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STN-DBS affects language processing differentially in Parkinson's disease: Multiple-case MEG study

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Objectives: In this study, we investigated the effects of bilateral and unilateral deep brain stimulation of the subthalamic nucleus (STN-DBS) in PD patients on neural responses associated with two aspects of spoken language processing: semantics of action-related verbs and morphosyntactic processing.

Materials and methods: Using a passive unattended paradigm to present spoken linguistic stimuli, we recorded magnetoencephalographic (MEG) responses in three PD patients in four DBS conditions: left unilateral STN-DBS, right unilateral STN-DBS, bilateral STN-DBS, and no STN-DBS. To ensure that any observed effects of DBS on the neuromagnetic responses could be attributed to the linguistic context per se and were not merely induced by the electrical stimulation, we assessed the effects of STN-DBS on linguistic contrasts within each stimulation condition. Hence, we contrasted the processing of action vs. abstract verbs as well as the processing of correct vs. incorrect morphosyntactic inflections within each DBS condition.

Results: The results revealed that, compared to the DBS-off state, both bilateral and right unilateral stimulation of the STN yielded significant dissociations in the processing of action and abstract verbs, with greater neuromagnetic responses for action verbs compared to abstract verbs. For morphosyntax processing, only left unilateral stimulation yielded significant dissociations (relative to the DBS-off state), with greater neuromagnetic responses to the incorrect inflections compared to the correct inflections.

Conclusion: The results reflect differential effects of unilateral and bilateral STN-DBS on neuromagnetic responses associated with the processing of spoken language. They suggest that different specific aspects of linguistic information processing in PD are affected differently by STN-DBS.

KEYWORDS
action verb, bilateral, deep brain stimulation, language, magnetoencephalography, morphosyntax, Parkinson's disease, unilateral

1 | INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative disorder typically presenting with motor symptoms including resting tremor, rigidity, and bradykinesia.[1] In addition to the classical motor manifestations, patients with PD can also manifest heterogeneous cognitive symptoms including deterioration in the executive functions[2] and language.[3]

Deep brain stimulation of the sub-thalamic nucleus (STN-DBS) is an effective surgical treatment that helps control advanced PD motor symptoms that are refractory to pharmacological therapy.[4] Although the therapeutic effectiveness of STN-DBS on the motor symptoms is well documented, the impact of this treatment on cognition is still controversial.[5] One ability that has been extensively reported to decline in PD patients after STN-DBS is verbal fluency.[6] However, the reported effects of STN-DBS on other language aspects, including lexico-semantic and grammatical processing, are variable with reports of both negative[7-9] and positive outcomes.[7,10-13] This divergence may, on the one hand, be in part attributed to the complexity of the neurophysiological mechanisms associated with STN-DBS and the variable physiological functionality of different STN circuits.[14] On the other hand, it may also arise from different effects of stimulating the left and right STN since the asymmetric depletion of the dopaminergic neurons in PD is known to affect cognitive functions differentially in PD patients.[15,16] This is further complicated by the fact that language functions are left-lateralized in most healthy individuals both at the cortical and subcortical levels, particularly for syntactic processing.[17,18]

Only few studies have thus far investigated the effects of unilateral stimulation of the STN on other language functions besides speech production, all with variable results.[8,19,20] One caveat of the existing literature is that the majority of previous studies have focused on assessing the effects of DBS on language production.[7-10,12,19-21] To our knowledge, no study has systematically investigated the effects of DBS on language comprehension. Furthermore, studies on the effects of DBS on language functions have assessed the performance of PD patients in tasks that required overt responses by the patients (e.g., verbal responses and button presses).[7-12,19-21] These tasks may be inconvenient for patients with motor deficits, thereby introducing bias or errors in the obtained measures. Additionally, such behavioral measures only provide an indirect insight into the neural mechanisms of DBS effects on language processing.

In relation to unraveling the neurophysiological mechanisms underpinning DBS effects in general, and DBS effects on language functions in particular, the use of magnetoencephalography (MEG) holds a great promise. This technique allows for precise tracking of the neural correlates associated with language processing with high temporal resolution on the scale of milliseconds, which is particularly important for this highly dynamic cognitive function.

In this study, we set out to use MEG to investigate the effects of bilateral and unilateral DBS of the STN on two aspects of language processing in PD patients: action verb semantics and morphosyntax. Previous studies have associated action verb processing[22,23] as well as morphosyntactic processing[7,17] with cortico-subcortical circuits involving the basal ganglia. Furthermore, neuroimaging studies have demonstrated that DBS of the STN modulates the cortical activity in many areas including prefrontal cortex, premotor cortex, sensorimotor cortex, and supplementary motor cortex.[24-28] Thus, we hypothesized both aspects to be affected by STN-DBS, and differentially so by unilateral and bilateral stimulation relative to the DBS-off state, although, due to contradicting reports in the literature, we could not make specific predictions about the exact direction of these putative effects.

