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Subthalamic nucleus stimulation and spontaneous language production in Parkinson's disease: A double laterality problem

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ABSTRACT

Background: Asymmetric degeneration of dopaminergic neurons, are characteristic for Parkinson's disease (PD). Despite the lateralized representation of language, the correlation of asymmetric degeneration of nigrostriatal networks in PD with language performance has scarcely been examined.
Objective/hypothesis: The laterality of dopamine depletion influences language deficits in PD and thus modulates the effects of subthalamic nucleus (STN) stimulation on language production.
Methods: The spontaneous language production of patients with predominant dopamine depletion of the left (PD-left) and right (PD-right) hemisphere was compared in four stimulation conditions.
Results: PD-right made comparatively more verb inflection errors than PD-left. Bilateral STN stimulation improves spontaneous language production only for PD-left.
Conclusions: The laterality of dopamine depletion influences spontaneous language production and the effect of STN stimulation on linguistic functions. However, it is probably only one of the many variables influencing the effect of STN stimulation on language production.

1. Introduction

There is an increasing evidence for subcortical involvement in language processes (Chan, Ryan, & Bever, 2011; De Letter, Van Borsel, & Santens, 2012; Robles, Gatignol, Capelle, Mitchell, & Duffau, 2005). However, it is still a matter of debate whether these linguistic functions are processed in subcortical structures themselves or rather in a network encompassing cortical and subcortical areas.

A hallmark of PD is the asymmetry of motor symptoms, which reflects the asymmetric degeneration of dopaminergic neurons (Djaldetti, Ziv, & Melamed, 2006; Kempster, Gibb, Stern, & Lees, 1989). This unilateral predominance of symptoms is generally noticeable throughout the course of the disease, even long after the disease becomes clinically bilateral (Antonini et al., 1995; Cronin-Golomb, 2010; Djaldetti et al., 2006). The brain tries to mitigate the dopamine deficiencies with compensatory neural responses. Compensatory mechanisms that have been described are: expansion of activated cortical areas, increased excitability of cortical areas, and involvement of contralateral hemisphere (Kojovic et al., 2012; Spagnolo et al., 2013). This compensatory reorganisation can influence the interhemispheric balance (Spagnolo et al., 2013). In motor tasks, the lateralized dopamine deficits are compensated by expanding the normal motor network to areas that are usually only activated in complex movements and/or by increasing the excitability of motor areas. In early PD, this increased excitability is only present in the most affected hemisphere, creating an imbalance between both hemispheres. As PD advances, this imbalance disappears, due to an increased excitability of both hemispheres (Spagnolo et al., 2013).

Although motor problems are the most visible lateralized symptoms, asymmetric degeneration also affects non-motor and cognitive functions (Cubo, Martinez Martín, Martin-Gonzalez, Rodríguez-Blázquez, & Kulisevsky, 2010; Kempster et al., 1989; Riederer & Sian-Hülsmann, 2012; Verreyt, Nys, Santens, & Vingerhoets, 2011). For example, difficulties with orientation, mental imagery, and visuospatial attention are observed in PD patients with more severe right-hemispheric dopamine depletion. On the other hand, problems in verbal memory are more

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associated with profound nigrostriatal degeneration in the left hemisphere. Studies examining executive functions lead to an equivocal answer with respect to asymmetry (Verreyt et al., 2011).

The cortical representation of syntactic language functions is strongly lateralized to the left hemisphere, whereas semantics functions are more bilaterally represented (Dominey & Inui, 2009; Lindell, 2006; Menenti, Segaert, & Hagoort, 2012). Despite this lateralized representation of language, the correlation of asymmetric degeneration of nigrostriatal networks and language has rarely been examined, merely as a subpart in general cognitive studies (Verreyt et al., 2011). Holtgraves, McNamara, Cappaert, and Durso (2010) assessed the linguistic complexity of spontaneous language production by measuring sentence length and the proportion of function words and verbs. Patients with more severe right-hemispheric dopamine depletion were found to produce significantly fewer verbs and more simplified linguistic output than patients with more severe left-hemispheric dopamine depletion. Because pragmatic processes are closely related and associated with dopaminergic networks of the right frontal lobe, Holtgraves et al. (2010) suggested that decreased linguistic complexity reflects a pragmatic deficit of the right frontal cortex. A second study reported an electrophysiological investigation on semantic comprehension of action words (De Letter et al., 2012). The current densities in ten predefined brain areas were measured during a covert word-reading task, on and off Levodopa administration. An increase of neural activity for semantic processing was found after Levodopa intake. Normally, a bilateral distribution would be expected in healthy controls, but in some subjects the cortical activity was strongly lateralized. However, none of the patients described had higher dopamine sensitivity in the most affected hemisphere, suggesting a larger dopamine-related effect on cognitive networks in the less affected hemisphere.

Deep Brain Stimulation (DBS) has become an established therapeutic option for advanced PD with motor fluctuations that are refractory to medical treatment (Kleiner-Fisman et al., 2006; Klostermann, Krugel, & Wahl, 2012). At present, in most centers performing DBS, the subthalamic nucleus (STN) is the target of choice, as high-frequency stimulation in this nucleus improves all cardinal motor symptoms of PD, allowing a reduction of dopaminergic antiparkinson drug treatment (Fasano, Daniele, & Albanese, 2012). Although the working mechanism of DBS is still unclear, DBS is presumed to override the oscillatory patterns of the disrupted networks (Benabid et al., 1996; McIntyre & Hahn, 2010). The effect of STN stimulation on language variables is not as straightforward as on motor symptoms (Klostermann et al., 2012). Whelan, Murdoch, Theodoros, Hall, and Silburn (2003) were among the first to assess the effect of STN stimulation on different high-level language functions with a large assessment battery. Some linguistic functions improved, whereas some others deteriorated with STN stimulation. These contradictory results were also found in word generation studies (Castner et al., 2008; Silveri et al., 2012) and studies examining syntactic functions (Homer, Rubin, Horowitz, & Richter, 2012; Zanini et al., 2003, 2009).

The divergent DBS results indicate that various neural circuits within the STN have different physiological functions (McIntyre & Hahn, 2010; Temel, Blokland, Steinbusch, & Visser-Vandewalle, 2005; Thobois & Broussolle, 2012). Therefore, the optimal DBS stimulation parameters for motor results might not be the same as those for language or other cognitive functions.

