Parkinsonism and Related Disorders 15 (2009) 606–609

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Short communication

Grammar improvement following deep brain stimulation of the subthalamic and the pedunculopontine nuclei in advanced Parkinson's disease: A pilot study

Sergio Zanini [a,*], Vincenzo Moschella [b], Alessandro Stefani [b,c], Antonella Peppe [c], Mariangela Pierantozzi [b], Salvatore Galati [b], Alberto Costa [c], Paolo Mazzone [d], Paolo Stanzione [b,c]

[a] *Dipartimento di Patologia e Medicina Sperimentale e Clinica, University of Udine, Udine, Italy*
[b] *Dipartimento di Neuroscienze, Tor Vergata University, Rome, Italy*
[c] *IRCCS "Santa Lucia", Rome, Italy*
[d] *Neurochirurgia Funzionale e Stereotassica, Ospedale CTO, Rome, Italy*

ARTICLE INFO

Article history:
Received 2 April 2008
Received in revised form
4 December 2008
Accepted 6 December 2008

Keywords:
Deep brain stimulation
Language
Parkinson's disease
Pedunculopontine nucleus
Subthalamic nucleus

ABSTRACT

Combined deep brain stimulation of the subthalamic (STN) and pedunculopontine (PPN) nuclei has been recently proposed as surgical treatment of advanced Parkinson's disease. STN stimulation alone has been shown to provide selective improvement of the grammatical aspect of language. We studied five advanced Parkinson's disease patients who underwent combined deep brain stimulation (STN + PPN). Overall cognitive profile did not change. On the contrary, an interesting trend towards reduction of ungrammatical errors (particularly substitution of free and inflectional morphemes) was found when stimulating the STN, and also the PPN, when the STN was switched off. These findings replicate previous observations on the STN, and provide the rationale for further investigation of the role of the PPN in processing linguistic grammar.

1. Introduction

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) has become a widely accepted surgical treatment for cardinal motor features of advanced Parkinson's disease (PD) [1]. For almost a decade, bilateral STN-DBS has also been investigated in terms of neuropsychological effects. A recent meta-analysis [2] showed that the majority (65–80%) of patients show no significant changes in cognitive functions after surgery, apart from the reduction of verbal fluency.

Although speech modifications (mainly improvements) have been reported following STN-DBS, language has rarely been studied. This paper focuses on grammar (i.e. morphology and language syntax), which has been largely neglected (apart from one study [3] reporting that bilateral STN-DBS reduced errors on a grammatical comprehension task), even if PD patients were shown to present morphological and syntactical deficits in both formal grammatical tasks (e.g. grammatical comprehension) and in spontaneous language production [4]. It has been suggested that basal ganglia sustain the implicit/procedural acquisition of grammar during early childhood and contribute to its processing during adulthood [5].

In a previous study [6], we showed that bilateral STN-DBS, in addition to motor improvement, had selective positive effects on morphological and syntactical features of the language on a story generation task. Those findings were ascribed to the restoration of a functional equilibrium within basal ganglia and between basal ganglia and frontal cortex (mainly, Broca's area). To expand this study [6], we decided to determine whether pedunculopontine nucleus (PPN) stimulation or the combined DBS of the STN and the PPN in advanced PD patients would produce the same positive effects on linguistic grammar. This combined surgical targeting has been recently shown to provide encouraging preliminary clinical results at 6 month follow-up [7]. No neuropsychological reports are currently available for this new surgical procedure.

2. Materials and methods

2.1. Patients

The five selected patients (patients' age 45, 67, 49, 56, 69 years; formal education range: 5–13 years) with advanced PD (disease duration: 8–16 years) had already undergone simultaneous combined bilateral STN- and PPN-DBS. They belonged to

* Correspondence to: Present address: Associazione "La Nostra Famiglia" – IRCCS "E. Medea" – Polo Regionale del Friuli Venezia-Giulia, Via Cialdini 29, 33037 Pasian di Prato (UD), Italy. Tel.: +39 0432 693111; fax: +39 0432 693106.
E-mail address: sergio.zanini@pp.lnf.it (S. Zanini).