2 | METHODS

2.1 | Participants

Five PD patients treated with STN-DBS implantation participated in this study. All patients had electrodes implanted bilaterally in the STN for at least 6 months. All patients were right-handed native Danish speakers (handedness was assessed using Edinburgh inventory)[29]. One patient was excluded from the study due to intolerance and discomfort after switching off the DBS on both sides. Another patient was excluded due to poor data quality. Thus, three patients were included in the final analysis (3 males, right-handed, mean age of 64.7, SD = 1.7). The patients were assessed by a neurologist using the Unified Parkinson's Disease Rating Scale, subscore III (UPDRS-III) in order to evaluate their motor symptoms,[30] the Montreal Cognitive Assessment (MoCA) to ensure normal cognition and rule

TABLE 1 Demographic and clinical characteristics of the patients

					Stimulation setting		UPDRS-III				
I	Age	Gender	MDI	MOCA	Left STN	Right STN	DBS on (baseline)	DBS off	DBS left	DBS right	DBS on
PD 1	63	M	6	N	2.1 V, 60 µs, 130 Hz	2.1 V, 60 µs, 130 Hz	11	24	22	20	13
PD 2	64	M	8	N	3.3 V, 60 µs, 130 Hz	3.0 V, 60 µs, 130 Hz	16	33	21	10	6
PD 3	67	M	10	N	3.3 V, 60 µs, 150 Hz	3.1 V, 60 µs, 150 Hz	22	42	25	30	19

out dementia,[31] and the Major Depression Inventory (MDI) to rule out depression.[32] Demographic and clinical information obtained from the patients are listed in Table 1. Written consent was obtained from each patient. The study was approved by The Central Denmark Region Committees on Health Research Ethics (*Nr. 63868*).

2.2 | Language stimuli

A set of spoken Danish words and pseudowords was used in this study, aimed at testing neural processing of two types of linguistic information: action-related semantics and morphosyntax. The semantic contrast consisted of two action verbs (*"slikke"* [slegə] (to lick) and *"spytte"* [sbødə] (to spit)), whose brain responses were compared to those of two abstract verbs (*"slutte"* [sludə] (to end) and *"svække"* [svɛgə] (to weaken)). The second syllables of these verbs (i.e., "*-kke*" and "*-tte*") had identical acoustic features and were counterbalanced between the action and abstract verbs to ensure minimal acoustic confounds (see Table 2 for a list of all stimuli). Additionally, four acoustically matched meaningless pseudowords were created (*"*slitte"* [sledə], *"*spykke"* [sbøgə], *"*slukke"* [slugə], and *"*svætte"* [svɛdə]), which were used as fillers to ensure that the onset of the second syllable served as the divergence point, allowing us to precisely time-lock brain responses to this time point.

Similarly, for the morphosyntactic contrast, we constructed counterbalanced noun-suffix combinations based on four nouns (*"slot"* [slʌd] (castle), *"stykke"* [sdøgə] (piece), *"skytte"* [sgødə] (shooter), *"stok"* [sdʌg] (stick)) where each noun was cross-spliced twice with the two morphemes *-(e)n and -(e)t* that express definiteness of nouns in Danish for common and neuter gender, respectively. Hence, depending on its gender, each noun produced a grammatically correct inflection (*"slottet", "stykket", "skytten" and "stokken")* and its grammatically incorrect inflectional counterpart (*"*slotten", "*stykken", "*skyttet" and "*stokket"*). This design entails that both correct and incorrect inflection sets have exactly the same stems and affixes (combined differently), while the divergence point is again at the second syllable onset. Note that the incorrectly inflected nouns are not pseudowords in the same sense as the meaningless pseudowords fillers above because the incorrectly inflected nouns are composed of real existing morphemes—base stems (meaningful nouns) affixed with real inflectional morphemes, and thus, they are subject to morphosyntactic parsing and combinatorial processing.[33] These morphemes (both stems and affixes) are expected to have long-term neural memory representations while the meaningless pseudowords are not expected to have any monomorphemic representations.[34]

A digital recording (44.1 kHz, 32 bit) of a male native speaker of Danish was used to construct the stimuli. The first syllables of all types of stimuli (e.g., *"spy-" or "sty-"*) had the same duration of 315 ms followed by a silent gap of 35 ms. The second syllables of the real verbs and their pseudoword counterparts (i.e., *"-tte" and "-kke"*) had the same duration of 140 ms. Thus, the total duration of each of the semantic stimuli was 490 ms. For the morphosyntactic stimuli, the second syllables (e.g., "*-tten*" or "*-kket*") had the same duration of 170 ms, resulting in a total duration of 520 ms. Stimulus editing was done using Praat 6.0.43[35] and Adobe Audition CC (Adobe Inc.).

