

## RESEARCH ARTICLE

# Lateralized Effect of Thalamic Deep Brain Stimulation Location on Verbal Abstraction

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**ABSTRACT: Background:** Regionalized thalamic activity has been implicated in language function, and yet the effect of thalamic deep brain stimulation (DBS) on language-related clinical outcomes is underexplored.

**Objective:** The objective of this study was to determine if the location of stimulation within the thalamus correlates with changes in language-related neuropsychological outcomes following DBS for essential tremor.

**Methods:** Thirty patients with essential tremor underwent comprehensive neuropsychological evaluations before and after DBS surgery targeting the ventral intermediate nucleus of the thalamus. Changes in neuropsychological functions were evaluated. The relationships between language-related outcomes and stimulation location were assessed using both categorical and linear methods. Any significant results were further validated using linear discriminant analysis.

**Results:** Most neuropsychological functions remained unchanged at the group level. However, outcome on a measure of verbal abstraction was significantly dependent on stimulation location along the anterior–posterior

axis within the left ventral lateral thalamus, with anterior stimulation associated with reduced verbal abstraction performance. This result was supported by linear discriminant analysis, which showed that stimulation locations with improved and reduced verbal abstraction function were best separated by a vector nearly parallel to the anterior–posterior axis. No stimulation location dependence was found for verbal abstraction outcome in the right thalamus or for outcomes of other language functions in either hemisphere.

**Conclusion:** We demonstrate an effect of thalamic DBS on verbal abstraction as a function of left thalamic topography. This finding provides clinical evidence for the lateralization and regionalization of thalamic language function that may be relevant for understanding non-motor effects of stimulation. © 2021 International Parkinson and Movement Disorder Society

**Key Words:** verbal abstraction; language; thalamic deep brain stimulation; stimulation location; laterality

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Deep brain stimulation (DBS) targeting the ventral intermediate nucleus (Vim) of the thalamus has been effective in alleviating motor symptoms in essential tremor (ET) patients. However, as the thalamus is involved in complex sensorimotor and cognitive processes<sup>1</sup> and the ventral lateral thalamus (where the Vim is located) participates in both basal ganglia-thalamocortical and cerebellothalamocortical circuits, potential nonmotor effects of Vim DBS warrant consideration.

Regionalized language function within the left thalamus was first established in a series of thalamic stimulation studies conducted by Ojemann et al.<sup>2</sup> More recent

work with thalamic event-related potential recordings demonstrated that thalamic structures are involved in the analysis of syntactic and semantic parameters of acoustically presented sentences.<sup>3,4</sup> Vim DBS, therefore, has the potential to affect language functions in ET patients, but the effects on language-related outcomes typically are not assessed in the routine practice of DBS for ET.

A few studies have evaluated the effects of thalamic DBS on language and other cognitive functions.<sup>5-12</sup> Although it is generally agreed that Vim DBS does not affect overall cognitive function,<sup>6-9</sup> conclusions regarding language outcomes after Vim DBS have been divergent.<sup>5-12</sup> For instance, verbal fluency performance has been reported to improve,<sup>5</sup> decline,<sup>6,10-12</sup> or remain unchanged after Vim stimulation.<sup>7-9</sup> Some researchers have proposed that the effects of Vim DBS on language functions may be attributed to functionally distinct thalamocortical circuits affected by the stimulation.<sup>6,10-12</sup> However, the relationships between stimulation side and stimulation location within the ventral lateral thalamus and language-related outcomes have not been investigated carefully using modern analytic tools and techniques. Accordingly, we systematically evaluated neuropsychological outcomes in ET patients after Vim DBS surgery and tested whether there was stimulation location dependence of language-related outcomes within the ventral lateral thalamus. We hypothesized that changes in measures of language function vary in relation to stimulation location within the left ventral lateral thalamus.

## Methods

### Participants

We retrospectively identified 30 patients with ET (13 women,  $67.2 \pm 8.9$  years) who underwent DBS surgery targeting the Vim and who completed both pre- and postoperative neuropsychological evaluations. All participants provided written informed consent under a protocol approved by the university's institutional review board. Of 26 right-handed subjects, 22 underwent bilateral DBS lead implantation, 2 underwent unilateral left-sided implantation, and 2 subjects with an existing left-sided implant underwent right-sided lead implantation. All 4 left-handed subjects underwent bilateral DBS lead implantation. Patients had an average of  $14.1 \pm 2.9$  years of education, and average age at formal diagnosis of ET was  $50.1 \pm 17.5$  years. None of the participants had significant cognitive impairment, as revealed by the preoperative neuropsychological evaluation. Subjects' demographic and clinical characteristics are summarized in Table 1.