Furthermore, DBS is an interesting method to assess the effects of unilateral STN stimulation on the dopaminergic network, especially because of the asymmetry in dopamine degeneration (Castner et al., 2007). In contrast to speech, the effects of unilateral STN stimulation on language have been rarely tested and no research has been done on the interaction of DBS with asymmetric dopamine depletion in language tasks. One study reporting the lateralized effects of STN stimulation on language outcomes, yielded worse linguistic outcome of left STN stimulation compared to stimulation of the right STN (Schulz et al., 2012). The authors hypothesized that the negative influence of bilateral stimulation on language function likely originates from stimulation of the left STN. The discrepancy between stimulation of the right and left STN was associated with the lateralization of linguistic functions. In a recent study (Batens et al.) we investigated the effect of STN stimulation on spontaneous language production in four stimulation conditions (bilateral stimulation on, bilateral stimulation off, stimulation of the left STN only, stimulation of the right STN only). No significant differences between stimulation conditions were found, despite the linguistic differences with normal controls. We concluded that the effects of STN stimulation on spontaneous language production were highly individual, reflecting a complex interplay of multiple factors of which lateralization of the nigrostriatal degeneration is one.

To obtain a better understanding of the factors underlying language production in PD and the effect that DBS has on linguistic processing, we assessed the interaction between DBS and asymmetric dopamine depletion on linguistic outcomes. No previous studies have addressed this issue.

The aim of this study was to investigate the interaction between DBS and asymmetric dopamine depletion on linguistic outcomes in patients with PD, answering the following specific research questions:

1. Does asymmetric dopamine depletion influence semantic and morphosyntactic aspects of spontaneous language production of PD?
2. Does STN stimulation interact with the side of predominant dopamine depletion in the production of spontaneous language?

2. Methods

2.1. Patients

Fourteen participants in the advanced stage of idiopathic PD (following the definition of Gelb, Oliver, & Gilman, 1999) were included in this study. They were all considered appropriate candidates for STN stimulation because of severe and fluctuating symptoms that affected the quality of life. Before surgery, all subjects underwent intensive neurological and neuropsychological testing. Clinical assessment and magnetic resonance imaging (MRI) indicated that there were no co-morbid neurological diseases. Neuropsychological assessment revealed no signs of dementia or major depression. None of the patients had a history of psychiatric disorders or substance abuse.

The subjects were divided into two groups depending on the lateralization of motor symptoms. Seven patients had primarily left-sided motor disturbances reflecting predominant right hemispheric dopamine depletion (PD-right). The other seven PD patients had primarily right-sided motor disturbances with predominant left hemispheric dopamine depletion (PD-left). Motor symptom predominance was agreed upon by the motor scores of the UPDRS, the clinical evaluation of the neurologist, and the patient's subjective feelings of motor asymmetry. To ensure that nobody had developed dementia since DBS surgery, all patients were screened using Montreal Cognitive Assessment (MOCA) (Dalrymple-Alford et al., 2010) before inclusion in this study. The clinical and demographic features are further described in Table 1. The stimulation parameters of each subject are summarized in Table 2. Both groups did not differ significantly from each other concerning age, duration of PD, duration of DBS and amplitude of stimulation.

Table 1
Medical and demographic features of PD patients.

Patient	Age (years)*	Hand preference [a]	Language predominance [b]	Motor symptoms predominance	PD duration (years)*	DBS duration (months)*	NSVO-Z (%) [c]	MOCA [d]
1	66	10	Left	Right	13	6	95*	23
2	58	10	Left	Right	10	37	99	21
3	71	10	Left	Right	19	35	100	27
4	56	10	Left	Right	16	12	98	25
5	57	10	Left	Right	16	93	83*	27
6	54	10	Left	Right	10	20	98	21
7	71	10	Left	Right	15	40	98	23
8	47	10	Left	Left	12	3	96	25
9	57	-1	Left	Left	14	7	98	25
10	41	-6	Left	Left	13	106	86*	23
11	57	10	Left	Left	14	65	83*	22
12	60	-3	Left	Left	14	36	90*	26
13	73	9	Left	Left	15	87	98	21
14	53	10	Left	Left	16	80	87*	28

[a] Hand preference is measured with the Dutch Handedness inventory, scores may range from −10 for extreme left-handedness until +10 for extreme right handedness (Van Strien, 1992).
[b] Hemispheric language dominance is defined with the dichotic listening task.
[c] NSVO-Z = the Dutch Intelligibility Assessment at sentence level (Martens et al., 2010), *a score lower than 96% is considered to be dysarthric for people under the age of 70.
[d] MOCA = Montreal Cognitive Assessment (Dalrymple-Alford et al., 2010). *At the time of inclusion.

Table 2
Summary of the individual stimulation parameters.

Patient	Left stimulator				Right stimulator			
	Pole	Ampl (V)	Pulse width (μs)	Freq (Hz)	Pole	Ampl (V)	Pulse width (μs)	Freq (Hz)
PD-left								
1	1-case+	1.8	90	130	9-case+	2.2	90	130
2	1-2+	4.5	90	130	9-case+	4	90	130
3	3-case+	3.7	90	130	10+11-	2.5	60	130
4	2-3-	2.5	90	130	9-10-11+	2.7	90	130
5	1-2+	5.3	90	130	9-10-11+	5	90	130
6	2-3-case+	1.8	90	130	8+9-10-11+	3	90	130
7	0+1-2-3+	3.1	60	130	10-case+	3.1	60	130
PD-right								
8	0-1-	2.2	90	130	10-11-	2.6	90	130
9	1-case+	3	60	130	9-case+	3	60	130
10	1-2-	2	90	130	10-case+	1.1	60	130
11	3+2-	4	90	130	9-11+	4.3	90	130
12	1-case+	2.3	90	130	9-10-	2.3	90	130
13	1-2-	2.9	60	130	10-case+	3.3	60	130
14	2-case+	3.5	60	160	11-case+	2	60	160

PD-left = patient with predominantly left hemispheric dopamine depletion; PD-right = patient with predominantly right hemispheric dopamine depletion; Ampl = amplitude; Freq = frequency.

2.2. Neurosurgery

The neurosurgical placement of electrodes in the STN was done using a conventional stereotactic technique with indirect targeting, combining atlas coordinates, micro-electrode recording and intra-operative macro-electrode stimulation to determine optimal location of stimulation contacts. Quadripolar electrodes (Medtronic 3389, Medtronic, Minneapolis) were implanted and external stimulation was done for at least one week before implantation and connection to the pulse generator in the abdominal wall.

2.3. Neurolinguistic analysis

Patients were all native Dutch speakers, who reported no premorbid language disorders, vision or hearing problems. Handedness was determined by the Dutch Handedness inventory (Van Strien, 1992) for which scores may range from −10 for extreme left-handedness to +10 for extreme right handedness. Ten patients were completely right handed (+10), one strongly right handed (+9), one moderately left handed (−6) and two ambidextrous (−1 and −3). In the PD-left group, all patients were right-handed. There were two ambidextrous persons and one left handed person in the PD-right group. The hemispheric language predominance was defined by means of a dichotic listening task (Kimura, 1961) and indicated that the left hemisphere was the language dominant hemisphere for all PD patients.