2.3 | Stimulus presentation

Stimulus presentation was done using an equiprobable paradigm that we have previously validated for use with patients.[36] The paradigm allows simultaneous testing of different linguistic contrasts while keeping the testing session very short and not requiring any focused attention or overt stimulus-related task from the patient.[36] The paradigm included two separate sequences, one for the semantic stimuli and one for the morphosyntactic ones. In the semantic sequence, we presented action and abstract verbs and the respective pseudoword fillers equiprobably and pseudo-randomly. Each stimulus was repeated 100 times, thus the whole sequence contained 800 trials in total. The morphosyntactic sequence had the same presentation fashion where all inflectional forms (both correct and incorrect) were presented pseudo-randomly and equiprobably with each stimulus item repeated 100 times (800 trials in total). Pseudo-randomization of the stimuli within each sequence was done on subsequent trains of 40 stimulus items, such that no two identical items could follow each other, while ensuring

TABLE 2 Stimuli

Semantic forms	Lexical	Pseudowords
Action verbs	slikke [slegə] (to lick)	*slitte [sledə]
	spytte [sbødə] (to spit)	*spykke [sbøgə]
Abstract verbs	slutte [sludə] (to end)	*slukke [slugə]
	svække [svɛgə] (to weaken)	*svætte [svɛdə]
Morphosyntactic forms	**Correct morphosyntax**	**Incorrect morphosyntax**
Concrete nouns	stykket [sdøgəd] (the piece)	*stykken [sdøgən]
	slottet [slʌdəd] (the castle)	*slotten [slʌdən]
	stokken [sdʌgən] (the stick)	*stokket [sdʌgəd]
	skytten [sgødən] (the shooter)	*skyttet [sgødəd]

Note: Asterisks (*) denote pseudo-forms.

a relatively balanced distribution of the stimuli within each sequence. Stimulus-onset asynchrony (SOA) was jittered between 1050 and 1150 ms, with a mean of 1100 ms. Thus, each sequence had a duration of ~15 min.

2.4 | Procedure

Before starting the experiment, PD patients underwent neurological and neuropsychological assessments (MoCA, MDI, and initial UPDRS-III). They arrived at the MEG laboratory in the morning after at least 12 hours withdrawal from dopaminergic medication, but with DBS on. The neurologist then switched off the DBS and while waiting for the effects of the DBS to wash out,[37,38] patients were prepared for the MEG recording (~30 min). Before placing the patients in the MEG system, they underwent UPDRS-III assessment (~10 min) to attest that they were in a "practically defined off state" (i.e., off from both medication and DBS).[38] The PD patients underwent MEG recordings four times during the experiment (see Figure 1): STN-DBS off, left unilateral STN-DBS, right unilateral STN-DBS and bilateral STN-DBS. Immediately before the first session started, the patients underwent a brief hearing screening (~10 min) to ensure that the headphones were positioned correctly and that the sound level was suitable for the patient.

Magnetoencephalographic measurements were performed in supine position. Each MEG recording session lasted for approximately 30 min. Participants were given breaks (1-2 min) within each session. During each MEG recording, patients were presented with the auditory stimuli through in-ear-tubes (Etymotic ER-30). There was no task required from the patients. Patients were only instructed to ignore the auditory input and focus on watching a silent film that was projected on a screen placed at a suitable distance from the patient.

The order of DBS sessions was optimized for the patient comfort. The first MEG recording was with DBS turned off. For the second session, the DBS was set to left unilateral STN stimulation and for the third session to right unilateral STN stimulation. The last recording session was done with bilateral STN stimulation. Patients were recorded in the four DBS settings with 30 min intervals in-between (where patients were taken out of the MEG system) to allow for the changed DBS stimulation parameters to take effect.[38] Patients were assessed with the UPDRS-III scoring to evaluate their motor symptoms and attest the effect of the changed DBS settings immediately before each recording session started. After the last recording session, patients received their anti-parkinsonian medication under the supervision of the neurologist on site. Approximately 1 hour after their medication intake (and after 2 hours with their DBS in its original settings), a final clinical assessment of the patient's motor functions (UPDRS-III) was performed to ensure that the effects of medication and DBS were fully restored, and the patient could be sent home. Throughout the entire experiment, patients were observed by the on-site neurology specialist in movement disorders and DBS treatment.