**TABLE 1.** Subjects' demographics, clinical characteristics, and stimulation settings

Variable	Value
Subject number	30
Age at surgery (years)	67.2 (8.9)
Sex	17 M/13 F
Handedness	26 R/4 L
Education (years)	14.1 (2.9)
Age at onset (years)	38 (22.7)
Age at formal diagnosis (years)	50.1 (17.5)
Disease duration (years)	28.6 (17.7)
Preoperative NPT to surgery (months)	1.8 (1.3)
Surgery to postoperative NPT (months)	12.3 (12)
Side of surgery	26 bilateral, 2 left, 2 right
Side of stimulation	25 bilateral, 3 left, 2 right
Lead model	24 Medtronic 3387, 5 St. Jude 6173, 1 Boston Scientific Vercise
Stimulation mode	24 CV, 6 CC
Stimulation amplitude	Left 2.70 (1.16) V for CV, 2.23 (0.99) mA for CC
	Right 2.57 (0.77) V for CV, 2.59 (0.81) mA for CC
Stimulation frequency (Hz)	Left 156.43 (21.6)
	Right 154.44 (19.58)
Stimulation width (microseconds)	Left 60 (n = 24), 90 (n = 3), 120 (n = 1)
	Right 60 (n = 22), 70 (n = 2), 80 (n = 2), 90 (n = 1)
Medication	Preoperative Beta-blockers (n = 11), antiepileptic drugs (n = 18), benzodiazepines (n = 4)
	Postoperative Beta-blockers (n = 9), antiepileptic drugs (n = 12), benzodiazepines (n = 3)

Data are presented as mean with standard deviation (SD) in parentheses. M, male; F, female; R, right-handedness; L, left-handedness; NPT, neuropsychological testing; CV, constant voltage; CC, constant current.

### Neuropsychological Assessment

Subjects underwent comprehensive neuropsychological evaluations, on average 2 months ( $1.8 \pm 1.3$  months) before and 12 months ( $12.3 \pm 12.0$  months) after electrode implantation. Patients were on their usual antitremor medications, if applicable, during the evaluations, which included beta-blockers (eg, propranolol), antiepileptic drugs (eg, primidone), and benzodiazepines (eg, clonazepam). Table 1 summarizes the number of patients taking each class of drugs pre- and postoperatively. No other medications known to affect central nervous functioning were being used at the time of assessment. Postoperative evaluations were completed in the ON-stimulation state. The neuropsychological test battery was constructed to evaluate a range

of cognitive functions, including executive function, language, learning, memory, attention and information processing, visuospatial processing, and affect (ie, anxiety, apathy, and depression). Various aspects of language function were assessed using several subtests: Picture Naming and Semantic (ie, category) Fluency subtests of the Repeatable Battery for the Assessment of Neuropsychological Status-A, Boston Naming Test (BNT), Controlled Oral Word Association Test (COWAT), which measures phonemic fluency, and Vocabulary and Similarities subtests of the Wechsler Abbreviated Scale of Intelligence—Second Edition (WASI-II), which measure expressive vocabulary and verbal abstraction, respectively. Combined, Vocabulary and Similarities make up the Verbal Comprehension Index of the WASI-II. Some patients were not administered all the tests because of patient fatigue or patient-initiated scheduling constraints. Raw test scores were standardized to T scores (mean  $\pm$  SD, 50  $\pm$  10), which allowed arithmetical operations and group-level comparisons.  $\Delta$ T scores were then calculated by subtracting preoperative T scores from postoperative scores.

### Surgery and Stimulation Programing

All patients underwent frame-based DBS surgery in the awake state, targeting the Vim nucleus as previously described.<sup>13</sup> Medtronic 3387 leads were placed in 24 subjects (Medtronic, Minneapolis, MN), St. Jude 6173 leads were placed in 5 subjects (Abbott Laboratories, Lake Bluff, IL), and Boston Scientific Vercise leads were placed in 1 subject (Boston Scientific, Marlborough, MA). Significant tremor control with intraoperative stimulation testing was achieved in all patients. No surgical complications were reported. For each subject, the most recent documented stimulator configuration immediately preceding the postoperative neuropsychological assessment (on average  $3.9 \pm 3.3$  months before the assessment) was used to determine the active stimulation location for each subject. All the subjects had their implanted stimulators turned on and configured at the time of neuropsychological evaluation, except 1 bilaterally implanted subject whose right-side stimulator remained powered off after the surgery, and this subject was equated with those having left unilateral stimulation. In the 2 subjects with right-side lead implantation, the stimulation settings of their existing left-side stimulators remained unchanged from the time of preoperative evaluation; they were treated as having had right unilateral stimulation. Medtronic stimulators were configured in constant voltage mode, whereas St. Jude and Boston Scientific stimulators were programmed in constant current mode. Detailed stimulation information is provided in Table 1.

### Electrode Localization and Volume of Tissue Activated Estimation

Active contact locations were determined using a LEAD-DBS toolbox,<sup>14,15</sup> as previously described.<sup>16</sup> In brief, DBS leads were semiautomatically reconstructed in Montreal Neurological Institute (MNI) ICBM152 NLIN 2009b stereotactic space<sup>17</sup> together with the DISTAL atlas,<sup>18</sup> and MNI coordinates of all the electrodes were extracted. A finite element method–based volume of tissue-activated (VTA) model implemented in LEAD-DBS was then applied to estimate the local volumes of tissues activated by stimulation, which was able to model both constant voltage and constant current stimulations in monopolar, multipolar, and interleaving configurations (see references<sup>15,19</sup> for a detailed methodological description). An example of lead and VTA reconstruction is shown in Figure 1A. An anatomical structure in the DISTAL atlas was considered activated if its intersection volume with VTA was greater than 1 mm<sup>3</sup>, as DBS effects have been observed with a minimum stimulated volume of  $\sim 1$  mm<sup>3</sup> for the nuclei of interest.<sup>20,21</sup> The geometric center of each such VTA was used to represent the active stimulation location for every subject (Fig. 1B).