The speech intelligibility of all subjects was judged using the "Nederlandstalig spraakverstaanbaarheidsonderzoek zinsniveau" (NSVO-Z), the Dutch version of "Dutch Intelligibility Assessment at sentence level" (DIA-S) (Martens, Van Nuffelen, Van den Putte, Wuyts, & De Bodt, 2010), in order to verify that speech intelligibility was not an interfering factor for reliable transcriptions of the language samples. NSVO-Z is a computer program that randomly selects 18 nonsense sentences from a database containing 1200 sentences, blinded from the test evaluator. The subject was asked to read the sentences aloud while being recorded. Next, all sentences were transcribed and compared to the target sentences. The intelligibility score was calculated as the percentage of correctly identified words. For people under the age of 70, a score lower than 96% is considered to be dysarthric. Above the age of

70, a score below 93.1% is labeled dysarthric. Subjects with a NSVO-Z score lower than 80% were excluded from this study. Based on the NSVO-Z results, two out of seven PD-left patients and four out of seven PD-right patients were labeled dysarthric.

The language analysis was conducted using the standardized method for quantitative analysis of spontaneous language production from the 'Analysis of Spontaneous Speech in Aphasia' (ASTA) (Boxum, van der Scheer, & Zwaga, 2010) in order to be able to refer to the normative data of the ASTA (van der Scheer, Zwaga, & Jonkers, 2011). The ASTA describes how to collect, transcribe and analyze spontaneous language samples. The language samples are obtained by means of a semi-standardized interview without time constraints. The subjects have to answer open-ended autobiographical questions. The questions were referring to topics such as work, family and housing, traveling, leisure and general interests. At least three different topics were addressed during one interview. The first 300 words of each interview were orthographically transcribed for analysis.

Semantic analyses were conducted by counting the number of nouns, lexical verbs and the variety of nouns and lexical verbs (type-token ratio). Type-token ratios were calculated by dividing the number of different nouns or lexical verbs by the total number of nouns or lexical verbs. Morphosyntactic evaluation was conducted by counting the number of copula and modal verbs, mean length of utterance (MLU), percentage of correct sentences and finiteness index (proportion of correctly inflected verbs divided by the total number of clauses containing a verb). In order to be able to interpret the results of the present study, some knowledge about syntactic construction of the Dutch language is required. In Dutch, copula and modal verbs are highly frequent and irregular verbs. They are accounted as closed-class words that contain hardly any lexical information (Bastiaanse, 2011). Lexical verbs are open-class words that have a lexical and a grammatical function in a sentence, determining the sentence structure and relationships with time and agreement (Altmann & Troche, 2011).

All transcriptions and analyses were independently done by two experienced speech pathologists, who were blinded from patients' dopamine depletion asymmetry and the STN stimulation condition. Subsequently the results were compared and mutual consensus was reached in case of a discrepant judgment.

The patients were assessed in four STN stimulation conditions: bilateral stimulation on, bilateral stimulation off, stimulation of the left STN only, stimulation of the right STN only. To avoid order or sequence effects within subjects, conditions were randomized. The patients maintained their optimal doses of medication during testing. All testing was conducted on the same day. After switching to a new stimulation condition, there was at least a fifteen-minute break to reassure that the patient was adapted to the new STN stimulation condition.

The audio samples were recorded digitally on a notebook (Dell Latitude E 6500) using a condenser stereo microphone (Sony ECM-MS907) and the acoustic software Praat (Boersma, 2002). Recording took place in a quiet room without distractions.

Patients were aware of the study aims and agreed to participate by signing an informed consent. This study was approved by the Ethical Committee of Ghent University.

2.4. Statistical analysis

All statistical analyses were performed in IBM SPSS Statistics 21 for windows. Significance level for all tests was set at $\leqslant .05$. The linguistic measures of both PD groups in bilateral stimulation off were mutually compared by means of a Mann–Whitney test. In addition, the linguistic measures of both PD groups in all stimulation conditions were compared separately with the normative data of the ASTA via a one-sample t test.

The effect of STN stimulation on the linguistic variables of both PD groups were evaluated pairwise, bilateral stimulation on versus bilateral stimulation off and left simulation only versus right stimulation only, using mixed repeated measures ANOVA with stimulation condition as within-subject variable and asymmetric dopamine depletion as between-subjects factor. Post-hoc, each PD group was separately tested for main effects of stimulation using pairwise comparisons with Bonferroni correction. To substantiate the statistical result found in the comparison of left stimulation only versus right stimulation only for the number of copula and modal verbs, an additional Wilcoxon sign rank test was conducted to compare these stimulation effects for both PD groups separately.

3. Results

3.1. Linguistic difference depending on asymmetric dopamine depletion

In the mutual comparison of both PD groups the finiteness index was the only linguistic parameter that differed significantly ($p = .049$). PD-right had a significant lower finiteness index compared to PD-left.

To obtain an overall impression of the linguistic characteristics of the two PD groups separately in contrast with healthy subjects, all linguistic variables in the condition without STN stimulation were compared with the ASTA norms (Table 3). Both PD groups did not differ significantly from the normative data for the number of verbs and the type-token ratio of nouns. PD-left produced a significant lower number of nouns and had a higher type-token ratio of lexical verbs than the norm data. In contrast, PD-right only produced a significantly higher type-token ratio of lexical verbs. PD-left had a significantly lower MLU with an excessive number of copula and modal verbs. PD-right also had a significantly lower MLU but did not show increase of copula and modal verbs. Furthermore, the percentage of correct sentences and the finiteness index were, for both PD groups, significantly lower than the normative data.

3.2. Effects of STN stimulation depending on asymmetric dopamine depletion

In order to obtain a general overview, the linguistic variables were compared to normative values of the ASTA for both groups in each stimulation condition (Table 3). For the number of nouns the results per stimulation condition depended on the lateralization of PD. For PD-left, the number of nouns was beneath the normative data in the condition bilateral stimulation off, only stimulation of the left STN and only stimulation of the right STN. For PD-right, the number of nouns was beneath the normative data in the condition: bilateral stimulation on and only left STN stimulation. Type token ratio of nouns and number of lexical verbs were within the normative data in every stimulation condition for both PD-groups. Type-token ratio of lexical verbs was for both PD-groups only significant higher than normative data in the condition bilateral stimulation off. The number of copula and modal verbs for PD-left was significant higher than normative data in the conditions bilateral stimulation off and only stimulation of the left STN. The number of copula and modal verbs for PD-right remained within the normal range for all stimulation condition. MLU was significantly lower than normative data for PD-left in the conditions: bilateral stimulation off and stimulation of the left STN. For PD-right, MLU was significantly lower than normative data with bilateral stimulation on and off. The percentage of correct sentences remained for both PD-groups below the normative

Table 3
Descriptive data of both PD groups, the mean score of the ASTA normative data and the results of the one sample *t*-test in all stimulation conditions.