2.5 | Magnetoencephalographic recordings

Magnetoencephalographic data were recorded using a 306-channel, CE-approved, Elekta Neuromag Triux MEG system (Elekta Neuromag Oy) placed in a magnetically shielded room with acoustic isolation (Vacuum Schmelzer Gmbh). MEG data were measured from 204 planar gradiometers and 102 magnetometers with 1 kHz sampling rate and an online passband of 0.1–330 Hz. Bipolar horizontal and vertical electrooculograms (EOG) as well as bipolar electrocardiogram (ECG) were also recorded. Three cardinal landmarks (nasion and left and right pre-auricular points) along with the head shape and the positions of four head position indicator coils (HPIs) were digitized using a Polhemus FASTRAK setup (Polhemus). Continuous head position tracking during the MEG recording was not possible in the three sessions where the DBS was turned on due to interference with the HPI coils from the DBS. Therefore, at the end of each of these sessions, and while the patient was still lying down in the same position in the MEG scanner, the neurologist switched off the DBS on both sides before effectuating the next settings, and a very brief recording (1 min "dummy" recording) was done with HPI tracking to get a measurement of the head position that would reflect the position of the patient's head inside the MEG helmet during the preceding recording session.

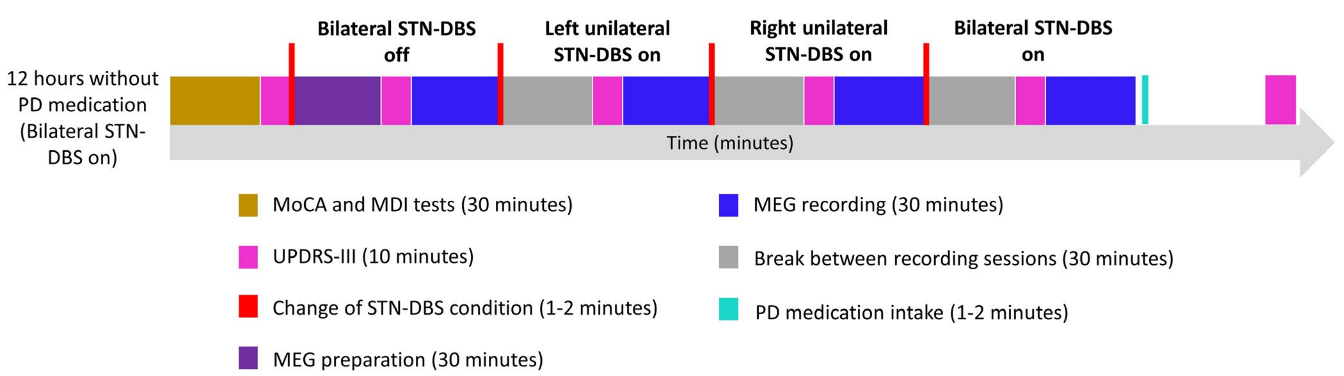

FIGURE 1 Overview of the experimental procedure

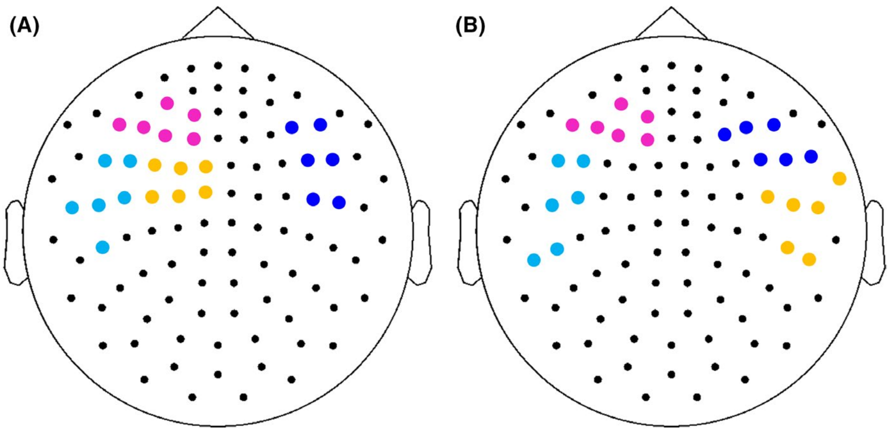

FIGURE 2 Sensor ROIs selection based on an independent sample of participants (each colored point illustrates the position of one pair of gradiometers). (A) Sensor ROIs selection for the semantic contrast analysis. (B) Sensor ROIs selection for the morphosyntactic contrast analysis