### Linear Discriminant Analysis

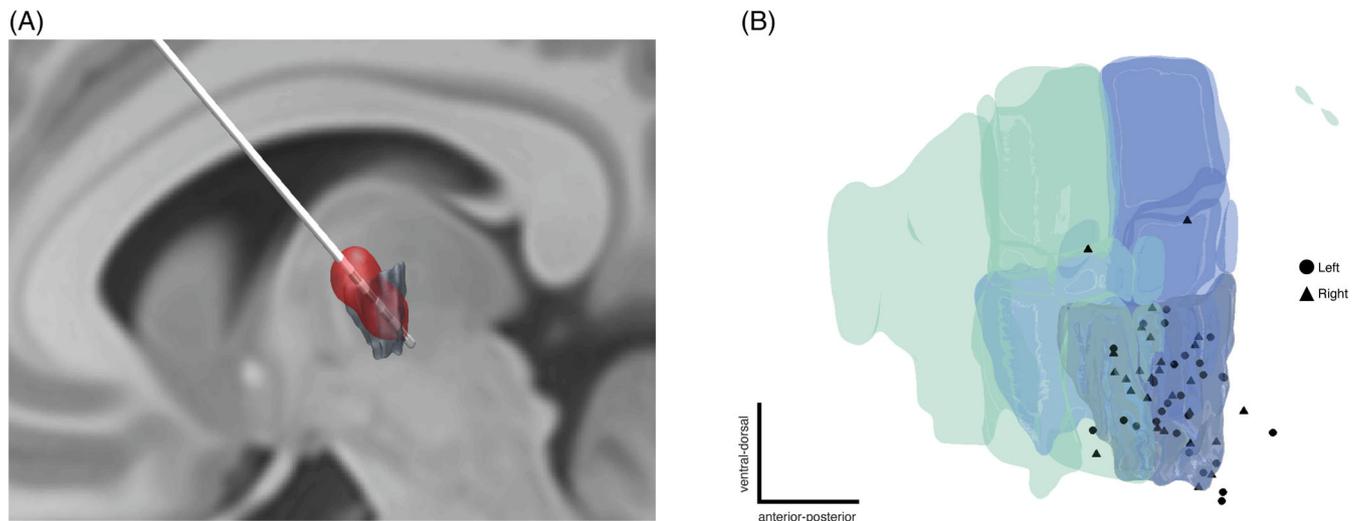
Linear discriminant analysis (LDA), a machine-learning classifier, was used to better characterize the location distributions of stimulation effects on language outcomes: for a language subtest studied, subjects were divided into 2 groups based on their  $\Delta$ T scores of the subtest (group of  $\Delta$ T > 0 and group of  $\Delta$ T  $\leq$  0). A vector that maximized the separability of the 2 groups in terms of their stimulation locations was determined by LDA in each side. Separability (S) of the 2 groups was depicted by the ratio of between-group variance ( $\sigma^2_{\text{between}}$ ) to within-group variance ( $\sigma^2_{\text{within}}$ ):

$$S = \frac{\delta^2_{\text{between}}}{\delta^2_{\text{within}}}$$

Subjects' stimulation locations along the LDA vector were then linearly correlated with their  $\Delta$ T scores to provide a statistical test for the LDA result.

### Statistical Analysis

All statistical analyses were performed in MATLAB R2017b (MathWorks, Natick, MA) and R version 3.5.2 (R Development Core Team). Between-group comparisons were made using paired or unpaired *t* tests. The relationship between 2 variables was measured using a linear regression model. Linear mixed-effects models were applied to control for confounding factors. Variable interaction was examined using 2-way



**FIG. 1.** Electrode localization and VTA calculation. **(A)** Sagittal view of an example DBS lead with its VTA (red) and the Vim target (gray) superimposed on a T2-weighted image. **(B)** Stimulation centers in all subjects are plotted together with the Vim (gray), VLP (blue), and VA-VLa (green). Left-side stimulation locations are marked with circles, and right-side stimulation locations are transposed to the left and marked with triangles. VLP, ventral lateral posterior nucleus; VA, ventral anterior nucleus; VLa, ventral lateral anterior nucleus. [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

analysis of variance (ANOVA). Effect sizes were estimated with Cohen's  $d$  for  $t$  tests or with Pearson's  $\rho$  for linear regression analyses. Statistical significance was defined as  $P < 0.05$ . False discovery rate (FDR) corrections were applied for multiple comparisons ( $\alpha = 0.05$ ).