	Stimulation condition	Mean ASTA	PD-left				PD-right			
			Mean PD	Stand. dev	*t*	*p*	Mean PD	Stand. dev	*t*	*p*
Number of nouns	Bilateral off	48	38.0	10.1	−2.633	.039*	40.3	11.47	−1.78	.125
	Bilateral on	48	45.1	6.44	−1.174	.285	36.3	10.00	−3.10	.021*
	Only left	48	39.0	5.16	−4.611	.004*	36.0	9.06	−3.51	.013*
	Only right	48	41.3	6.99	−2.540	.044*	40.3	13.19	−1.55	.173
TTR nouns	Bilateral off	.76	. 730	.130	−.611	.564	.801	.088	1.24	.261
	Bilateral on	.76	.733	.121	−.594	.574	.801	.082	1.33	.230
	Only left	.76	.811	.072	1.88	.109	.786	.068	1.00	.354
	Only right	.76	.809	.100	1.29	.246	.709	.091	−1.50	.185
Number of lexical verbs	Bilateral off	29	28.7	5.19	−.146	.889	26.7	3.73	−1.62	.156
	Bilateral on	29	28.3	4.57	−.413	.694	29.3	4.99	.151	.885
	Only left	29	30.3	5.06	.673	.526	28.4	4.20	−.360	.731
	Only right	29	30.4	3.55	1.06	.328	29.6	7.00	.216	.836
TTR lexical verbs	Bilateral off	.63	.730	.071	3.73	.010*	.713	.070	3.12	.020*
	Bilateral on	.63	.676	.063	1.91	.105	.683	.082	1.71	.137
	Only left	.63	.693	.110	1.51	.182	.659	.130	.582	.582
	Only right	.63	.690	.160	.990	.361	.677	.116	1.08	.324
Number of copula and modal verbs	Bilateral off	12	17.4	3.99	3.60	.011*	14.3	6.82	.886	.410
	Bilateral on	12	15.9	5.18	1.97	.096	14.4	5.53	1.16	.290
	Only left	12	19.0	4.36	4.25	.005*	15.0	4.24	1.87	.111
	Only right	12	13.4	5.71	.662	.533	14.1	3.98	1.43	.204
MLU	Bilateral off	8.63	6.99	1.09	−3.97	.007*	7.35	1.03	−3.31	.016*
	Bilateral on	8.63	8.49	2.02	−.183	.860	6.92	1.34	−3.37	.015*
	Only left	8.63	7.87	.576	−3.51	.013*	7.74	1.20	−1.96	.098
	Only right	8.63	7.73	2.47	−.96	.375	6.58	1.44	−3.78	.009*
% correct sentences	Bilateral off	.93	.731	.098	−5.37	.000*	.676	.155	−4.34	.005*
	Bilateral on	.93	.723	.057	−9.55	.002*	.770	.080	−5.32	.002*
	Only left	.93	.703	.091	−6.61	.001*	.736	.165	−3.11	.021*
	Only right	.93	.743	.128	−3.87	.008*	.711	.159	−3.64	.011*
Finiteness index	Bilateral off	.99	.967	.019	−3.20	.019*	.946	.026	−4.44	.004*
	Bilateral on	.99	.941	.036	−3.55	.012*	.971	.031	−1.60	.162
	Only left	.99	.950	.033	−3.24	.018*	.950	.034	−3.14	.020*
	Only right	.99	.967	.038	−1.58	.164	.963	.043	−1.65	.150

PD-left = patients with predominant dopamine depletion of the left hemisphere; PD-right = patients with predominant dopamine depletion of the right hemisphere; TTR = type token ratio; % correct sentences = percentage of correct sentences; MLU = mean length of utterance; Stand. dev = standard deviation.
* $p < 0.05$.

data, irrespective of the stimulation condition. Finally, the finiteness index was only within the normal range for PD-left when the right STN only was stimulated. For PD-right, the finiteness index was within normal range in the condition bilateral stimulation off and only stimulation of the left STN.

The mixed repeated measures ANOVA with bilateral stimulation (on versus off) as within-subject variable and asymmetric dopamine depletion as between-subject factor revealed no main effects for stimulation nor asymmetric dopamine depletion. However, there were significant interaction effects between bilateral stimulation (on versus off) and the lateralization of dopamine depletion for three linguistic parameters: number of nouns ($F(1,12) = 6.086$, $p = .030$), MLU ($F(1,12) = 4.858$, $p = .048$) and finiteness index ($F(1,12) = 5.355$, $p = .038$). Further pairwise Bonferroni corrected post hoc analysis revealed that bilateral stimulation yielded a significantly increase in both the number of nouns ($p = .045$) and MLU ($p = .032$) for PD-left, compared to no stimulation. For PD-left, there was no significant difference between bilateral stimulation on and off for the finiteness index. The Bonferroni corrected post hoc tests demonstrated no significant difference between bilateral stimulation on and off for PD-right in the number of nouns, MLU, and the finiteness index.

The mixed repeated measures ANOVA with left STN stimulation only versus right STN stimulation only as within-subject variable and asymmetric dopamine depletion as between-subjects factor, showed a significant main effect for stimulation in the number of copula and modal verbs ($F(1,12) = 5.283$, $p = .040$). There were no significant main effects for asymmetric dopamine depletion. No significant interaction effects could be reported between stimulation of the left STN only and stimulation of the right STN only with the lateralization of dopamine depletion on the linguistic parameters. The additional comparison of both stimulation conditions for both PD groups separately, indicated for PD-left a borderline significant difference between left STN stimulation only and right STN stimulation only ($p = .061$). No significant differences were found between stimulation conditions for PD-right. The results for the parameters number of nouns, number of copula and modal verbs, MLU and finiteness index are, for both groups, visualized in Fig. 1.

4. Discussion

The current study aimed to investigate the interaction between asymmetry of dopamine depletion with alterations of spontaneous language production. Secondly, the influence of different conditions of STN stimulation on spontaneous language production was examined.

