Stimulation of the pedunculopontine nucleus area in Parkinson's disease: effects on speech and intelligibility

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Improvement of gait disorders following pedunculopontine nucleus area stimulation in patients with Parkinson’s disease has previously been reported and led us to propose this surgical treatment to patients who progressively developed severe gait disorders and freezing despite optimal dopaminergic drug treatment and subthalamic nucleus stimulation. The outcome of our prospective study on the first six patients was somewhat mitigated, as freezing of gait and falls related to freezing were improved by low frequency electrical stimulation of the pedunculopontine nucleus area in some, but not all, patients. Here, we report the speech data prospectively collected in these patients with Parkinson’s disease. Indeed, because subthalamic nucleus surgery may lead to speech impairment and a worsening of dysarthria in some patients with Parkinson’s disease, we felt it was important to precisely examine any possible modulations of speech for a novel target for deep brain stimulation. Our results suggested a trend towards speech degradation related to the pedunculopontine nucleus area surgery (off stimulation) for aero-phonatory control (maximum phonation time), phono-articulatory coordination (oral diadochokinesis) and speech intelligibility. Possibly, the observed speech degradation may also be linked to the clinical characteristics of the group of patients. The influence of pedunculopontine nucleus area stimulation per se was more complex, depending on the nature of the task: it had a deleterious effect on maximum phonation time and oral diadochokinesis, and mixed effects on speech intelligibility. Whereas levodopa intake and subthalamic nucleus stimulation alone had no and positive effects on speech dimensions, respectively, a negative interaction between the two treatments was observed both before and after pedunculopontine nucleus area surgery. This combination effect did not seem to be modulated by pedunculopontine nucleus area stimulation. Although limited in our group of patients, speech impairment following pedunculopontine nucleus area stimulation is a possible outcome that should be considered before undertaking such surgery. Deleterious effects could be dependent on electrode insertion in this brainstem structure, more than on current spread to nearby structures involved in speech control. The effect of deep brain stimulation on speech in patients with Parkinson’s disease remains a challenging and exploratory research area.
Introduction

Initial reports of dramatic improvement of gait disorders following pedunculopontine nucleus area (PPNa) stimulation (Mazzone et al., 2005; Plaha and Gill, 2005; Stefani et al., 2007) supported the idea that the PPNa is involved in the control of locomotion in humans as had been shown in animal models (Garcia-Rill et al., 1987; Munro-Davies et al., 1999; Pahapill and Lozano, 2000; Nandi et al., 2002; Takakusaki et al., 2003; Jenkinson et al., 2009). The outcome of our prospective study of PPNa stimulation in six patients with Parkinson’s disease and severe gait disorders and freezing despite optimal dopaminergic drug treatment and subthalamic nucleus (STN) stimulation (Ferraye et al., 2010) led to more mitigated results. Freezing of gait and falls related to freezing were improved by low frequency electrical stimulation of the PPNa in some, but not all, patients. Other well-controlled studies reached similar results, showing a reduction of falls in some patients with Parkinson’s disease and gait disorders under unilateral PPNa stimulation (Moro et al., 2010). In these studies, no serious adverse events were observed. However, side-effects such as oscillopsia, paraesthesia and/or limb myoclonus, although reversible, could hinder voltage increase (Ferraye et al., 2009, 2010). Other authors did not report such side effects, likely due to differences in final stereotactic coordinates, leading to a different degree of modulation of structures close to the PPNa (Yelnik, 2007; Zrinzo et al., 2007, 2008; Mazzone et al., 2011, 2013).

Deep brain stimulation (DBS) of other targets, such as the STN, has proved very efficient in alleviating the cardinal motor symptoms of Parkinson’s disease, but it can lead to stimulation-induced speech impairment in some patients, sometimes exacerbating a pre-existent dysarthria. Current diffusion has been proposed as a possible explanation for such speech impairment side-effects: e.g. current diffusion towards both the spinal (Pinto et al., 2005) and the cerebell-thalamo-cortical (Astrom et al., 2010) tracts. Considering that the PPNa, which belongs to the mesencephalic reticular formation, lies in somewhat close proximity of passing fibres and relay nuclei of the cranial nerves (such as nucleus ambiguus of the vagus nerve), as well as the superior cerebellar peduncles, one can hypothesize that current spread towards these structures could affect speech in patients with PPNa stimulation. For example, a PET experiment involving healthy volunteers has shown the involvement of the periaqueductal grey matter (PAG) in human vocalization, as the PAG is connected with cortical and subcortical structures involved in voiced speech self-monitoring (Schulz et al., 2005). These authors described functional connectivity between the PAG and both the premotor/motor and temporal/parietal cortices. They suggested that bilateral activations in the posterior superior temporal gyri and supramarginal gyri may support self-monitoring and feedback regulation of human phonation. A recent functional MRI study confirmed such links between the PAG and structures involved in speech production both in healthy subjects and patients with Parkinson’s disease (Rektorova et al., 2012). In addition, strengthening of connectivity between the PAG and the basal ganglia, posterior superior temporal gyrus, supramarginal and fusiform gyri, and inferior parietal lobule was observed in medicated patients with Parkinson’s disease as compared to controls, highlighting functional reorganization in brain areas involved in feedback control of voiced speech (Rektorova et al., 2012).