1353-8020/$ – see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.parkreldis.2008.12.003

the cohort of Stefani and collaborators (for inclusion criteria, combined surgical targeting, technical details, clinical and pharmaceutical follow-up, refer to methodology and clinical data reported in [7]) and were selected for this study exclusively for neurolinguistic testing. No specific inclusion and/or exclusion criteria were applied. During the present neurolinguistic investigation, patients were maintained on the optimal doses of medications (levodopa 600–800 mg, pramipexole 1.15–2.1 mg) and stimulation parameters (2–3 V, 90 μs pulse width, 185 Hz for the STN, and 1.5–2.2 V, 60 μs pulse width, 25 Hz for the PPN) according to the post-surgery clinical follow-up. Patients were studied between 6 and 12 months after surgery. This study was carried out at the University of Rome, Tor Vergata, to minimize patients' discomfort and was conducted in compliance with the Helsinki Declaration: patients were aware of the study aims and agreed to participate by signing an informed consent.

2.2. Neuropsychological and neurolinguistic assessments

The main aim of the study was to investigate the effects of STN, PPN and combined (STN–PPN) deep brain stimulation on spontaneous language production. The UPDRS-part III was administered solely to verify the stimulation ON and OFF conditions during neurolinguistic testing, since the motor benefit of combined (STN + PPN)-DBS has already been established [7]. Language production was sampled by means of a story generation task, where patients were required to generate a short story using the template of 6 cards. Language production was tape-recorded for subsequent analysis. Then, a detailed neurolinguistic analysis was performed to assess all linguistic levels. In particular, speech complexity was analysed by counting the number of utterances produced. Speech fluency was assessed by counting the number of speech blocks. Phonology was analysed by counting the number of phonemic paraphasias (substitution of one or more phonemes within a single word). Lexical semantics were assessed by counting the total number of words produced, the number of different words (types) produced (number of different lexical elements belonging to the open-class category, namely verbs, nouns and adjectives), and the number of neologisms (use of meaningless non-words such as *cospivo*), semantic and verbal paraphasias (substitution of a target word with a semantically related one, such as *table* for *chair*, or by a non-related one, such as *semaphore*), and anomias. Finally, the morphological and syntactical level (grammar) was investigated by assessing the percentage of morphological and syntactical errors (errors of omission, substitution, addition of free grammatical morphemes such as prepositions, articles, pronouns, conjunctions, auxiliary verbs; errors of omission or substitution of full verbs, or errors of substitution of inflectional morphemes such as failure in respecting correct noun–verb or adjective–noun association) out of the total number of morphological and syntactic obligatory contexts (i.e. the number of linguistic situations in which specific morphological and syntactic rules must be applied).

A baseline neuropsychological profile of the five patients was carried out assessing attention, short- and long-term memory, executive functions, verbal fluency, and visuoconstructive skills. The following conditions were applied: pre-surgery medication on and post-surgery (6 months later) stimulation and medication on.

2.3. Design and statistical analysis

A within-subject repeated measures design was used. Patients were assessed four times when on medication: STNon–PPNon *vs.* STNoff–PPNon *vs.* STNon–PPNoff *vs.* STNoff–PPNoff. Stimulation conditions were counterbalanced across patients (i.e. the first patient started in the first condition, the second patient in the second condition, and so forth). Off and on conditions were assessed 20–30 min after the electrodes were switched off/on, both for STN and PPN. The study aimed at assessing the possible effects of each subcortical nucleus activity on language production. Non-parametric statistics (χ^2 and Kendall's W tests, when suitable) were used.

3. Results

3.1. Neurological assessment

In agreement with [7], we found that combined DBS resulted in a significant motor improvement (Kendall's $W_3 = 0.94$, $p < 0.003$). In comparison to PPN stimulation, STN stimulation produced major benefits (Table 1); however, a synergistic effect of the combined stimulation was observed.

3.2. Neuropsychological assessment

Before surgery and in medication on condition, the 5 patients showed only mild signs of dysexecutive functions (too few categories and too many perseverative errors on the Wisconsin Card Sorting Test), being all the other cognitive domains spared. At post-surgical follow-up with combined stimulation on (STN + PPN) and medication on, the neuropsychological profile was unchanged (Table 1).