4.1. Linguistic difference depending on asymmetric dopamine depletion

The laterality of motor symptoms is associated with spontaneous language production. In the direct comparison of both PD-groups, the PD-right group had a lower finiteness index, indicating more mistakes in verb inflection than the PD-left group. Verb inflection deficits in PD have been described before (Colman et al., 2009; Longworth, Keenan, Barker, Marslen-Wilson, & Tyler,

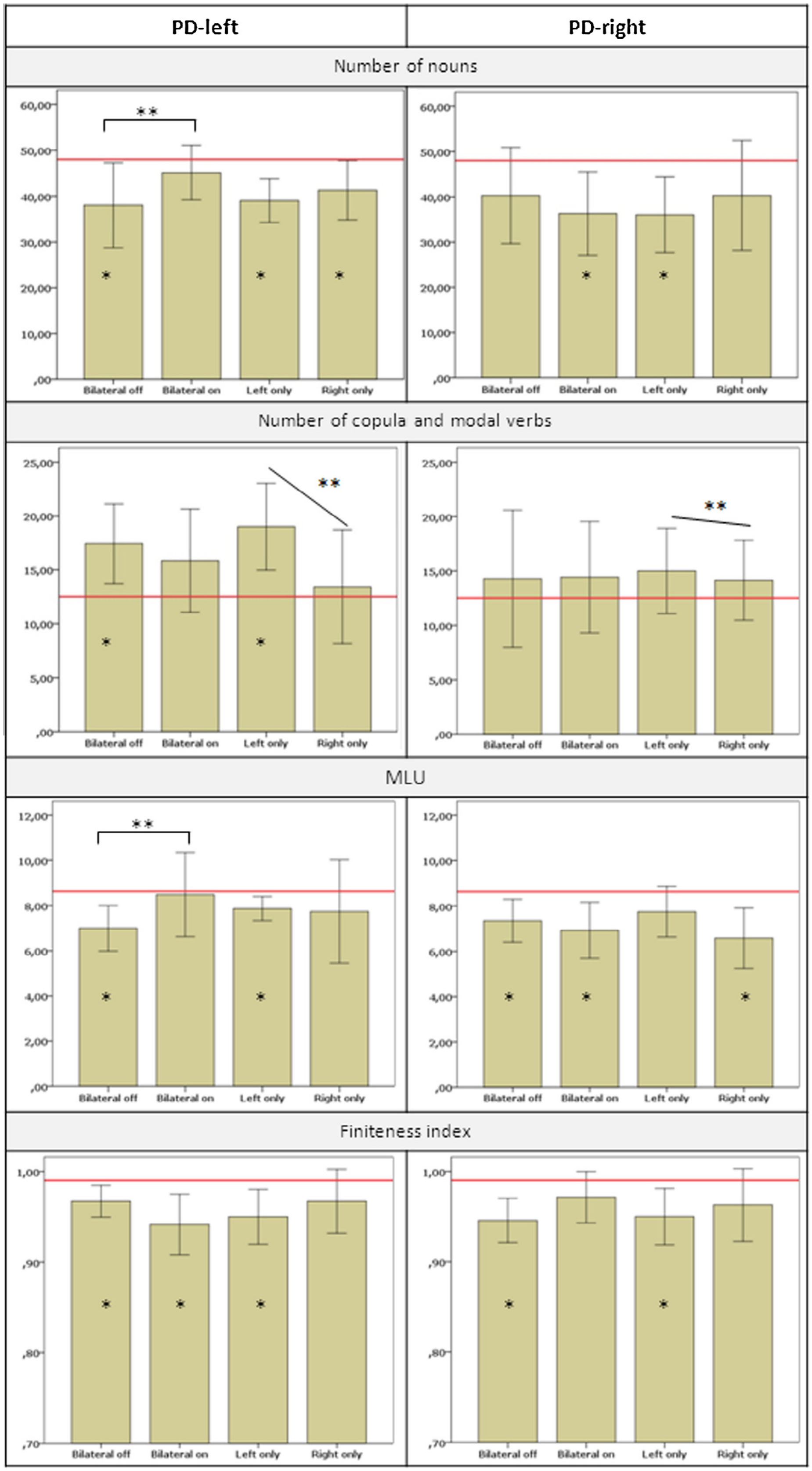

Fig. 1. Comparison of the mean score with 95% confidence intervals of each PD group separately for the parameters number of nouns, number of copular and modals verbs, mean length of utterance (MLU), and finiteness index with the norm scores. The horizontal line represents the norm mean for each parameter. *X*-axis represents the four stimulation conditions, bilateral STN stimulation off (bilateral off), bilateral STN stimulation on (bilateral on), left STN stimulation only (left only), right STN stimulation only (right only). *Significant deviation from norm mean $p < .05$; **Main stimulation effect $p < .05$.

2005; Ullman et al., 1997), but never in relationship with dopamine depletion asymmetry. Colman et al. (2009) suggested that executive dysfunctions underlie verb inflection problems. However, no compelling evidences have been found for different performances between PD-right and PD-left in executive functioning (Verreyt et al., 2011). In this study, the interference of executive functioning cannot be refuted nor confirmed, due to a lack of specific objective data on this topic for our subjects. Another possibility is that the low finiteness index in PD-right results from the deterioration of the left hemispheric syntactic language functions. Because of the extent of the disease, although dopamine depletion was still asymmetric, all subjects already showed bilateral deterioration of the nigrostriatal system. When comparing both PD groups with the normative data, there were some indications that low finiteness index originated from left hemispheric syntactic language dysfunctions. First, there was a significant decrease of the finiteness index in both PD groups, indicating that both groups encounter difficulties with verb inflection compared to healthy subjects. In addition, there were a reduced number of nouns and an increased number of copula and modal verbs in PD-left compared to the normative data, which were not present in the comparison between PD-right and the normative data. The reduced number of nouns found for the PD-left group can be explained in terms of their grammatical function (Grossman et al., 2003; Peran et al., 2003). Nouns obtain a thematic role in a grammatical structure and can be partially replaced by function words (e.g. pronouns), in contrast with verbs, which have a dominant role in sentence generation, as an assigner of thematic roles (Altmann & Troche, 2011). The increased use of copula and modal verbs can be interpreted as a compensatory mechanism to overcome morphosyntactic difficulties by postponing the mapping of open class words onto the grammatical structure (Hinaut & Dominey, 2013) or by avoiding inflection of lexical verbs. Although these findings come from an indirect comparison of both PD groups via normative data, it appears that only PD-left patients have an excessive use of copula and modal verbs and a reduced number of nouns. So perhaps these deviations are a compensatory strategy which is not present in PD-right patients. Unfortunately, because of the lack of functional imaging data in this study, all assumptions on neural reorganization are speculative. A longitudinal study on the evolution of spontaneous language and the possible compensatory mechanism introduced during the different stages of the disease using functional imaging would be valuable to investigate this more fundamentally.