Little is known regarding the influence of PPNa stimulation on speech production. An improvement in voluntary opening and closing of the mouth under stimulation of the pedunculopontine tegmental nucleus was reported (Mazzone et al., 2012), whereas in a study of grammar processing, no effect of PPNa stimulation on speech parameters (number of utterances, phonological construction) was found (Zanini et al., 2009). Although these two reports provided some information regarding a possible role of the stimulated target in motor or higher-order processes related to speech, nearly all remains to be known regarding the influence of PPNa stimulation on speech per se. In the present study, we analysed speech data prospectively collected in seven patients with Parkinson’s disease with STN stimulation who underwent PPNa surgery because of severe freezing of gait. Indeed, STN DBS may lead to speech impairment and a worsening of dysarthria in some patients (Pinto et al., 2004, 2005; Tripoliti et al., 2008, 2011, 2014). Therefore, as the PPNa is being investigated as a novel DBS target in movement disorders, it seemed important to precisely monitor speech outcome following this new surgery to understand both the eligibility of patients for this surgical procedure and any potential adverse effects. Clinical and gait data of six of these patients have been reported previously (Piallat et al., 2009; Ferraye et al., 2010).

Materials and methods

Patients and study design

Seven patients with Parkinson’s disease participated in the study. All patients presented with severe freezing of gait under chronic l-DOPA and bilateral STN stimulation treatment. They were included because gait disorders and freezing were their main complaints. They underwent bilateral electrode implantation within the PPNa according to the surgical procedure previously published (Ferraye et al., 2010). Exclusion criteria were surgical contraindications and cognitive impairment (score < 130 on the Mattis dementia rating scale). Patients’ characteristics are summarized in Table 1. Mean ages (± standard deviation (SD)) at Parkinson’s disease diagnosis, STN surgery and PPNa surgery were 41.7 ± 9.7 years, 56.8 ± 6.7 years and 63.0 ± 5.8 years, respectively. The mean (±SD) disease duration was 21.7 ± 6.5 years. Before PPNa surgery, Unified Parkinson’s Disease Rating Scale (UPDRS, Fahn et al., 1987) motor score improvement induced by l-DOPA when the STN stimulation was turned off,
was 42 ± 18% in average, ranging from 16 to 63% (Ferraye et al., 2010). The study was conducted at the Grenoble University Hospital in accordance with the Declaration of Helsinki (WHO, 2008) and was approved by the local ethics committee. Before participating, all patients provided written informed consent. Chronic PPNa stimulation electrical parameters settings were: 1.2–3.8 V for voltage, 60–90 μs for pulse width and 15–30 Hz for frequency; these stimulation parameters induced improvement in freezing of gait, albeit sometimes moderate, in six of the patients (Ferraye et al., 2010).

The clinical study lasted for 1 year. Speech recordings were carried out along with the clinical and gait assessments, that is: (i) before surgery (at baseline, assessment A0); (ii) during a double-blind trial carried out between four (assessment A1) and 6 months after PPNa surgery (assessment A3); and (iii) 12 months after PPNa surgery (assessment A12) (Ferraye et al., 2010). For the double-blind trial, recordings of assessments A1 and A3 were performed after 1 month of PPNa stimulation either off or on: the first PPNa condition (either off or on) was set at the beginning of Month 4, and the speech recording A1 was performed at the end of the month; PPNa stimulation was then turned off during Month 5, and the wash-out speech recording (A2) was realized at the end of the month (PPNa stimulation off); finally, the second PPNa stimulation condition (either off or on) was set at the beginning of Month 6, and the A3 speech recording was done at the end of the month (Fig. 1). The A12 assessment allowed speech recordings under all therapeutic combination possibilities. In total, 18 speech recordings were obtained under eight possible therapeutic conditions over the course of the study.

### Speech tasks and temporal aero-phonatory parameters

Speech was recorded within the Grenoble Neurology ward, in a quiet non-soundproof room. Patients’ speech was recorded using a dedicated digital and portable device (Microtrack 24/92, M-Audio®, Avid®), connected with a head-mounted microphone (AKG®, model K440). First, the patients were instructed to take a deep breath, and then to pronounce and sustain the vowel /a/ comfortably for as long and as steadily as they could; they were instructed to complete the task three times and not to strain their voice. Second, an oral diadochokinesis task was performed: the patients had to repeat the pseudoword ‘pataka’ at a fast rate for 30 s. Finally, the patients were asked to pronounce 10 words and 10 sentences provided by the French adaptation (Auzou et al., 1998) of the intelligibility section of the Frenchay Dysarthria Assessment, version 1 (Enderby, 1980).

Each task corresponded to a specific speech file: four files were thus acquired for each patient and for each of the therapeutic conditions (vowel /a/, diadochokinesis, words and sentences). Before analysis, these audio files were blindly preprocessed (labelling, segmentation) under a dedicated software environment (Phonédit-Signaix; http://www.lpl-aix.fr/~lpldev/phonedit/). For the vowel /a/ task, an acoustic analysis was automatically performed based on the calculation of the maximum phonation time (MPT, in ms) within the signal window comprised between two cursors delineating the beginning and the end of the production. The diadochokinesis task allowed for the calculation of breath group durations (in ms), i.e. each period during which the pseudoword was repeated during a single expiration. The words and sentences were used in the assessment of speech intelligibility.

### Speech intelligibility

The first step of the assessment procedure was a manual labelling of stimuli (the words and the sentences produced by the patients) within the recorded audio files to allow for the automatic extraction of the files, one file corresponding to one stimulus. Rather than using a single listener, the words and sentences produced by the patients were evaluated by a group of listeners composing an auditory jury. The auditory jury fulfilled the following criteria: (i) French-native speakers, without any history of auditory and/or visual deficit; (ii) unfamiliar with speech modifications of any neurodegenerative disease; (iii) naïve with regard to the aim of the experiment. Thirty-three listeners (29 females, four males; mean age ± SD = 25.5 ± 12.1 years; mean educational status ± SD = 13.1 ± 2.3 years after the fifth grade of French elementary school) were included and participated in the intelligibility assessment. The members of the jury were blind as to the conditions under which the recording had been made.