3.3. Neurolinguistic assessment

Only morphological and syntactic errors were affected by DBS conditions. No changes were found concerning phonology, lexical semantics and speech characteristics (complexity, number of utterances produced, fluency and number of speech blocks) when Chi-square or Kendall's W tests were run on single parameters (Table 2).

We found only a trend towards an asymmetric distribution of grammatical errors across the different stimulating conditions. In fact, when analysing these errors across the four stimulation conditions, with patients' data collapsed, an asymmetric distribution was found (Kendall test: $\chi^2_3 = 9.74$, $p < 0.03$), and this also held for 3 out of 5 patients (χ^2_3 always >12.35, $p < 0.007$), when individual performances were assessed. However, when comparing the amounts of errors between single pairs of stimulation conditions to explore the specific effect of the type of stimulation, on the

Table 1
Motor and neuropsychological profiles.

	Stimulation condition			
	STN + PPN+	STN–PPN+	STN + PPN−	STN–PPN−
Motor performance				
UPDRS-III (motor scale)	12.4	26.4	16.8	33.4

Neuropsychological profile	Pre-surgery	Post-surgery (STN + PPN+)	Cut-off
MMSE	29.7	29	27
Raven Progressive Matrices	28.7	26.6	19
WCST – number of categories	4[a]	3.6[a]	4.3
WCST – number of perseverative errors	7.7[a]	7	7.7
Phonemic verbal fluency	19.7	22.8	17
Forward digit span	5.3	4.8	3.8
Corsi block test	4.7	4.8	3.5
Story memory – immediate recall	5.3	5.7	3.1
Story memory – delayed recall	5.2	5.6	2.4
RAVLT – immediate recall	31.3	39.6	29
RAVLT – delayed recall	7	7.2	4.7
Copy of geometrical shapes	8.7	7.4	7.2

DBS+/− refers to stimulation on/off conditions; MMSE: Mini Mental State Examination; RAVLT: Rey Auditory Verbal Learning Test.
[a] Pathologic performance; test cut-off values come from Italian standardization (values are set at 2 standard deviations below mean).

Table 2
Results of neurolinguistic analysis in patients with advanced Parkinson's disease treated with combined STN and PPN stimulation.

	Stimulation condition			
	STN + PPN+	STN–PPN+	STN + PPN−	STN–PPN−
Speech complexity				
Number of utterances	8.4	7.6	9.2	10.6
Speech fluency				
Number of speech blocks and stuttered words	3.6	4.8	7	5.8
Phonology				
Number of phonemic paraphasias	0.2	1	1	2.2
Lexical semantics				
Total number of words	79	75.4	95	92.6
Total number of different words	31.2	25.2	31.4	28.8
Total number of anomias	2.4	3.2	1.6	1.8
Total number of neologisms	0	0	0	0
Total number of verbal/semantic paraphasias	0.6	0.6	1.8	1
Morphology and Syntax				
All patients – Total % of morphological and syntactic errors[a]	1.9 [7/378]	6.6 [22/335]	2.6 [11/418]	11.2 [45/403]
Patient 1	1.4	5.7	2	6.4
Patient 2[b]	1.1	5.6	4.8	16.1
Patient 3[b]	3.9	11.7	1.2	14.1
Patient 4[b]	0	0	0	9.8
Patient 5	2.9	10	5.1	9.7

[a] Refers to statistically significant different scores ($p < 0.05$) across the four different stimulation conditions when patients' data were treated as a group. Absolute numbers of errors out of the total amounts of grammatical obligatory contexts are reported in square brackets. Individual patients' data on grammatical errors are reported as percentage out of the total amount of grammatical obligatory contexts.