2.6 | MEG data preprocessing

To obtain sufficient suppression of the artifacts induced by the DBS harmonic frequencies as well as external magnetic sources, raw MEG data were first low-pass filtered at 40 Hz using a 4th order Butterworth filter as implemented in MNE-Python version 0.19.[39] Data were then processed using the temporal extension of signal-space separation algorithm (tSSS)[40] as implemented in MaxFilter v.2.2.15 software (Elekta Neuromag) with a subspace correlation limit of 0.9 and length of data buffering of 32 s. For the MEG data recorded with DBS off on both sides, head movement compensation was made using the initial head position measured at the beginning of the recording session. For the MEG data recorded in each of the other three sessions, the head positions measured by the HPI coils in the dummy recording immediately after each session were used as head positions for the entirety of the relevant recording sessions. Further processing was done using MNE-Python version 0.19. Data were high-pass filtered at 1 Hz to remove low-frequency drifts. To remove artifacts caused by heartbeats and eye-movements, ICA with the *"fastica"* algorithm[41] was applied on data from gradiometers only. After ICA, there were no bad gradiometers in either of the patients' data. Epochs were generated from −100 to 1050 ms after the stimulus onset, and baseline correction was applied with a 100-ms pre-stimulus interval. Epochs in which gradiometers' amplitudes exceeded 4000 fT/cm were excluded. There was per patient a mean of 0.3 (SD: 0.2) rejected epochs for the data with bilateral DBS, a mean of 0.2 (SD: 0.1) rejected epochs for the data with left DBS, a mean of 0.2 (SD: 0.2) for the data with right DBS, and no epochs were rejected for the data with DBS off. As already stated, one patient was excluded from further analysis when checked for data quality (absence of a clear obligatory N100m auditory response to the sound stimuli), leaving three patients for the final analyses.

2.7 | Sensor space analysis

For sensor space analysis, the selection of sensors and time windows was adopted from the results of a spatiotemporal permutation analysis of MEG data recorded with the same paradigm in another study (see Figure S1) which used a healthy elderly group and a group of early-stage PD patients treated with anti-parkinsonian medication only (i.e., without DBS implants). Four clusters, each consisting of 12 gradiometers (6 pairs with 2 planar gradiometers in each), were identified in the healthy elderly and early-stage PD patients and passed on as sensors-of-interest (SOIs) to these analyses. Importantly, the inclusion of six pairs of gradiometers in each cluster was to ensure better signal-to-noise ratio (SNR) than can be achieved with one or two pairs, and thus, more robust results.

For the semantic contrast (action verbs vs. abstract verbs), the clusters were distributed over the left temporal, left frontal, central, and right frontotemporal regions (see Figure 2A). These clusters were chosen based on the results from the healthy elderly group only as the early-stage PD group showed no significant results for this contrast. For the morphosyntactic contrast (correct vs. incorrect inflections), the clusters were distributed over the left temporal, left frontal, right temporal, and right frontal regions (see Figure 2B), based on both healthy and early-stage PD data, combined.

While we based our selection directly on the activity observed in an independent study using the same stimuli, we also ensured that the selected sensors in each condition overlapped with the cortical areas commonly associated with the processing of the language aspect tested in each condition, respectively (see Figure 2). It is important, however, to keep in mind that the activity registered in sensor space by any MEG sensor is neuro-anatomically imprecise due to the spread of neural activity caused by volume conduction as well as the fact that their locations with respect to individual heads vary to some extent between subjects.

Analyses were carried out on the epochs by quantifying the neuromagnetic activation by calculating the square root of the sum of squared amplitudes (root mean square, RMS) of each pair of gradiometers. For each epoch, baseline correction was re-applied after computing the RMSs using the 100 ms pre-stimulus interval. Finally, for each epoch, the mean amplitudes over the time window of interest were computed. For the semantic contrast, a time window of 500–600 ms (after word onset) was used based on the spatiotemporal permutation results of the independent sample (see Figure S1A). For the morphosyntactic contrast, the same type of permutation statistics suggested a time window of 595–725 ms (after word onset) (see Figure S1B).

2.8 | Statistical analysis

To assess the effects of different DBS conditions on the patients' neural responses elicited by each linguistic contrast, we performed linear mixed-effects analysis using the R package *lme4* version 1.1–23[42] as implemented in R software version 3.6.1. [43] For each linguistic contrast, a series of model comparisons were performed. Data were first standardized using z-scores. We then constructed a null model taking into account individual patient variation by including a random intercept for each patient. Furthermore, the null model accounted for the variability of the topographical distribution of the sensors' clusters by including a random intercept for each cluster. Next, to test for potential effects of the different DBS conditions we constructed a model that also included the four DBS conditions (*off*, *left*, *right*, and bilateral) as a fixed effect. To test for the effects of the different types of language stimuli, we then constructed a model that also included word group as a fixed effect with two levels (semantics: action verbs vs. abstract verbs; and morphosyntax: incorrect vs. correct inflectional forms). Finally, to test for the interaction between the DBS conditions and the linguistic contrasts, we constructed a full model by also including the interaction term between stimulation and word group. All models were fitted using maximum likelihood estimation and were compared using likelihood ratio test.