Each stimulus (a word or a sentence) was listened to by three different members of the auditory jury. A computerized and random presentation of auditory stimuli was used (http://www.lpl-aix.fr/~lpldev/perceval/). The stimuli were delivered via headphones. The listeners, comfortably seated in front of a computer screen, were instructed to write what they had understood. When the stimulus was a
single word, the participants were asked to write down the actual word. The sentences were all constructed upon the same pattern, i.e. [noun + verb], the noun being the same across all sentences (in French ‘L’enfant…’, meaning ‘The child…’ in English); only the action verb differed across sentences. Thus, in this sentence context presentation, only the verb was to be transcribed by the listeners. When the listeners did not understand the word or the sentence, they were asked to proceed to the next stimulus by pressing the ‘return’ button of the keyboard. No second listening was possible.

Two sessions were performed under a test-retest protocol. The retest occurred 1 week after the first session. For the retest, the set of stimuli used for each listener was the same as for the first run, but the stimuli were presented in a different random order. The purpose of this retest session was to increase the reliability of the listeners’ responses. We expected a learning effect, that is, a global increase of correct responses for the retest session as compared to the test whatever the treatment condition, as listeners should become more familiar with the task. More importantly, we expected that the effects induced by the treatment conditions would remain the same across the two sessions.

**Statistical analyses**

All analyses were conducted using linear or logit mixed models to account for the grouping structure (patients, listeners, stimuli) of the data and for their nature (unbalanced, partially crossed/nested). Package lme4 (Bates et al., 2013) was used in R software (R Development Core Team, 2013). All non-significant interactions were removed using a backward stepwise procedure and using likelihood ratio tests to compare models. When possible, P-values were computed using a parametric bootstrap procedure and noted as $P_{boot}$; the significance of statistical threshold was set at 0.05.

The dependent variables for the linear mixed models were the MPT duration for the sustained vowel /a/ and the log-transformed breath group durations for the diadochokinesis task. The log-transformation of the breath group durations enhanced the normality of the distribution of the residuals of the model. Random slopes were added for the within-patient variables ($\alpha$-DOPA, PPNa and STN stimulations) to account for the variability across the seven patients. All these random effects were allowed to be correlated. For the intelligibility analysis, a mixed logit model was fitted with the binary response correct/incorrect as the dependent variable. A supplementary random slope was added for the within-listener variable (test session) to account for the variability across the 30 listeners. A random intercept was also added to account for the variability across the stimuli. This model estimated the correct answer probability, i.e. the intelligibility probability. The phonetic comparison between the reference orthographic transcription of the word presented to the patients and the free orthographic transcription provided by the listeners allowed for the generation of a variable reporting incorrect/correct transcriptions (or answers), mapped to the unintelligibility/intelligibility of the stimulus. When no response was given, we considered that the stimulus could not be transcribed. Therefore, it was considered as unintelligible and the no-response was coded as incorrect.

**Main effect of the pedunculopontine nucleus area stimulation: outcome of the double-blind trial**

The PPNa main effect was determined by adjusting models that used postoperative data subsets (A1, A2 and A3), OFF/ON $\alpha$-DOPA, on STN stimulation, off/on PPNa stimulation. $\alpha$-DOPA and PPNa stimulation were the two predictors, with two levels each (off, on). Interaction between predictors was also considered.

For MPT, duration of the vowel /a/ was the dependent variable and 114 measures were available. There was no significant interaction between the two predictors, $\alpha$-DOPA and PPNa stimulation treatments (likelihood ratio test, $\chi^2 =1.88, df = 1, P = 0.17$): the model without this interaction was considered for analysis. For the diadochokinesis task, the number of measures depended on the number of breath groups produced by the patients: 324 observations were available for the analysis. There was no significant interaction between the two predictors, $\alpha$-DOPA and PPNa stimulation treatments (likelihood ratio test, $\chi^2 = 0.52, df = 1, P = 0.47$). The model without this interaction was considered for analysis. For the intelligibility assessment, the actual number of available responses was 5054. The predictors were $\alpha$-DOPA (OFF, ON), PPNa stimulation (off, on), context presentation (single-word, sentence) and session (test, retest). All interactions removed with the backward elimination procedure were clearly non-significant (likelihood ratio test, $\chi^2 < 2, P > 0.15$).

**Pre-surgery versus 1 year follow-up comparisons**

These statistical analyses were conducted by adjusting models that used the preoperative (A0) and the 1-year follow-up (A12) postoperative data subsets, and the same dependent variables as for the double-blind trial. The three predictors were $\alpha$-DOPA (two levels: OFF, ON), STN stimulation (two levels: off, on) and PPNa state (three levels: preoperative, off, on). Interaction between predictors was also considered.

For the MPT analysis, duration of the vowel /a/ was the dependent variable and 225 observations were used. The interaction between the three predictors ($\alpha$-DOPA, STN and PPNa) was non-significant (likelihood ratio test, $\chi^2 = 0.31, df = 2, P = 0.85$), as were the 2-way interactions between STN and PPNa (likelihood ratio test, $\chi^2 = 0.22, df = 2, P = 0.89$) and between $\alpha$-DOPA and PPNa (likelihood ratio test, $\chi^2 = 1.8, df = 2, P = 0.4$). The model without these interactions was considered for analysis. For the diadochokinesis task analysis, graphical inspection showed erratic and weak reliable realizations for breath group ranks superior to eight (~10% of the 522 observations). These data were dropped from the analysis and a total of 470 observations were used. The non-significant interactions (all likelihood ratio test $P$ values $> 0.26$), including the three-way ($\alpha$-DOPA, STN and PPNa) and the two-way (STN and PPNa) interactions between predictors, were removed from the final model. For the intelligibility assessment, 9776 productions were available for analysis. The predictors were $\alpha$-DOPA (OFF, ON), STN stimulation (off, on), PPNa state (preoperative, off, on), context presentation (single-word, sentence) and session (test, retest). All non-significant interactions were removed using a backward elimination procedure (all likelihood ratio test $P$ values $> 0.15$). The model without these interactions was considered for analysis.