[b] Refers to individual patients' data in whom statistically significant differences were found across the four different stimulation conditions. No statistical difference was found between single pairs of stimulating conditions when post-hoc Bonferroni's correction for multiple comparisons was applied ($p < 0.008$) (see text).

post-hoc analysis (p value set at 0.008 following Bonferroni's correction for multiple comparisons – 6 post-hoc comparisons), no statistically significant differences were found. This result can be partially explained by the relatively small percentage of errors, on the one hand, and, mostly, by the small group of patients, on the other. Therefore, only a plausible trend towards significant differences between stimulating conditions was found. In fact, looking at the percentages of errors (Table 2), STNon–PPNon and STNon–PPNoff conditions reduced errors (1.9% and 2.6%, respectively) approximately five and four times more in comparison to the STNoff–PPNoff condition (11.2%), (this held for 3 out of 5 patients when individual patients' data were considered), and the STNoff–PPNon condition reduced errors by 50% (6.6% *vs.* 11.2%) in comparison to the STNoff–PPNoff condition (this held for 2 out of 5 patients when individual patients' data were considered). In summary, our findings suggest only a trend towards an asymmetric distribution of grammatical errors across the different stimulating conditions (i.e. reduction of grammatical errors following stimulation of the STN or the PPN) and have to be interpreted cautiously.

Finally, when considering the types of grammatical errors produced by patients across the different stimulating conditions, the addition and the omission of free grammatical morphemes were extremely rare and their percentage of occurrence was not modified by the deep brain stimulation conditions. On the contrary, the substitution of free grammatical morphemes and inflectional morphemes was more frequent and followed the same profile of occurrence with respect to the deep brain stimulation conditions, as mentioned above.

4. Discussion

In agreement with the findings of Stefani et al. [7], a significant motor improvement following the combined STN- and PPN-DBS was found in terms of UPDRS-part III scores. A larger contribution seemed to be determined more by STN than PPN stimulation, but this is largely due to the overestimation of limb motor functions, for which STN-DBS is more effective than PPN-STN, on the UPDRS-part III. In fact, PPN stimulation seems to be more effective for axial signs [7].

The overall neuropsychological profile (i.e. mild dysexecutive syndrome) did not change when comparing pre-surgical medication "on" and post-surgical medication "on"/combined stimulation "on" evaluations, in agreement with previous studies [2] on the effects of STN-DBS. Thus, this new surgical procedure appears to be cognitively safe, at least as far as we can imply from this small group of patients. Obviously, longer follow-ups and larger groups are necessary to draw any conclusions.

Neurolinguistic findings are particularly interesting: speech complexity (number of utterances) and speech fluency (speech blocks) were not affected by the different stimulating conditions, as well as phonology (phonological paraphasias) and lexical semantics (lexical access and verbal/semantic paraphasias). On the contrary, an interesting trend towards grammar improvement was found following STN- and PPN-DBS. This also applies to some patients when individual patient's data were considered. No clear-cut statistically significant effects were found; however, looking at crude percentages of errors compared with the no-stimulation condition (STN–PPN−), STN stimulation seemed to be quite effective in reducing errors (2.6% *vs.* 11.2%) close to the double stimulation condition (1.9%). PPN stimulation reduced morphological and syntactical errors almost by 50% (6.6% *vs.* 11.2%). Whether this suggests an independent effect on grammar for the PPN is difficult to say. On the contrary, the synergistic effect of combined DBS was negligible when compared with the effect obtained by STN stimulation alone (1.9% *vs.* 2.6%).

In conclusion, these findings replicate previous results [6] as far as STN stimulation is concerned, and extend them to a possible effect of PPN stimulation. No firm conclusion can be drawn on the basis of such a small cohort of patients (in particular, these preliminary findings do not modify the selection criteria for combined DBS in advanced PD). However, we might try to interpret our findings in terms of PD pathophysiology and restoration of basal ganglia functional equilibrium following DBS.

The net effect of endogenous dopaminergic depletion in PD determines a wide imbalance of basal ganglia neurophysiology, followed by severe modifications of cortical activity and excitability. DBS of the STN as well as of the globus pallidus – pars interna (GPi) and, recently, of the PPN, has been suggested to restore or compensate such physiological functions with a net effect of relevant improvement, at least as far as motor functions are concerned. However, understanding why STN- and PPN-DBS should promote language improvement (particularly grammar) is far from easy. Language improvement should not be a surprise as basal ganglia are known to be involved in grammar processing [4]. However, stating that the PD-related basal ganglia functional disequilibrium is corrected by the DBS of subcortical nuclei, with a consequent correction of the disequilibrium of basal ganglia – frontal cortex pathways, and therefore, of language processes mechanisms, does not explain the pathophysiology of these phenomena.