## Results

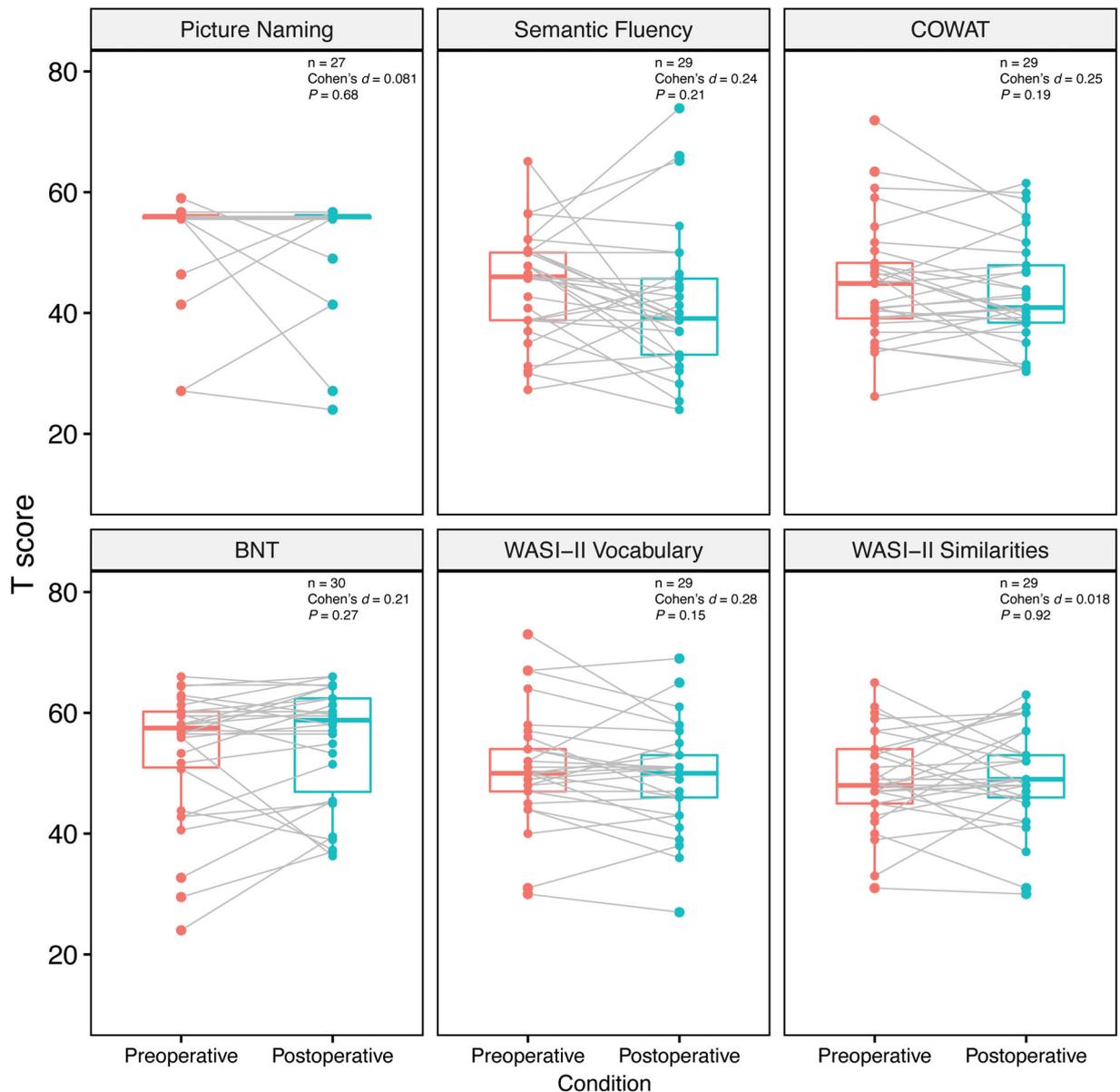
### General Neuropsychological Outcomes

Mini-Mental State Examination scores did not change significantly after DBS surgery (2-tailed paired  $t$  test  $t^{26} = -1.51$ , Cohen's  $d = 0.29$ ,  $P = 0.14$ ; Fig. S1). Likewise, other cognitive test scores before and after surgery did not yield any significant results (2-tailed paired  $t$  test, FDR corrected; see Table S1 for detailed comparison results). These results indicate that Vim DBS was not associated with any broad changes in cognitive function. Similarly, subjects' average language function, as measured by the 6 language subtests, did not show significant changes after surgery either (2-tailed paired  $t$  test; Picture Naming:  $t^{26} = -0.42$ , Cohen's  $d = 0.081$ ,  $P = 0.68$ ; Semantic Fluency:  $t^{28} = -1.3$ , Cohen's  $d = 0.24$ ,  $P = 0.21$ ; COWAT:  $t^{28} = -1.34$ , Cohen's  $d = 0.25$ ,  $P = 0.19$ ; BNT:  $t^{29} = 1.13$ , Cohen's  $d = 0.21$ ,  $P = 0.27$ ; WASI-II Vocabulary:  $t^{28} = -1.5$ , Cohen's  $d = 0.28$ ,  $P = 0.15$ ; WASI-II Similarities:  $t^{28} = 0.1$ , Cohen's  $d = 0.018$ ,  $P = 0.92$ ; Fig. 2).