**Results**

**Double-blind trial: main effect of pedunculopontine nucleus area stimulation**

The subset of data for analyses of the PPNa stimulation main effect was provided by the postoperative assessments (A1, A2, A3).
STN stimulation remained on during these assessments. The stimulation parameter settings are displayed in Table 2. Bipolar stimulation was used when the thresholds for side effects were too limiting under monopolar stimulation.

Maximum phonation time
PPNa stimulation reduced the MPT by 1200 ms, without reaching statistical significance ($\beta = -1219$, $t = -1.65$, $P_{boot} = 0.09$). L-DOPA administration had a significant deleterious effect ($\beta = -3.164$, $t = -2.28$, $P_{boot} = 0.026$), reducing the MPT by 3100 ms (Fig. 2).

Diadochokinesis breath group duration
PPNa stimulation ($\beta = -0.24$, $t = -2.0$, $P_{boot} = 0.04$) and L-DOPA ($\beta = -0.337$, $t = -3.3$, $P_{boot} = 0.001$) both significantly decreased breath group durations, up to 21% and 30%, respectively (Fig. 2). We further examined the data by including the breath group rank in the model, i.e. considering the number and the rank of the breath groups needed to complete the 30-s repetition of the pseudoword ‘pataka’. The aim was to look for any relationship between the breath group rank and treatment effects (i.e. L-DOPA and PPNa stimulation). This additional analysis only highlighted a fatigue effect, constant across all treatment conditions, showing that the higher the rank, the shorter the duration.

Speech intelligibility
As expected, the effect of the session factor was significant ($\beta = -0.49$, $z = -6.1$, $P < 0.0001$), indicating a better score of correct responses for the retest session (Fig. 2). There were no significant interactions between this factor and any other predictor, confirming the reliability of the listeners’ responses. As expected also, the probability of correct responses was globally lower for the single-word than for the sentence context ($\beta = -1.26$, $z = -32.89$, $P = 0.0037$).

PPNa stimulation alone marginally increased the probability of correct responses (sentence context: $\beta = 0.6$, $z = 1.86$, $P = 0.06$; single-word context: $\beta = 0.567$; the difference between the two contexts being non-significant: $\beta = -0.033$, $z = -0.12$, $P = 0.9$). L-DOPA alone did not induce any significant decrease of the probability of correct responses (decrease of about two percentage points in sentence context: $\beta = -0.257$, $z = -0.78$, $P = 0.43$; and ~15 percentage points in single-word context: $\beta = -0.577$; the difference between the two contexts was non-significant: $\beta = 0.327$, $z = 1.46$, $P = 0.14$). The three-way interaction between L-DOPA, PPNa stimulation and context presentation was significant ($\beta = -1.254$, $z = -3.1$, $P = 0.0016$). Examination of this interaction revealed that there was no significant interaction between L-DOPA and PPNa stimulation in the sentence context ($\beta = -0.068$, $z = -0.23$, $P = 0.82$), while the combined treatment had a deleterious effect in the single-word context.

In summary, L-DOPA had a significant deleterious effect on both MPT and diadochokinesis. PPNa stimulation also had somewhat of a deleterious effect, but significance was reached only for diadochokinesis. For intelligibility, there was no evidence for any L-DOPA and/or PPNa stimulation deleterious effects, except for the combined ON l-DOPA/off PPNa stimulation condition in the single-word context.

Pre-surgery versus 1-year follow-up comparisons
For these analyses, preoperative (four conditions, combining OFF/ON L-DOPA and off/on STN stimulation) and A12 postoperative (eight conditions, combining OFF/ON L-DOPA, off/on STN stimulation and off/on PPNa stimulation) data subsets were considered. Stimulation parameters at 1-year follow-up are shown in Table 3. The stimulation parameters were stable for at least 1 month before the A12 assessment. All patients had cyclic stimulation with night arrest, except for Patient 6 (who forgot to switch his stimulation off at night).

Regarding the clinical and perceptual assessment of speech across the study, individual scores of the UPDRS item 18 are reported in Table 4. The patients in the present study presented with variable effects of L-DOPA on speech before PPNa surgery. Based on the global clinical evaluation scoring (item 18 of the UPDRS), four patients presented with some improvement under L-DOPA whereas two did not (one patient was not taking any dopaminergic treatment). Individual data of the speech parameters measured are also provided (Supplementary material). No global impression emerges, as any speech change is highly dependent on the task and treatment combination state.