3 | RESULTS

The statistical results of both linguistic contrasts are listed in Table 3 and visualized in Figure 3.

3.1 | Semantic contrast (action verbs vs. abstract verbs)

Model comparisons for the semantic contrast between action verbs and abstract verbs revealed that there was an effect of the interaction between DBS condition and word group (χ^2 (3) = 33.06, *p* value < 0.00001; see Figure 3A). Full model refitted with restricted maximum likelihood (REML) yielded two significant interactions; between the DBS condition (off vs. bilateral) and action/abstract word group (β estimate = 0.062, SE = 0.016, 95% CI = [0.030, 0.095]) as well as between the DBS condition (off vs. right) and word group (β estimate = 0.051, SE = 0.016, 95% CI = [0.019, 0.083]). The estimated fixed effects (β estimates), standard errors, and the 95% confidence intervals are listed in Table 3.

Following up these significant interactions between DBS condition and action/abstract word group revealed that (1) in the bilateral DBS condition, the standardized mean response amplitude for action verbs (mean = 0.055, SD = 0.166) was greater than that for abstract verbs (mean = −0.008, SD = 0.113), and (2) in the right DBS condition, the standardized mean response amplitude for action verbs (mean = 0.033, SD = 0.136) was greater than that for abstract verbs (mean = −0.019, SD = 0.109).

TABLE 3 Summary results of the final models

Fixed effects	β estimates	Standard errors (SE)	95% Confidence intervals
Semantic contrast			
Intercept	−0.014	0.140	−0.315, 0.287
DBS condition *left DBS*	0.022	0.012	−0.001, 0.045
DBS condition *bilateral DBS*	0.006	0.012	−0.017, 0.029
DBS condition *right DBS*	−0.005	0.012	−0.028, 0.018
Word group *action verbs*	0.001	0.012	−0.022, 0.023
Left DBS × action verbs	−0.017	0.016	−0.049, 0.016
Bilateral DBS × action verbs*	0.062	0.016	0.030, 0.095
Right DBS × action verbs*	0.051	0.016	0.019, 0.083
Morphosyntactic contrast			
Intercept	−0.013	0.128	−0.288, 0.262
DBS condition *left DBS*	−0.007	0.008	−0.023, 0.009
DBS condition *bilateral DBS*	0.038	0.008	0.022, 0.054
DBS condition *right DBS*	0.018	0.008	0.002, 0.034
Word group *incorrect forms*	−0.020	0.008	−0.036, -0.003
Left DBS × incorrect forms*	0.043	0.012	0.020, 0.066
Bilateral DBS × incorrect forms	0.021	0.012	−0.002, 0.043
Right DBS × incorrect forms	0.022	0.012	−0.001, 0.045

Note: The reference condition of the DBS fixed effect is *DBS off*. The reference condition of the word group fixed effect is *abstract verbs*. Asterisk '*' denotes significant interaction.