### Verbal Abstraction Ability Depends on Stimulation Location in the Left Thalamus

Although the majority of the subjects received ventral lateral posterior nucleus (VLP, the ventral portion of which corresponds to the Vim<sup>22</sup>) activation on both

sides (left, 25/28; right, 26/27), in each hemisphere approximately half the subjects also received ventral lateral anterior nucleus (VLa) and/or ventral anterior nucleus (VA) activation (VA-VLa activated vs not activated: 15 vs 13 in the left, 15 vs 12 in the right). Therefore, language subtest outcomes were compared in subjects with and without VA-VLa activation in the left and right hemispheres. Although comparisons for other language subtests did not yield significant results in either hemisphere (2-tailed 2-sample  $t$  test, FDR corrected; see Supplementary Table S2 for detailed statistical results), a significant performance difference between subjects with and without left VA-VLa activation was observed on Similarities, a subtest of WASI-II that measures verbal abstraction by asking patients to verbally describe how 2 objects (concrete items) or concepts (abstract items) are similar (2-tailed 2-sample  $t$  test  $t^{25} = -3.91$ , Cohen's  $d = 1.52$ ,  $P = 0.00062$ , adjusted  $P = 0.0037$ ; Fig. 3A). Subjects with left VA-VLa activation performed worse after surgery ( $\Delta T = -4.07$ , 2-tailed paired  $t$  test  $t^{14} = -2.48$ , Cohen's  $d = 0.64$ ,  $P = 0.026$ ), whereas subjects without left VA-VLa activation exhibited significantly better performance after surgery ( $\Delta T = 5.75$ , 2-tailed paired  $t$  test  $t^{11} = 3$ , Cohen's  $d = 0.87$ ,  $P = 0.012$ ). To further explore the observed topography for Similarities outcome, a linear regression model was applied, which revealed that stimulation location along the anterior-posterior axis (MNI-defined  $y$  coordinate) within the left ventral lateral thalamus significantly correlated with Similarities outcome, with anterior stimulation more likely to be associated with reduced task performance ( $n = 27$ , coefficient estimate =  $-1.92$ , SE =  $0.63$ ,  $\rho = -0.52$ ,  $P = 0.005$ ; Fig. 3C). In contrast, there was