Maximum phonation time
The model revealed that preoperative MPT did not differ significantly from the postoperative PPNa off stimulation ($\beta = -1.013$, $t = -0.99$, $P_{boot} = 0.29$), neither from the postoperative PPNa on stimulation ($\beta = -2.027$, $t = -1.47$, $P_{boot} = 0.096$) (Fig. 3). There was no significant effect of L-DOPA administration alone ($\beta = -4.22$, $t = -0.4$, $P_{boot} = 0.7$). There was a significant beneficial effect of STN stimulation alone, increasing MPT by up to 2600 ms

<table>
<thead>
<tr>
<th>Patient</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contacts</td>
<td>0+1−2−</td>
<td>4+5−</td>
<td>0−1+</td>
<td>4−5+</td>
<td>0−</td>
<td>4−</td>
<td>0−1+</td>
</tr>
<tr>
<td>Voltage (V)</td>
<td>1.8</td>
<td>1.4</td>
<td>3.2</td>
<td>3</td>
<td>2</td>
<td>1.6</td>
<td>3</td>
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<tr>
<td>Pulse width (μs)</td>
<td>60</td>
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This effect was lost under L-DOPA, as indicated by the marginal interaction between L-DOPA and STN stimulation ($\beta = 2639, t = 2.2, P_{\text{boot}} = 0.02$). This effect was lost under L-DOPA, as indicated by the marginal interaction between L-DOPA and STN stimulation ($\beta = 2639, t = 2.2, P_{\text{boot}} = 0.02$).

Diadochokinesis breath group duration

Preoperative breath group durations did not differ significantly from both the postoperative PPNa off ($\beta = -1719, t = -1.87, P_{\text{boot}} = 0.06$), and on stimulation states ($\beta = -0.23, t = -1.99, P_{\text{boot}} = 0.09$) (Fig. 3). There was no significant effect of L-DOPA alone ($\beta = 0.06, t = 0.66, P_{\text{boot}} = 0.5$). There was a significant beneficial effect of STN stimulation alone ($\beta = 0.21, t = 2.58, P_{\text{boot}} = 0.01$), increasing breath group durations by 22%. This beneficial effect disappeared under L-DOPA, as revealed by the significant interaction between L-DOPA and STN stimulation ($\beta = -0.36, t = -3.26, P_{\text{boot}} = 0.001$): breath group durations...
and postoperative states under the two contexts. The preoperative and PPNa state revealed different changes between preoperative and postoperative states whether OFF l-DOPA (on PPNa: $\beta = -0.26$, $z = -1.1$, $P = 0.28$; on PPNa: $\beta = -0.38$, $z = -1.5$, $P = 0.13$) or ON l-DOPA (off PPNa: $\beta = -0.47$, $z = -1.86$, $P = 0.06$; on PPNa: $\beta = -0.15$, $z = -0.6$, $P = 0.55$). This was true under both STN stimulation conditions, the interaction between STN stimulation and PPNa state being non-significant (likelihood ratio test, $\chi^2 = 0.4$, df = 2, $P = 0.8$).

No significant main effect of l-DOPA alone, i.e. off STN stimulation, was found. Conversely, there was a significant beneficial effect of STN stimulation alone, i.e. OFF l-DOPA ($\beta = 0.736$, $z = 3.8$, $P = 0.0001$). Examination of the significant interaction between l-DOPA and STN stimulation ($\beta = -0.81$, $z = -6.97$, $P < 0.0001$) revealed a deleterious effect of these combined treatments on speech intelligibility.

In summary, for the MPT and diadochokinesis tasks, analyses did not reveal any significant change between preoperative and postoperative PPNa stimulation states. For speech intelligibility, in the sentence context only, the postoperative off and on PPNa states were significantly degraded as compared with the preoperative state. For all speech tasks, there was a positive effect of STN stimulation that was inhibited by the administration of l-DOPA.

### Discussion

We examined the effects of PPNa stimulation, l-DOPA administration, and STN stimulation alone and combined on speech production, comparing PPNa preoperative and postoperative
treatment states. The results of the postoperative double-blind trial, conducted under STN stimulation, showed a significant deleterious effect of L-DOPA on temporal aero-phonatory speech variables (MPT and diadochokinesis). PPNa stimulation also had a deleterious effect on these speech measures, but the effect was only significant for diadochokinesis. Regarding intelligibility, there was no evidence for any L-DOPA and/or PPNa stimulation deleterious effects (except for the combined ON L-DOPA/on PPNa stimulation condition in the single-word context). The analysis of the preoperative and 1-year postoperative assessments enabled comparisons of all treatment conditions. Overall, for the MPT and diadochokinesis tasks, we did not find any significant change between the preoperative and postoperative PPNa stimulation states. Similarly, comparison of PPNa stimulation off versus on conditions did not reveal any large influence on speech. However, speech intelligibility in the sentence context was significantly impaired under the postoperative off and on PPNa states, as compared to the preoperative state. For all speech tasks, there was a positive effect of STN stimulation that was inhibited by L-DOPA: whether before or after PPNa surgery, there was a significant

![Graphs showing the effects of PPNa state, L-DOPA, and STN stimulation on speech measures.](http://brain.oxfordjournals.org/)

**Figure 3** Pre- versus post-PPNa surgery: effects of the PPNa state (pre-op, off, on), L-DOPA (OFF, ON) and STN stimulation (off, on). **Top left:** MPT (in ms); **top right:** breath group duration (in ms), measured during the diadochokinesis (DDK) task; **bottom:** speech intelligibility, as measured by the correct answer probability (results of the test assessments). The displayed mean values are those predicted by the statistical models (from the fixed effects only).
deleterious interaction between L-DOPA and STN stimulation so that the beneficial effect of STN stimulation observed when the patients were OFF medication was blocked by administration of L-DOPA. Yet administration of L-DOPA had little effect when the patients were off STN stimulation. The significance of these results will be discussed in reference to the brainstem structures known to be involved in vocal behaviour (observed in animal studies) and speech motor control (demonstrated in humans), before considering antagonist interactions mechanisms between treatments as an explanation for speech modulations.