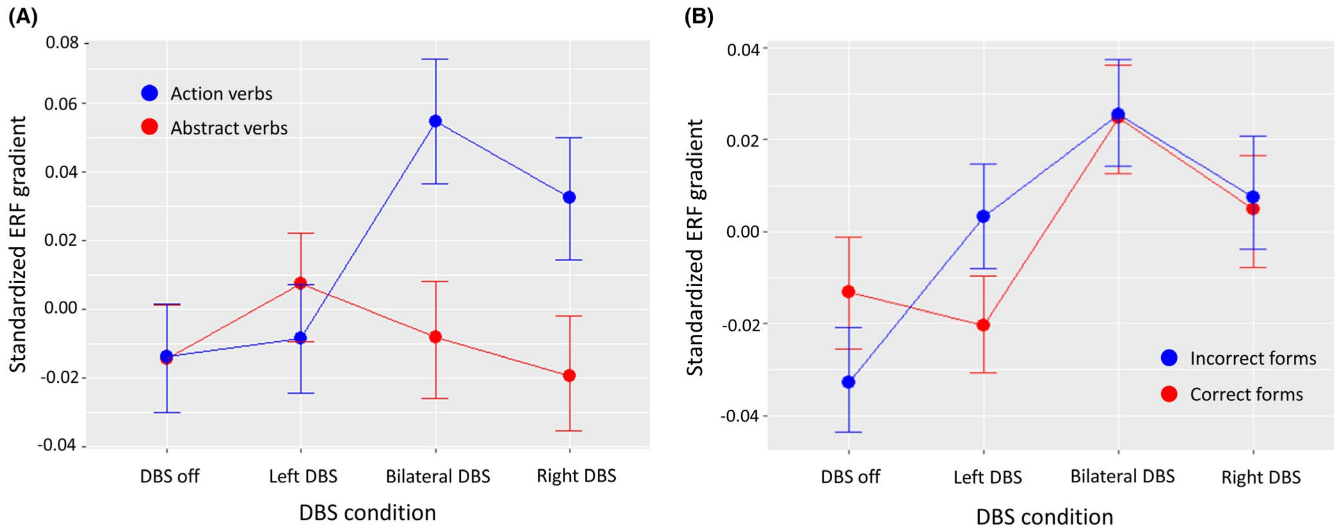

FIGURE 3 Standardized amplitudes of ROI-average MEG responses to semantic stimuli (A) and morphosyntactic stimuli (B) for different DBS conditions (off, left, bilateral and right)

3.2 | Morphosyntactic contrast (correct vs. incorrect forms)

Model comparisons for the morphosyntactic contrast between the correct and incorrect inflectional forms revealed that there was an effect of the interaction between DBS condition and word group (χ^2 (3) = 13.759, p value = 0.003; see Figure 3B). The full model refitted with the restricted maximum likelihood revealed a significant interaction (β estimate = 0.043, SE = 0.012, 95% CI = [0.020, 0.066]) between the DBS condition (off vs. left) and word group (correct vs. incorrect forms). The estimated fixed effects (β estimates), standard errors, and the 95% confidence intervals are listed in Table 3.

Following up the significant interaction between the DBS condition and word group revealed that the standardized mean response amplitude to the incorrect forms (mean = 0.003, SD = 0.057) was greater than that to correct forms (mean = −0.020, SD = 0.101) in the left DBS condition only.

4 | DISCUSSION

The present study provides a first insight into the effects of bilateral and unilateral STN-DBS on neural responses associated with two aspects of language processing in PD patients: action verb and morphosyntactic processing. Our design allowed us to contrast the linguistic stimuli within each DBS condition to ensure that the effects of the DBS on the neuromagnetic responses were not induced by the electrical stimulation itself. The results showed differential effects of the bilateral and unilateral STN-DBS on the neural responses associated with the two linguistic aspects examined in this study. Below we discuss the results of each linguistic aspect separately.

4.1 | Effects of STN-DBS on action and abstract verb processing

Relative to the DBS-off state, both bilateral and right-sided stimulation of the STN produced significant dissociations in the neural activity with greater neuromagnetic responses for the processing of action verbs compared to the abstract ones, whereas this was not the case for the left-sided STN-DBS. The fact that right-sided and bilateral STN-DBS modulated the neural activity associated different verb semantics suggests that STN stimulation may have differential effects on language processing depending on the nature of the underlying linguistic representations.

According to the embodied cognition view, the meaning of action words is partly understood via motor simulations,[44] therefore, comprehension of action words would automatically activate the corresponding cortical motor areas which are involved in representing action-related semantics.[45,46] Furthermore, the processing of action verbs has been associated with a cortico-subcortical network (including the motor and premotor cortices) that is mediated by the basal ganglia.[22,47]

Importantly, neuroimaging studies have shown that bilateral STN-DBS modulates the neural activity in the motor circuit of the basal ganglia[28] including the supplementary motor cortex, primary motor cortex, and premotor cortex.[27,48] Thus, it might be that the processing of action verbs benefits from the normalization of the basal ganglia motor circuit as effectuated by bilateral STN-DBS. Indeed, some studies have found that bilateral STN-DBS has selective influence on the processing of action verbs as well as improved naming of actions.[10,11] These findings may help explain the observed effects of bilateral STN-DBS in this study on the neural activity associated with the processing of action verbs but not abstract verbs.

Interestingly, our findings revealed that right-sided stimulation of the STN produced similar dissociative effects as did bilateral stimulation, while left-sided stimulation of the STN yielded no significant differences in the neural responses to action and abstract verbs processing compared to the off stimulation state. Currently, there is still little information available on the effects of unilateral STN-DBS on different language functions besides speech production.[8,19,20] Schulz et al.[8] reported that right-sided STN-DBS in PD patients yielded better language measures for semantic verbal fluency as well as sentence comprehension compared to left-sided stimulation. Improved speech production during right-sided compared to left-sided stimulation of the STN has also been reported in several previous studies,[49-51] which is in line with the present result.