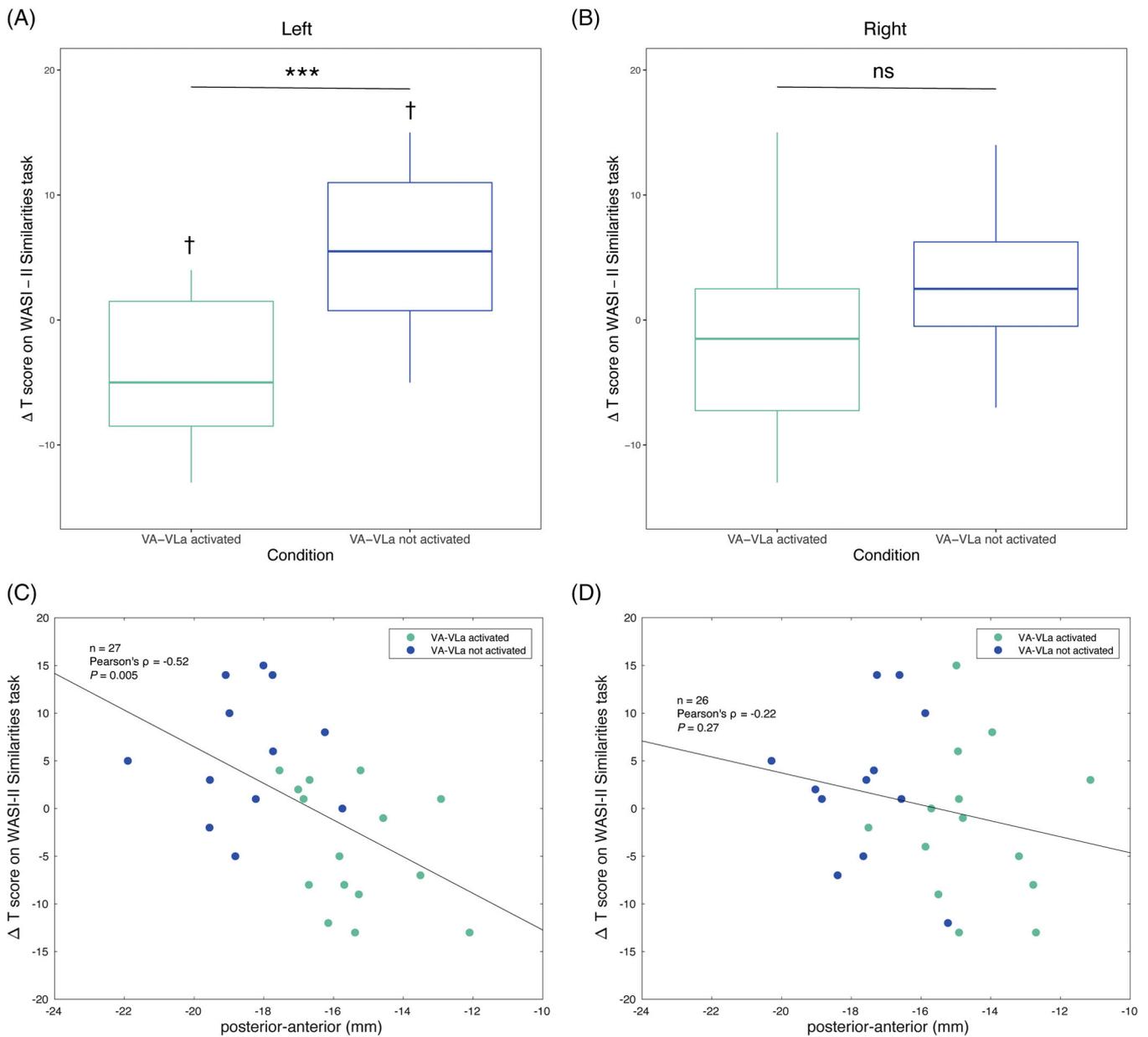


**FIG. 2.** Language functions do not show significant changes on average, as revealed by comparisons of subjects' performances on Picture-Naming test, Semantic Fluency test, COWAT, BNT, WASI-II Vocabulary test, and WASI-II Similarities test before and after surgery (2-tailed paired *t* test). [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

not a significant effect of right VA-VLa activation on Similarities outcome (2-tailed 2-sample *t* test  $t^{24} = -1.3$ , Cohen's  $d = 0.51$ ,  $P = 0.21$ , adjusted  $P = 0.62$ ; Fig. 3B), and linear regression analysis in the right hemisphere yielded a nonsignificant result with a smaller slope ( $n = 26$ , coefficient estimate =  $-0.84$ , SE =  $0.74$ ,  $\rho = -0.22$ ,  $P = 0.27$ ; Fig. 3D), although comparison of left- and right-side slopes of linear regression models failed to reach statistical significance (1-tailed 2-sample *t* test  $t^{49} = 1.12$ , Cohen's  $d = 0.32$ ,  $P = 0.13$ ). No interaction effect of left- and right-side VA-VLa stimulation conditions on Similarities outcome was observed (2-way ANOVA,  $n = 25$ ,  $F = 0.83$ ,  $P = 0.37$ ; see Table S3

for detailed statistical results). No significant relationship between Similarities outcome and stimulation location along either the ventral-dorsal axis (MNI-defined  $z$  coordinate) or lateral-medial axis (MNI-defined  $x$  coordinate), or between other language subtest outcome and stimulation location along any axis was observed in either hemisphere (linear correlation, FDR corrected).

To control for the possible confounding effects of other stimulation parameters on the observed stimulation location dependence of Similarities outcome in the left hemisphere, a linear mixed-effects model was further fitted to the data, entering the  $y$  coordinate of



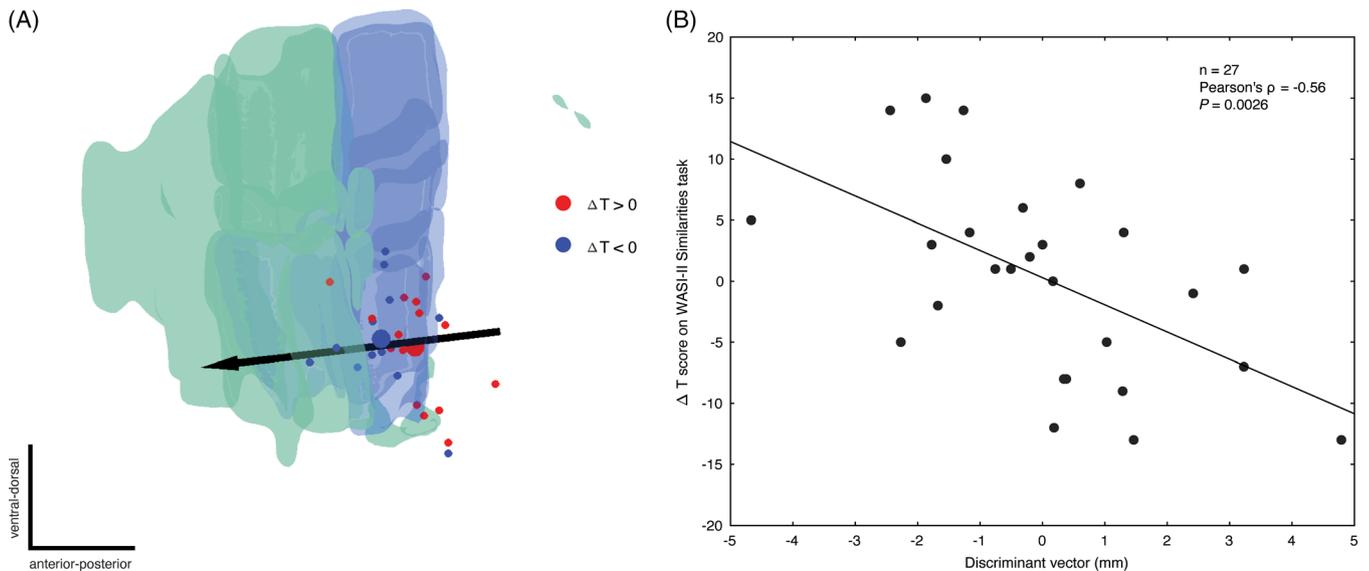
**FIG. 3.** Verbal abstraction outcome depends on stimulation location in the left but not the right thalamus. **(A–B)** Comparisons of Similarities performance changes ( $\Delta T$ ) between subjects with and without VA-VLa activation in the left hemisphere **(A)** and in the right hemisphere **(B)**. **(C–D)** Similarities  $\Delta T$  scores are correlated with the locations of subjects' stimulation centers along the anterior–posterior axis in the left side **(C)** and in the right side **(D)**. Stimulations that activated VA-VLa are marked in green; otherwise they are blue-colored. Two-tailed paired  $t$  test,  $^{\dagger}P < 0.05$ ; 2-tailed 2-sample  $t$  test,  $***P < 0.001$ ; ns, not significant. [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