We will first examine the apparent contradiction in the outcome of the two analyses regarding the influence of PPNa stimulation on speech. Indeed, while comparison of the PPNa stimulation off and on data collected during the double-blind A1 to A3 assessments showed a deleterious effect on breath group duration and, to a lesser extent, on MPT, no such degradation was found when comparing the PPNa off and on conditions 1 year after surgery. Nevertheless, although the effects did not reach statistical significance but for speech intelligibility, all speech variables were degraded 1 year after surgery, as compared to the preoperative state: indeed, the relative magnitude of the changes, i.e. the reduction of performance between the pre- and postoperative states as expressed in per cent of baseline level, were noteworthy (~10 to 20% of the initial MPT or diadochokinesis durations). The lack of statistical significance of these deleterious effects on speech aero-phonatory measures was likely due to the high variability between patients as well as the small number of patients. Thus, although the final outcome at 1 year resembles a lesion effect, rather than a stimulation effect, this is likely not the whole story. Indeed, our own as well as other published studies examining the influence of PPNa stimulation on gait have reported long-lasting effects (up to 2 weeks) after switching off the generator (Ferraye et al., 2010; Moro et al., 2010; Ostrem et al., 2010). In the present study, the wash-out between the two stimulation conditions at 1-year follow-up was 24 h, a retrospectively insufficient duration to wash-out the after-effect of 6 months of chronic stimulation. In contrast, during the double-blind study, patients were evaluated at least 1 month after the stimulator arrest (2 months for the A2 assessment for the patients whose first randomized condition, A1, was off). Thus, only the data from the double-blind study actually reflect a true PPNa stimulation effect, and our data clearly demonstrate a deleterious effect of PPNa stimulation on the aero-phonatory variables. Yet, our results also strongly suggest that PPNa surgery in itself may have somewhat deleterious effects on speech production. This may not come as a total surprise, provided the role of ponto-mesencephalic structures in voice control and speech production.

**Brainstem structures involved in vocalization**

Mainly, two cerebral pathways of sound generation in humans can be pointed out (Ackermann, 2008): (i) one subserving non-verbal vocalizations and involving projections from the anterior cingulate gyrus and adjacent mesiofrontal areas via midbrain structures, such as the PAG and adjacent tegmentum, to central pattern generators and cranial nerve motor nuclei located within the lower brainstem; (ii) and a second one allowing for proper human speech production (i.e. verbal utterances), associated with a more extensive brain network (cf. Price, 2012, for a review). Thus, apart from the relay nuclei involved in the pyramidal and extra-pyramidal pathways, including the ponto-cerebellar pathways, other midbrain regions are known to be involved in vocal production.

As described in animal studies, the brainstem tegmentum, and particularly the PAG, is an important convergence zone for orofacial motor neurons (Fardin et al., 1984; Zhang et al., 1995; Davis et al., 1996; Jurgens, 2002). The function of the PAG is not fully understood, as it is known to be involved in several quite distinct functions, e.g. analgesia or defensive behaviour (Behbehani, 1995). Segregation of these functions within the PAG has been suggested upon the recent understanding of its anatomical subdivisions (Linnman et al., 2012). Regarding vocal behaviour, it has been proposed that

>the PAG serves as a link between sensory and motivation-controlling structures on the one hand, and the periambigual reticular formation coordinating the activity of the different pharyngeal muscles on the other’ (Jurgens, 1994). Indeed, limbic structures such as the anterior cingulate, the thalamus and the hypothalamus project fibres into the PAG. Animal studies also showed that enhancement of vocal production following injections of GABAergic and glutamatergic agonists was not due to the activation of passing fibres but to the periaqueductal neurons themselves (Lu and Jurgens, 1993; Siebert and Jurgens, 2003). Rather than being the site of vocal pattern generation, the PAG could be serving gating functions (Siebert and Jurgens, 2003). In addition, the PAG controls the synchronous activity of neurons of the lower brainstem that are known to control vocal fold tension and respiration (Davis et al., 1996). This latter fact argues for a possible dependence of our experimental tasks on PAG activity: in the double-blind trial, which elicited the off versus on PPNa stimulation comparison, a relative negative impact of PPNa stimulation was observed for the two more ‘vocal’ tasks, namely the maximal phonation time and the diadochokinesis task. However, for the more ‘verbal tasks’, namely the word and sentence production, this effect was not observed. For this latter task, it was as if the motor cortical vocal control pathway bypassed the PAG (Jurgens, 2009).

Yet, vocal production cannot be restricted to the PAG and one should also consider the dorsolateral tegmentum and the prelemniscal area located between the superior colliculus and the superior olive. The ventrolateral parabrachial region is also involved in speech motor control, as demonstrated in animal studies of respiration (Chamberlin and Saper, 1994). Finally, animal studies have demonstrated an almost complete lack of direct connections between the various pharyngeal motor neurons along the neuraxis, from the level of the pontine brainstem down to the lumbar spinal cord (Jurgens, 2009). This suggested a role for the reticular formation of the lower brainstem in vocal motor coordination, as it is extensively and concomitantly connected with all phonatory motor nuclei. Thus, neurophysiological examination of brainstem...
Should any effect on speech be expected when stimulating midbrain structures?

Regarding the PPNa itself, low-frequency stimulation of the pedunculopontine tegmental nucleus significantly improved opening- and-closing jaw movements in 14 patients with Parkinson’s disease without medication (Mazzone et al., 2012). This finding underlined the role of the brainstem nuclei in oromotor control, which is very relevant in speech motor control. In our own patients, the stimulation sites were the dorsal PPN and the ventral part of the cuneiform nucleus (Ferraye et al., 2010). This area is more medial, superior, and posterior to the one targeted by Mazzone et al. (2012). Our results at 1 year demonstrated a trend towards significance for the deterioration of all assessed speech dimensions, whether the PPNa stimulation was turned off or on, when compared to the preoperative state. As stated previously, a long-lasting effect of the stimulation was a likely reason for the lack of differences between the PPNa off and on states. Although we cannot exclude a deleterious effect of the surgery per se on speech, the data from the double-blind trial strongly suggest that turning on PPNa stimulation, that is, delivering current, may exacerbate speech changes.