Two recent papers might help in understanding the underlying mechanisms. In a computational study on basal ganglia and, particularly, on STN functions in a decision-making setting, Frank [8] suggested that STN plays a critical role in selecting appropriate responses, especially when competing responses are available (this is a well known property of basal ganglia functions, at least as far as motor responses are concerned). It has been suggested that the activity of selecting the appropriate response depends on the inhibition of premature responses. Therefore, one might speculate that a parallelism exists between the selection of the appropriate response and the selection of appropriate linguistic (grammatical) elements during spontaneous language production. It is important to underline the fact that the greater percentage of grammatical errors made by patients was selection of inappropriate grammatical units (e.g. inflectional morphemes).

The paper by Watson and Montgomery [9] was based on STN neurophysiological registrations during language production and language repetition. These authors identified neuronal units that modify their activity only several hundreds of milliseconds before language production, other units are activated only during language production (motor aspects of language production), and other units are activated only during language repetition (syllable repetition, a linguistic task weakly loaded with processes of linguistic elements selection, it being a mere repetition of what has been heard). Therefore, it seems likely that some neural groups within the STN might play an important role in the selection of linguistic elements to be released by the frontal cortex.

Clearly, the two papers [8,9] provide nothing more than a possible explanation that needs to be thoroughly investigated in further experimental studies on grammar improvement in PD following DBS of the STN, the PPN, or both. The relationship between the PPN-DBS and language still needs to be investigated. Currently, experimental data are insufficient to adequately address this issue. However, all recent studies emphasise the deep anatomical [10] and neurophysiological [11] relationship between the PPN and the STN, together with other basal ganglia nuclei (e.g. substantia nigra, globus pallidus, thalamus). We believe our preliminary findings provide the rationale for further investigations.

Acknowledgments

We thank two anonymous referees for their helpful comments on a previous version of the manuscript.

References

[1] Krack P, Batir A, Van Blercom N, Chabardes S, Fraix V, Ardouin C, et al. Five-years follow-up of bilateral stimulation of the subthalamic nucleus in advanced Parkinson's disease. N Engl J Med 2003;349:1925–34.
[2] Parsons TD, Rogers SA, Braaten AJ, Woods SP, Tröster AI. Cognitive sequelae of subthalamic nucleus deep brain stimulation in Parkinson's disease: a meta-analysis. Lancet Neurol 2006;5:578–88.
[3] Moretti R, Torre P, Antonello RM, Capus L, Zambito Marsala S, Cattaruzza T, et al. Neuropsychological changes after subthalamic nucleus stimulation: a 12 month follow-up in nine patients with Parkinson's disease. Parkinsonism Relat Disord 2003;10:73–9.
[4] Murray LL. Spoken language production in Huntington's and Parkinson's disease. J Speech Lang Hear Res 2000;43:1350–66.
[5] Ullman MT. Contribution of memory circuits to language: the procedural/declarative model. Cognition 2004;92:231–70.
[6] Zanini S, Melatini A, Capus L, Gioulis M, Vassallo A, Bava A. Language recovery following subthalamic nucleus stimulation in Parkinson's disease. NeuroReport 2003;14(3):511–6.
[7] Stefani A, Lozano AM, Peppe A, Stanzione P, Galati S, Tropepi D, et al. Bilateral deep brain stimulation of the pedunculopontine and subthalamic nuclei in severe Parkinson's disease. Brain 2007;130:1596–607.
[8] Frank MJ. Hold your horses: a dynamic computational role for the subthalamic nucleus in decision making. Neural Netw 2006;19:1120–36.
[9] Watson P, Montgomery Jr EB. The relationship of neuronal activity within sensori-motor region of the subthalamic nucleus to speech. Brain Lang 2006;97:233–40.
[10] Aravamuthan BR, Muthusamy KA, Stein JF, Aziz TZ, Johansen-Berg H. Topography of cortical and subcortical connections of the human pedunculopontine and subthalamic nuclei. NeuroImage 2007;37:694–705.
[11] Galati S, Scarnati E, Mazzone P, Stanzione P, Stefani A. Deep brain stimulation promotes excitation and inhibition in subthalamic nucleus in Parkinson's disease. NeuroReport 2008;19(6):661–6.