stimulation location, pulse width, and stimulation frequency in the left side as independent variables, lead model and stimulation mode as random effects, and Similarities outcome as response variable. Under this model, stimulation location along the anterior–posterior axis in the left hemisphere was the only significant predictor of Similarities outcome ( $y$  coordinate of stimulation location: coefficient estimate =  $-2.21$ ,  $SE = 0.67$ ,  $P = 0.0033$ ; pulse width: coefficient estimate =  $0.071$ ,  $SE = 0.10$ ,  $P = 0.49$ ; stimulation frequency: coefficient estimate =  $0.039$ ,  $SE = 0.062$ ,

$P = 0.54$ ). In addition, possible interference on Similarities outcome by changes in other cognitive functions was tested and ruled out (linear correlation; see Table S4 for detailed statistical results).

### LDA Supports Stimulation Location Dependence of Verbal Abstraction Outcome in the Left Thalamus

LDA was applied in an effort to better characterize the location distribution of stimulation effect on



**FIG. 4.** LDA further supports discrimination of verbal abstraction outcome along anterior–posterior stimulation location in the left thalamus. **(A)** The discriminant vector determined by LDA that maximized the separability of left-side stimulation locations of subjects with Similarities  $\Delta T$  score  $> 0$  (red dots) and those of subjects with Similarities  $\Delta T$  score  $\leq 0$  (blue dots) is plotted together with the VA-VLa (green) and VLp (blue), viewed from a lateral direction. The large red and blue dots represent the geometric centers of the 2 groups. **(B)** The locations of left-side stimulation centers along the discriminant vector are linearly correlated with Similarities  $\Delta T$  scores. [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

Similarities outcome. As a result, the discriminant vector that maximized the separability of subjects with improved Similarities subtest ( $\Delta T > 0$ ) and those with reduced task performance ( $\Delta T \leq 0$ ) in terms of their stimulation locations in the left thalamus nearly paralleled the anterior–posterior axis (MNI coordinate of its unit vector:  $-0.031 [-0.98 \text{ to } 0.17]$ ; Fig. 4A). The relationship between the stimulation location along the discriminant vector and Similarities outcome was then tested by linear correlation with stimulations of improved task performance more likely to appear anteriorly ( $n = 27$ ,  $\rho = -0.56$ ,  $P = 0.0026$ ; Fig. 4B). The same statistical procedure was performed for the Similarities subtest in the right hemisphere and for other language subtests in both hemispheres, without significant findings (FDR corrected).

## Discussion

The primary goal of this study was to investigate whether and how aspects of language outcomes following Vim DBS depend on stimulation side and stimulation location within the ventral lateral thalamus, seeking clinical evidence for the lateralization and regionalization of thalamic language function. To this end, we analyzed neuropsychological changes after Vim DBS surgery in 30 ET subjects. Consistent with previous studies,<sup>6–9</sup> subjects' cognitive functions remained relatively unchanged at the group level after Vim DBS.

We discovered a significant relationship between the Similarities subtest outcome and stimulation location

along the anterior–posterior axis within the left ventral lateral thalamus. The Similarities subtest of WASI-II measures verbal abstraction by asking patients to verbally describe how 2 objects (concrete items) or concepts (abstract items) are similar, which involves elements of semantic memory, verbal concept formation, and verbal reasoning.<sup>23–25</sup> A comprehensive brain lesion–cognitive deficit mapping study demonstrated that impaired Similarities test performance is mainly associated with lesions in the left inferior frontal cortex (Broca's area).<sup>26</sup> However, subcortical substrates underlying verbal abstraction remain largely unknown. Our results suggest for the first time that the left ventral lateral thalamic nuclei are differentially involved in this language process.