It must be mentioned that these results cannot be blindly transposed to PD patients without DBS in off-medication condition. Firstly, all these patients maintained their optimal doses of medication during testing. It has been reported that medication improves linguistic functions (De Letter et al., 2012), so our results are probably better than without medication. Although an off-medication investigation would be preferable, it would induce effects of strains due to off-symptoms, which are eventually unsupportable for some patients. Furthermore, by maintaining the medication state the same in the four conditions, we tested only the effect of stimulation, not of medication. Secondly, no information is available at the moment on long-term effect of DBS stimulation on language and how it differs from non-STN DBS implanted patients. Finally, microlesioning caused by STN surgery and the presence of electrodes might influence the language outcome, but again no data on this subject is available at the moment.

4.2. Effects of STN stimulation depending on asymmetric dopamine depletion

Asymmetric dopaminergic denervation influences the effect of STN stimulation. These interactions are only detectable for PD-left in two conditions: with and without bilateral stimulation. PD-left patients have an increased MLU and number of nouns when stimulation is bilaterally on, compared to bilateral stimulation off. These interaction effects support the hypothesis of our previous study (Batens et al., 2014), that if you do not take asymmetric dopaminergic denervation into account the effects of STN stimulation on spontaneous language production are averaged out. However, it is likely that there are more variables interacting with the effect of STN stimulation, as the mean scores of the linguistic parameters of both PD-groups with the normative data clearly deviate differently from normative data, while they are not statistically detectable in direct comparisons. The same applies to the lateralized effect of STN stimulation (stimulation of the left STN only versus stimulation of the right STN only). There was one main effect detectable for the number of copula and modal verbs. Stimulation of the left STN only resulted in an excessive number of copula and modal verbs compared to stimulation of the right STN only. Although further statistically analysis did not reveal an interactions effect with asymmetric dopamine depletion, the differences between both PD-groups were clearly visible. The PD-left group had a larger number of copula and modal verbs than the PD-right group when only the left STN was stimulated. The additional statistical analysis revealed that with stimulation of the right STN only, the number of copula and modal verbs decreased noticeably for the PD-left group, while for the PD-right group this decrease was not as visible. So perhaps this main effect was rather an interaction effect that was not statistically measurable due to interference of other variables. Stimulation parameters are one of the variables that are known to influence the outcome of DBS. Stimulation parameters that are beneficial for motor function, which are of primary interest for the treating physicians, do not necessarily correspond to the optimal parameters for cognitive function or speech (Hershey et al., 2008; Tripoliti et al., 2008). Another consideration is that the localization of the electrode within the STN, with a resulting effect on different somatotopically arranged areas within the motor part of the STN, can influence the results (Tripoliti et al., 2008).

The PD-left group seems to benefit from STN stimulation for three linguistic parameters: number of nouns, MLU, and number of copula and modal verbs. Bilateral stimulation normalizes the number of nouns, and MLU. Stimulation of the right STN only normalizes the number of copula modal verbs (see discussion above). No linguistic changes were detectable when only the left STN was stimulated. These results suggest that for PD-left patients stimulation of the least dysfunctional nigrostriatal network is necessary to normalize spontaneous language production and contrast with the idea that STN stimulation has a negative effect on hemisphere specific language functions (Schulz et al., 2012).

For some linguistic parameters (percent of correct sentences and variation of lexical verbs) there seems to be no interaction between asymmetric dopamine depletion and STN stimulation. For the percentage of correct sentences, no differences are noticeable over the various stimulation conditions. It is possible that the percentage of correct sentences is not sensitive enough to detect minor changes in language production by STN stimulation. The variation of lexical verbs normalizes with STN stimulation, regardless of PD lateralization or stimulation condition. Perhaps, the increased variation of lexical verbs is due to a more general cognitive deficit present in PD patients, selection, and inhibition of competing alternatives. Because verbs have more lexical alternatives than nouns, they are probably more vulnerable to inhibitory disturbances (Peran et al., 2003). The suppression and selection of irrelevant and relevant alternatives demands balanced levels of dopamine, not only in the striatum but also in the prefrontal cortex. Imbalance within cortico-subcortical circuits can lead to a disturbance of competition and inhibition (Crescentini, Mondolo, Biasutti, & Shallice, 2008; Fallon, Williams-Gray, Barker, Owen, & Hampshire, 2013; Silveri et al., 2012), causing increased competition among lexical verbs in PD. STN stimulation probably restores the imbalance between competition and inhibition within the cortico-subcortical circuits (Crescentini et al., 2008; Fallon et al., 2013), regardless of which STN side is stimulated.

Although this study has limitations, (e.g. small sample size, tested while on anti-Parkinson medication) it encourages including asymmetric dopamine depletion as an influential variable in further linguistic PD studies. Larger study groups are necessary to unravel all variables that influence the spontaneous language production in PD. Finally, a better understanding of DBS effects and organization of language may contribute to more refined DBS settings and a better overall outcome.

5. Conclusion

Asymmetric dopamine depletion was one of the factors that interacted with the effect of STN stimulation on spontaneous language production. The spontaneous language production of PD patients differed depending on the hemisphere with the largest dopamine depletion. PD-right patients made proportionately more verb inflection errors than PD-left patients did. Only for PD-left patients, sentence production improved significantly by bilateral stimulation. Finally, even when asymmetric dopamine depletion was taken into account, the effect of STN stimulation varied depending on the linguistic parameters.

References

Altmann, L. J. P., & Troche, M. S. (2011). High-level language production in Parkinso's disease: A review. *Parkinson's Disease, 2011*, 12. http://dx.doi.org/10.4061/2011/238956.

Antonini, A., Vontobel, P., Psylla, M., Gunther, I., Maguire, P. R., Missimer, J., et al. (1995). Complementary positron emission tomographic studies of the striatal dopaminergic system in Parkinson's disease. *Archives of Neurology, 52*(12), 1183.

Bastiaanse, R. (2011). The retrieval and inflection of verbs in the spontaneous speech of fluent aphasic speakers. *Journal of Neurolinguistics, 24*(2), 163–172.

Batens, K., De Letter, M., Raedt, R., Duyck, W., Vanhoutte, S., Van Roost, D., et al. (2014). Lateralized effects of subthalamic nucleus stimulation on semantic and syntactic performance in spontaneous language production in people with Parkinson's disease. *Journal of Neurolinguistics, 32*, 31–41.