Neuromodulation of midbrain regions in humans, namely the PAG and periventricular grey matter, has been proposed since the 1970s for the treatment of chronic neuropathic pain (Hosobuchi et al., 1977; Richardson and Akl, 1977). This surgical procedure induced long-term and effective pain alleviation in selected patients (Kumar et al., 1997), the outcome depending on the nature and topography of the chronic pain (Pereira et al., 2013). Few side effects or complications have been reported (Bittar et al., 2005). Mainly, ventral PAG stimulation may induce various percepts, ranging from pleasant sensations, warmth and well-being at stimulation frequencies <50 Hz to perception of diffuse burning or anxiety at higher frequencies; dorsal PAG stimulation typically induces unpleasant sensations of fear, doom, anxiety and agitation (Kaplitt et al., 2003). Higher stimulation settings may induce gaze abnormalities via current spreading. In these studies on PAG and/or periventricular grey matter stimulation for intractable pain, none of the side-effects referred to any speech/voice deficits (Kumar et al., 1997; Kaplitt et al., 2003; Bittar et al., 2005; Pereira et al., 2013). Yet, electrical stimulation of the PAG can also provoke laughing (Sem-Jacobsen and Torkildsen, 1960) and its destruction, mutism (Esposito et al., 1999).

More recently, neuroimaging studies in humans have confirmed the connection between the PAG and cortical and subcortical structures involved either in speech production (Rektorova et al., 2012) or vocalization (Schulz et al., 2005). It is usually accepted that the maximal current spread diameter does not exceed 2 mm at the voltages we used, questioning the hypothesis that the current reached the PAG in our patients.

Hence, other midbrain structures being close to and located posterior to the targeted structure (Alam et al., 2011) might also be possible sites for current spread inducing speech modulation. The PPNa lies in somewhat close proximity with passing fibres and relay nuclei of the vagus nerve, so that PPNa stimulation could affect speech via current diffusion towards the corticobulbar tract. Indeed, extracerebral vagus nerve stimulation (Bergey, 2013) leads to side effects such as hoarseness and cough, even if transient (The Vagus Nerve Stimulation Study Group, 1995; Handforth et al., 1998) and reducing with time (Morris and Mueller, 1999). However, no functional signs of vagal stimulation were observed in our patients, suggesting that such possibility would be unlikely. Stimulation of the superior cerebellar peduncles neighbourhood may also provoke speech deficits, in case of current diffusion towards cortico-ponto-cerebellar fibres (Astrom et al., 2010). Shall we consider this possibility? The question lies open. Finally, the fact that STN and PPN surgeries may per se have exerted the deleterious effect on speech we report here cannot be excluded. Indeed, the trajectory and final target in the PPNa differs from those reported by other authors, who did not report speech degradation following sole PPN stimulation at therapeutic stimulating parameters. An interaction between STN and PPNa stimulations remains possible.

A deleterious treatment interaction on speech?

Pedunculopontine nucleus area and subthalamic nucleus stimulation

Our results failed to identify any effect resulting from the combination of both PPNa and STN stimulations. This is in keeping with previously published results. Indeed, improvements provided by STN and PPN stimulations, alone or combined, failed to affect speech motor dimensions explored in the sole study of grammar processing available so far (Zanini et al., 2009), where only morphological and syntactic errors seemed to be positively modulated by PPN and/or STN stimulations. In the Zanini et al. (2009) study, it is not possible to know whether there was any lesion effect, as no pre-surgery assessments were available. In addition, while in the Italian study the patients received bilateral STN and PPN electrodes in a single surgical session, in the present study PPNa surgery occurred several years after STN surgery. Hence, disease had further progressed between the two surgeries, likely contributing to speech worsening. Such differences impede direct comparison between the two studies. Possibly, the combination of PPN and STN stimulations can lead to a relative further improvement as compared with STN stimulation alone, despite the fact that PPNa stimulation alone, contrary to STN stimulation alone, hardly has any effect on the classical Parkinson’s disease motor triad (Ferraye et al., 2011). Such a synergistic effect between the two stimulations does not seem to hold regarding our speech evaluation. Also, the effects induced by PPNa stimulation might be ascribed to different levels of degeneration occurring in the PPNa area, which may involve acetylcholine and/or non-acetylcholine neurons (Braak and Del Tredici, 2004a; Pienaar et al., 2013) and fibres en passant rather than neuronal cell bodies (Mazzone et al., 2013). These possibilities may further differentiate the mechanism of action of DBS in the STN, in which a
relatively homogeneous population of neurons is present, from the mechanism underlying the DBS of PPNa, where the population of neurons is heterogeneous, with a consistent loss of cells in Parkinson’s disease (Braak et al., 2004b).