Batens et al.[20] found that only PD patients with dominant dopamine deficiency in the left hemisphere benefited from stimulating the right hemisphere during spontaneous language production, suggesting that the effects of STN-DBS on language processing may be associated with the laterality of dopamine depletion in PD patients. Whether the laterality of dopamine deficiency for the PD patients in the present study may have contributed to our observed STN-DBS effects is an open question since such disease-related information was not available for the patients in our study. However, the PD patients in Batens et al.[20] were tested while on their optimal medication dose unlike in our study where patients were tested while off medication to better target the effects of the DBS stimulation directly. In order to address this issue, future studies including larger cohorts of patients should strive to obtain data on the laterality of the dopamine deficiency in the included patients.

4.2 | Effects of STN-DBS on morphosyntactic processing

Contrary to the findings in the semantic condition, the results of the morphosyntactic condition revealed that, relative to the DBS-off state, only the left-sided stimulation of the STN yielded significant differences in the neural activity elicited by the morphosyntactic inflections, with enhanced neural responses for the incorrect inflections compared to the correct ones.

Grammatical processing in general, including syntax and morphosyntax, has been associated with left-lateralized cortical language areas, most often the left inferior frontal gyrus (Broca's area).[52,53] This left-lateralization has also been found at the subcortical level.[17,18,52] These left-lateralized cortical circuits are known to produce enhanced activity in response to ungrammatical combinations of stems and morphemes, which may reflect involvement of syntax-specific error detection mechanisms or the lack of morpheme-related priming.[54]

Thus, it seems plausible to speculate that left-sided STN-DBS may selectively influence automatic processing of morphosyntactic violations by modulating the activity in the left cortical language areas, most crucially Broca's area via its frontostriatal loop.[55] Furthermore, this suggests that STN stimulation may influence not only action-related processing, but also the processing of more abstract language features, such as combinatorial/morphosyntactic parsing of sequences of language elements. However, given the limited data in the present study, this suggestion should be treated with caution and its verification requires further studies with more PD patients.

In general, previously reported effects of STN-DBS on grammatical and morphological processing in PD patients have been largely variable.[7,8,12,13,19,20] Some studies have found that bilateral STN-DBS improved patients' ability to process morphosyntax as indicated by the significant reduction in the morphosyntactic errors made by the patients (e.g., substituting inflectional morphemes).[12,13] Others, on the other hand, have found that bilateral STN-DBS had a negative impact on grammatical processing in PD patients.[7] Both bilateral and left-sided stimulation of the STN also negatively impacted patients' performance during a sentence comprehension task.[8] In our study, both right-sided and bilateral STN-DBS had no dissociative effects on the neural responses to correct and incorrect morphosyntactic inflections compared to the off stimulation state. Although our findings seem to indicate that bilateral and right-sided stimulation of the STN do not affect automatic parsing of grammatical violations compared to no stimulation, such interpretation requires further investigations with larger cohorts of patients.

As already discussed in relation to the semantic condition, the laterality of dopamine depletion in the included patients may also have affected the observed effects of STN-DBS on morphosyntactic processing in PD patients in this study. Batens et al.[20] found that only PD with left-dominant dopamine depletion improved their performance in some morphosyntactic aspects of spontaneous language production during bilateral and right-sided STN stimulation.[8] However, differences in experimental procedure (different language tasks and PD medication control) as well as patient variability across studies are more likely to explain the divergence in the reported effects of STN-DBS on grammatical and morphological processing in PD patients.

4.3 | Limitations

An important limitation of the current study is the small cohort of PD patients included. However, other studies involving PD patients with DBS have obtained robust results with only few PD patients included.[56,57] Notably, this limitation is mainly due to the difficulties associated with the recruitment of PD patients treated with DBS as well as our experimental design entailing long recording time (approximately 5 hours) which made the participation in our study not fully endurable for several patients. We therefore emphasize the necessity of further studies with larger cohorts of patients to support or refute our findings and their interpretations.

Another limitation of the current study is the lack of direct comparison with data from healthy subjects undergoing an identical rigid testing regime. This inherently limits the scope of the interpretation of the observed differentiated effects of STN-DBS. That being said, in this study, we used a within-subject design and investigated how unilateral and bilateral stimulation of the STN may differently affect language processing in PD by employing the neural responses of PD patients during the DBS-off state as the baseline and control condition to which other stimulation conditions were compared in order to limit the variance induced by between-patient variability in the neural responses. While this within-subject comparison cannot be refuted, we still wish to emphasize the importance of the inclusion of healthy control cohorts in future studies.

5 | CONCLUSION

Despite the very small cohort of PD patients included in this study, the results provide a first demonstration of differential effects of unilateral and bilateral STN-DBS on neural language comprehension processes in PD patients which vary depending on the type of linguistic information and the laterality of DBS application. Crucially, all suggested interpretations must be further investigated with larger cohorts of patients.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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