Benabid, A. L., Pollak, P., Gao, D., Hoffmann, D., Limousin, P., Gay, E., et al. (1996). Chronic electrical stimulation of the ventralis intermedius nucleus of the thalamus as a treatment of movement disorders. *Journal of Neurosurgery, 84*(2), 203–214.

Boersma, P. (2002). Praat, a system for doing phonetics by computer. *Glot International, 5*(9/10), 341–345.

Boxum, E., van der Scheer, F., & Zwaga, M. (2010). ASTA: Analyse voor Spontane Taal bij Afasie. <http://www.klinischelinguistiek.nl/fileupload/20100910_ASTA_drukversie5B15D.pdf>.

Castner, J. E., Chenery, H. J., Silburn, P. A., Coyne, T. J., Sinclair, F., Smith, E. R., et al. (2008). Effects of subthalamic deep brain stimulation on noun/verb generation and selection from competing alternatives in Parkinson's disease. *Journal of Neurology Neurosurgery and Psychiatry, 79*(6), 700–705. http://dx.doi.org/10.1136/jnnp.2007.118729.

Castner, J. E., Copland, D. A., Silburn, P. A., Coyne, T. J., Sinclair, F., & Chenery, H. J. (2007). Lexical-semantic inhibitory mechanisms in Parkinson's disease as a function of subthalamic stimulation. *Neuropsychologia, 45*(14), 3167–3177. http://dx.doi.org/10.1016/j.neuropsychologia.2007.06.019.

Chan, S.-H., Ryan, L., & Bever, T. G. (2011). Role of the striatum in language: Syntactic and conceptual sequencing. *Brain and Language*.

Colman, K. S. F., Koerts, J., van Beilen, M., Leenders, K. L., Post, W. J., & Bastiaanse, R. (2009). The impact of executive functions on verb production in patients with Parkinson's disease. *Cortex, 45*(8), 930–942. http://dx.doi.org/10.1016/j.cortex.2008.12.010.

Crescentini, C., Mondolo, F., Biasutti, E., & Shallice, T. (2008). Supervisory and routine processes in noun and verb generation in nondemented patients with Parkinson's disease. *Neuropsychologia, 46*(2), 434–447. http://dx.doi.org/10.1016/j.neuropsychologia.2007.08.021.

Cronin-Golomb, A. (2010). Parkinson's disease as a disconnection syndrome. *Neuropsychology Review, 20*(2), 191–208.

Cubo, E., Martinez Martín, P., Martin-Gonzalez, J. A., Rodríguez-Blázquez, C., & Kulisevsky, J. (2010). Motor laterality asymmetry and nonmotor symptoms in Parkinson's disease. *Movement Disorders, 25*(1), 70–75.

Dalrymple-Alford, J., MacAskill, M., Nakas, C., Livingston, L., Graham, C., Crucian, G., et al. (2010). The MoCA well-suited screen for cognitive impairment in Parkinson disease. *Neurology, 75*(19), 1717–1725.

De Letter, M., Van Borsel, J., & Santens, P. (2012). An electrophysiological investigation of the effects of levodopa on semantic comprehension of action words in Parkinson's disease. *Journal of Neurolinguistics, 25*(2), 95–103. http://dx.doi.org/10.1016/j.jneuroling.2011.09.001.

Djaldetti, R., Ziv, I., & Melamed, E. (2006). The mystery of motor asymmetry in Parkinson's disease. *The Lancet Neurology, 5*(9), 796–802.

Dominey, P. F., & Inui, T. (2009). Cortico-striatal function in sentence comprehension: Insights from neurophysiology and modeling. *Cortex, 45*(8), 1012–1018. http://dx.doi.org/10.1016/j.cortex.2009.03.007.

Fallon, S. J., Williams-Gray, C. H., Barker, R. A., Owen, A. M., & Hampshire, A. (2013). Prefrontal dopamine levels determine the balance between cognitive stability and flexibility. *Cerebral Cortex, 23*(2), 361–369. http://dx.doi.org/10.1093/cercor/bhs025.

Fasano, A., Daniele, A., & Albanese, A. (2012). Treatment of motor and non-motor features of Parkinson's disease with deep brain stimulation. *Lancet Neurology, 11*(5), 429–442.

Gelb, D. J., Oliver, E., & Gilman, S. (1999). Diagnostic criteria for Parkinson disease. *Archives of Neurology, 56*(1), 33–39. http://dx.doi.org/10.1001/archneur.56.1.33.

Grossman, M., Cooke, A., DeVita, C., Lee, C., Alsop, D., Detre, J., et al. (2003). Grammatical and resource components of sentence processing in Parkinson's disease – An fMRI study. *Neurology, 60*(5), 775–781.

Hershey, T., Wu, J., Weaver, P. M., Perantie, D. C., Karimi, M., Tabbal, S. D., et al. (2008). Unilateral vs. bilateral STN DBS effects on working memory and motor function in Parkinson disease. *Experimental Neurology, 210*(2), 402–408. http://dx.doi.org/10.1016/j.expneurol.2007.11.011.

Hinaut, X., & Dominey, P. F. (2013). Real-time parallel processing of grammatical structure in the fronto-striatal system: A recurrent network simulation study using reservoir computing. *PloS One, 8*(2), e52946.

Holtgraves, T., McNamara, P., Cappaert, K., & Durso, R. (2010). Linguistic correlates of asymmetric motor symptom severity in Parkinson's disease. *Brain and Cognition, 72*(2), 189–196. http://dx.doi.org/10.1016/j.bandc.2009.08.004.

Homer, M. A., Rubin, S. S., Horowitz, T. D., & Richter, E. (2012). Linguistic testing during ON/OFF states of electrical stimulation in the associative portion of the subthalamic nucleus. *Neuromodulation: Technology at the Neural Interface, 15*(3), 238–245.

Kempster, P. A., Gibb, W. R. G., Stern, G. M., & Lees, A. J. (1989). Asymmetry of substantia nigra neuronal loss in Parkinsons-disease and its relevance to the mechanism of levodopa related motor fluctuations. *Journal of Neurology Neurosurgery and Psychiatry, 52*(1), 72–76. http://dx.doi.org/10.1136/jnnp.52.1.72.

Kimura, D. (1961). Cerebral-dominance and the perception of verbal stimuli. *Canadian Journal of Psychology, 15*(3), 166–171. http://dx.doi.org/10.1037/h0083219.

Kleiner-Fisman, G., Herzog, J., Fisman, D. N., Tamma, F., Lyons, K. E., Pahwa, R., et al. (2006). Subthalamic nucleus deep brain stimulation: Summary and meta-analysis of outcomes. *Movement Disorders, 21*, S290–S304. http://dx.doi.org/10.1002/mds.20962.

