Amgen Inc. and Football Research Inc. and personal fees from the National Football League and HITIQ outside the submitted work. Dr. Konrad reported grants from Medtronic during the conduct of the study. Dr. Bick reported personal fees for consulting from Varian Medical Systems outside the submitted work.

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Conception and design: Bick, AE Bishay, Hughes. Acquisition of data: AE Bishay, Lyons, Habib, Hughes, Long, Paulo, Summers, Dawant, Konrad, Dhima. Analysis and interpretation of data: Bick, AE Bishay, Lyons, Hughes, Qian, Paulo, Li, Englot. Drafting the article: AE Bishay, Lyons, Habib, Hughes. Critically revising the article: Bick, AE Bishay, Lyons, Habib, Hughes, Paulo, S Bishay, Terry, Englot, Dhima. Reviewed submitted version of manuscript: Bick, AE Bishay, Lyons, Habib, Hughes, Zargari, Qian, Paulo, Summers, Li, Terry, Dawant, Ball, Konrad, Englot, Dhima. Approved the final version of the manuscript on behalf of all authors: Bick. Statistical analysis: AE Bishay, Hughes. Administrative/technical/material support: Dawant, Dhima. Study supervision: Bick.

## Supplemental Information

### Online-Only Content

Supplemental material is available with the online version of the article.

*Supplementary Tables 1–4.* <https://thejns.org/doi/suppl/10.3171/2024.11.JNS241990>.

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