This functional heterogeneity of the left ventral lateral thalamus in language is reminiscent of the largely segregated anatomical connections within the structure: the VA and VL<sub>a</sub>, comprising the anterior portion, primarily receive afferents from the internal globus pallidus and substantia nigra pars reticulata and project extensively to the prefrontal cortex including Broca's area, whereas the VL<sub>p</sub>, located more posteriorly, is the principal recipient of cerebellar dentate nucleus input and preferentially relays the signal to the primary motor cortex.<sup>1,22,27–31</sup> Thus, the VA and VL<sub>a</sub> may contribute to verbal abstraction by actively modulating neural activity in the prefrontal thalamocortical circuits, in accordance with the “selective engagement” and “integrative hub” theories of human thalamic function.<sup>1,32</sup> Thus, compromised verbal abstraction in patients receiving left VA-VL<sub>a</sub> stimulation may ultimately result from differential effects on cortical activity.<sup>33</sup>

Interestingly, in contrast to the effect of VA-VLa-activated DBS, stimulations that were located more posteriorly and mainly activated presumed cerebellar-receiving territory resulted in improved verbal abstraction. This result seems incompatible with the notion that cerebellothalamocortical circuits subserve motor functions exclusively,<sup>30</sup> and in fact, retrograde tracing and functional imaging studies have identified connections between the cerebellum and prefrontal cortical areas, especially the dorsolateral prefrontal cortex, via the VLP.<sup>34–37</sup> Further, cerebellothalamocortical circuit dysfunction has been associated with decline in cognitive functions including verbal fluency, semantic encoding, and working memory.<sup>6,10,38</sup> Thus, VLP stimulation may activate a cerebellothalamocortical loop that subserves verbal abstraction.

The effects of Vim DBS on cognitive and language functions theoretically could be attributed to more medial intralaminar nuclei,<sup>11</sup> which have dense connections with the frontal cortex and have been suggested as a putative language-monitoring unit within the thalamus.<sup>3,39,40</sup> Our findings, however, revealed almost no lateral-medial gradient effect of DBS on verbal abstraction. Few studies have investigated the effects of intralaminar thalamic DBS on cognitive and language functions or have been able to record neurophysiological signal from the nuclei during cognitive and language tasks, which limits understanding of how the intralaminar nuclei are involved in these processes. In addition, the disparate effects of anterior versus posterior DBS in the left ventral lateral thalamus on verbal abstraction are better accounted for as an intrinsic property difference between anterior and posterior portions of the stimulated region as opposed to a single extrinsic generator.

Contrary to the left thalamic DBS, location dependence of DBS effect on Similarities outcome was not observed in the right thalamus, although difference in regression slopes did not reach statistical significance. This was likely because of a relatively small sample size, as large sample sizes are usually required to detect correlation differences.<sup>41–43</sup> Nonetheless, a significant and clearly greater gradient of stimulation effect on verbal abstraction outcome in the left thalamus that was corroborated by LDA suggests more left-lateralized language function at the thalamic level.

DBS-related changes, either at the group level or in a DBS location-dependent manner, were not observed for other language subtests in either hemisphere. One explanation might be that involvement of the ventral lateral thalamus is less specific for the language functions drawn on by these language subtests. Indeed, functional imaging and lesion mapping studies have shown distinct cortical regions accounting for different aspects of language cognition.<sup>26,44,45</sup> For example, compared with Similarities, Vocabulary, which also

measures aspects of verbal comprehension, including semantic knowledge and verbal concept formation,<sup>23–25</sup> has a significant lesion-deficit relationship with a more confined and medial prefrontal area.<sup>26</sup> In addition, Vocabulary is also generally simpler and draws on prefrontal function to a lesser extent (ie, it is less dependent on executive function), and therefore the task performance would not be expected to be affected much by potential modulations of thalamocortical networks after Vim DBS. Furthermore, other language tests, such as verbal fluency tasks,<sup>44</sup> involve multiple cortical areas whose connectivity to the thalamus may not overlap. This low specificity of thalamocortical circuits for aspects of language functions might also be responsible for the divergence of previously reported Vim DBS effects on language functions,<sup>5–11</sup> although the variation in stimulation location across studies is particularly confounding.

There are some limitations of this study. First, although we controlled for stimulation parameters in our linear model and also tested out possible correlations between Similarities outcome and other cognitive changes, there were more factors that may have confounded our results. Specifically, many patients reduced, stopped, or changed their antitremor medications after surgery. As some of the drugs such as topiramate and clonazepam are known to have cognitive impact,<sup>46,47</sup> changes in medications may affect patient performance on neuropsychological tests. In addition, interactions between medications and stimulation, if any, may theoretically influence our results. However, medication effects, as well as other uncontrollable factors such as disease state, were assumed to be randomly distributed among subjects, and stimulation location (the predictor variable of interest), which was determined solely based on optimal tremor control, would not be correlated with these factors. Therefore, our results may be fairly independent of these factors. Second, this study is retrospective in nature. Patients were identified retrospectively, and clinical information was retrieved from the medical charts. Therefore, there is a risk of selection and recall bias. Also, the retrospective nature of our study prevented us from performing OFF-stimulation neuropsychological assessment to examine possible surgical effects.

In summary, this study reports the stimulation location dependence of thalamic DBS on verbal abstraction outcome in the left ventral lateral thalamus, providing evidence for the lateralization and regionalization of thalamic language function. These data also suggest the clinical importance of avoiding stimulation that is too anterior to the Vim. ■

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## Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

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(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript: A. Writing of the First Draft, B. Review and Critique.

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