Klostermann, F., Krugel, L., & Wahl, M. (2012). Learning about language and speech from deep brain stimulation. *Journal of Neurolinguistics, 25*(2), 63–73. http://dx.doi.org/10.1016/j.jneuroling.2011.07.005.

Kojovic, M., Bologna, M., Kassavetis, P., Murase, N., Palomar, F. J., Berardelli, A., et al. (2012). Functional reorganization of sensorimotor cortex in early Parkinson disease. *Neurology, 78*(18), 1441–1448.

Lindell, A. K. (2006). In your right mind: Right hemisphere contributions to language processing and production. *Neuropsychology Review, 16*(3), 131–148.

Longworth, C. E., Keenan, S. E., Barker, R. A., Marslen-Wilson, W. D., & Tyler, L. K. (2005). The basal ganglia and rule-governed language use: Evidence from vascular and degenerative conditions. *Brain, 128*, 584–596. http://dx.doi.org/10.1093/brain/awh387.

Martens, H., Van Nuffelen, G., Van den Putte, L., Wuyts, F., & De Bodt, M. (2010). Meten van spraakverstaanbaarheid op zinsniveau bij volwassenen met een spraakstoornis: Introductie van het Nederlandstalig spraakverstaanbaarheid-sonderzoek-zinsniveau (NSVO-Z). *Logopedie* (2), 21–26.

McIntyre, C. C., & Hahn, P. J. (2010). Network perspectives on the mechanisms of deep brain stimulation. *Neurobiology of Disease, 38*(3), 329–337.

Menenti, L., Segaert, K., & Hagoort, P. (2012). The neuronal infrastructure of speaking. *Brain and Language, 122*(2), 71–80.

Peran, P., Rascol, O., Demonet, J. F., Celsis, P., Nespoulous, J. L., Dubois, B., et al. (2003). Deficit of verb generation in nondemented patients with Parkinson's disease. *Movement Disorders, 18*(2), 150–156. http://dx.doi.org/10.1002/mds.10306.

Riederer, P., & Sian-Hülsmann, J. (2012). The significance of neuronal lateralisation in Parkinson's disease. *Journal of Neural Transmission, 119*(8), 953–962.

Robles, S. G., Gatignol, P., Capelle, L., Mitchell, M. C., & Duffau, H. (2005). The role of dominant striatum in language: A study using intraoperative electrical stimulations. *Journal of Neurology, Neurosurgery & Psychiatry, 76*(7), 940–946. http://dx.doi.org/10.1136/jnnp.2004.045948.

Schulz, G. M., Hosey, L. A., Bradberry, T. J., Stager, S. V., Lee, L. C., Pawha, R., et al. (2012). Selective left, right and bilateral stimulation of subthalamic nuclei in Parkinson's disease: Differential effects on motor, speech and language function. *Journal of Parkinsons Disease, 2*(1), 29–40. http://dx.doi.org/10.3233/jpd-2012-11049.

Silveri, M. C., Ciccarelli, N., Baldonero, E., Piano, C., Zinno, M., Soleti, F., et al. (2012). Effects of stimulation of the subthalamic nucleus on naming and reading nouns and verbs in Parkinson's disease. *Neuropsychologia, 50*(8), 1980–1989. http://dx.doi.org/10.1016/j.neuropsychologia.2012.04.023.

Spagnolo, F., Coppi, E., Chieffo, R., Straffi, L., Fichera, M., Nuara, A., et al. (2013). Interhemispheric balance in Parkinson's disease: A transcranial magnetic stimulation study. *Brain Stimulation*.

Temel, Y., Blokland, A., Steinbusch, H. W. M., & Visser-Vandewalle, V. (2005). The functional role of the subthalamic nucleus in cognitive and limbic circuits. *Progress in Neurobiology, 76*(6), 393–413.

Thobois, S., & Broussolle, E. (2012). PET functional imaging of deep brain stimulation in Parkinson's disease. *Journal of Neurolinguistics, 25*(2), 133–138. http://dx.doi.org/10.1016/j.jneuroling.2011.08.005.

Tripoliti, E., Zrinzo, L., Martinez-Torres, I., Tisch, S., Frost, E., Borrell, E., et al. (2008). Effects of contact location and voltage amplitude on speech and movement in bilateral subthalamic nucleus deep brain stimulation. *Movement Disorders, 23*(16), 2377–2383.

Ullman, M. T., Corkin, S., Coppola, M., Hickok, G., Growdon, J. H., Koroshetz, W. J., et al. (1997). A neural dissociation within language: Evidence that the mental dictionary is part of declarative memory, and that grammatical rules are processed by the procedural system. *Journal of Cognitive Neuroscience, 9*(2), 266–276. http://dx.doi.org/10.1162/jocn.1997.9.2.266.

van der Scheer, F., Zwaga, M., & Jonkers, R. (2011). Normering van de ASTA, Analyse voor Spontane Taal bij Afasie. *Stem-, Spraak- en Taalpathologie, 17*(2), 19–30.

Van Strien, J. W. (1992). Classificatie van left- en rechtshandige proefpersonen. *Nederlands Tijdschrift voor de Psychologie, 47*, 88–92.

Verreyt, N., Nys, G. M. S., Santens, P., & Vingerhoets, G. (2011). Cognitive differences between patients with left-sided and right-sided Parkinson's disease. A review. *Neuropsychology Review, 21*(4), 405–424. http://dx.doi.org/10.1007/s11065-011-9182-x.

Whelan, B. M., Murdoch, B. E., Theodoros, D. G., Hall, B., & Silburn, P. (2003). Defining a role for the subthalamic nucleus within operative theoretical models of subcortical participation in language. *Journal of Neurology Neurosurgery and Psychiatry, 74*(11), 1543–1550. http://dx.doi.org/10.1136/jnnp.74.11.1543.

Zanini, S., Melatini, A., Capus, L., Gioulis, M., Vassallo, A., & Bava, A. (2003). Language recovery following subthalamic nucleus stimulation in Parkinson's disease. *Neuroreport, 14*(3), 511–516. http://dx.doi.org/10.1097/01.wnr.0000058775.36017.86.

Zanini, S., Moschella, V., Stefani, A., Peppe, A., Pierantozzi, M., Galati, S., et al. (2009). Grammar improvement following deep brain stimulation of the subthalamic and the pedunculopontine nuclei in advanced Parkinson's disease: A pilot study. *Parkinsonism & Related Disorders, 15*(8), 606–609. http://dx.doi.org/10.1016/j.parkreldis.2008.12.003.