l-DOPA and pedunculopontine nucleus area stimulation

It is important to note that disease evolution was quite advanced in the group of patients included in this study (mean disease duration = 21.7 ± 6.5 years). This must be kept in mind when trying to interpret the treatment and interaction effects, as both the progressive nature of Parkinson’s disease and possible additional pathological processes, namely non-dopaminergic, may have played a role in speech decline, which was already present before PPNa surgery. One cannot exclude that speech impairment could have developed as the disease progressed and l-DOPA became less effective. We did not find any interaction between dopaminergic therapy and PPNa stimulation (except for the sole three-ways interaction between l-DOPA, PPNa stimulation and context presentation in the double-blind trial). This is in-line with another study that failed to observe either a positive or negative interaction effect between dopaminergic therapy and PPN stimulation on oromotor jaw movements (Mazzone et al., 2012). Oromotor movements have been studied after unilateral PPNa stimulation. The comparison of this study with our present work and Zanini et al. (2009)’s study that also involved bilateral PPNa stimulation, may be hampered by the different configuration of current spreading, which was reasonably more confined under unilateral than bilateral stimulation. However, in the report by Mazzone et al. (2012), patients were studied in the acute phase, a few days after receiving a unilateral PPNa electrode. In addition, recordings were performed after a few minutes or hours of stimulation only, whereas our patients were examined after several months of chronic bilateral stimulation. It therefore seems quite difficult to try and compare the results of the two studies, as the methodology differs widely.

It is known that worsening of speech impairment with Parkinson’s disease progression parallels an increasing severity of non-dopaminergic cerebral lesions (Agid et al., 1990; Braak et al., 1995; Halliday et al., 2011). Although some studies pointed out beneficial effects of l-DOPA on Parkinson’s disease speech (Sanabria et al., 2001; Goberman et al., 2002; De Letter et al., 2007), others have reported a lack of significant change between the two medication conditions (De Letter et al., 2003; Skodda et al., 2011). The patients in the present study presented with variable effects of l-DOPA on speech before PPNa surgery. Based on the global clinical evaluation scoring (item 18 of the UPDRS), three patients presented with mild improvement under l-DOPA whereas three did not (one last patient was not taking any dopaminergic treatment). Results of the double-blind trial clearly demonstrated a deleterious effect of l-DOPA on speech parameters, without any significant negative interaction with PPNa stimulation.

l-DOPA and subthalamic nucleus stimulation

When comparing preoperative and 12-month postoperative states, whereas l-DOPA intake and STN stimulation alone had no and positive effects on speech dimensions, respectively, a negative interaction between these two treatments was observed both before and after PPNa surgery. Except for the one patient who did not take any l-DOPA, the remaining six patients had been receiving dopaminergic therapy for > 10 years. In addition, STN stimulation was also a chronic treatment for at least 4 years at the time of PPNa surgery. No consensus is available regarding the long term effects of the combination of dopaminergic therapy and STN stimulation on speech impairment. It is generally agreed that STN stimulation does not have any major effect on speech intelligibility.

Yet, degradation at 1-year follow-up was reported (Tripoliti et al., 2011, 2014). In our study, we observed an improvement, rather than degradation, of speech intelligibility under STN stimulation alone. This effect existed before the PPNa surgery and did not seem to be modulated by PPNa stimulation. Thus, our results open a new possibility that some observed decrease in speech intelligibility could be brought about by a negative interaction between dopaminergic and STN stimulation treatments: this antagonistic combination suggests that the beneficial STN stimulation effect was blocked by the l-DOPA administration.

This effect could also reflect a specific pathological mechanism associated with a negative interaction between l-DOPA intake and STN stimulation. Such a mechanism would depend on cross-modulations between basal ganglia components during speech, which are to date still not fully understood even under healthy conditions. When trying to understand the mechanisms of DBS, recent resting state functional MRI findings in Parkinson’s disease have provided evidence that STN-DBS modulates all components of the motor cortico-striato-thalamo-cortical loop, including the direct and indirect basal ganglia pathways (Kahan et al., 2014): specifically, the effective connectivity of the STN afferents and efferents were reduced, whereas cortico-striatal, thalamo-cortical and direct pathways were strengthened. Our results suggest that the patients’ speech benefited from STN stimulation per se (Fig. 3). This effect could be related to such basal ganglia modulations. However, decreased preoperative speech intelligibility ON medication and disease duration have been shown to rank among the most significant predictors of deterioration of speech intelligibility following STN surgery in the OFF medication/on STN stimulation state (Tripoliti et al., 2014). These authors reported that unlike motor outcome, the effect on speech was not related either to the patients’ age at the time of surgery or to the preoperative motor scores. Also, the only predictor of speech deterioration ON medication/on STN stimulation was the preoperative OFF medication speech score. Altogether, these findings would suggest that the presence of significant non-dopaminergic lesions preoperatively should predict a poor speech outcome after the surgery, whether with or without l-DOPA. Considering the fact that the patients of the present study had rather long disease duration, one could imagine that the loss of the beneficial effect of STN stimulation under l-DOPA could depend upon: (i) a strengthened cortico-striatal pathway by STN stimulation; which is (ii) exacerbated by the administration of exogenous l-DOPA. At the level of the striatum, both in its associative and sensorimotor parts, endogenous dopamine is released during speech (Simonyan et al., 2013). If the loss of dopaminergic neurons contributed to the speech deterioration over Parkinson’s disease progression, the inability of the patients to compensate for the combined effects of
L-DOPA and STN stimulation (Tripoliti et al., 2014) might result from a difficulty in managing the effect of exogenous L-DOPA in the context of a basal ganglia system modulated by STN stimulation. One possible explanation could then be the modification induced by L-DOPA of the striatal neuron firing patterns ‘restored’ by STN stimulation.

Conclusion

Stimulation of the PPNa cannot be considered as an additional and a late compensatory resource in the pathological process of Parkinson’s disease. On the contrary, it could represent a selective choice in relation to specific symptom patterns, which require a careful selection of patients and a new conceptual interpretation of the disease and surgery. Stimulation of the PPNa, and possibly of surrounding structures as in the case of a spread of current to adjacent pathways, may contribute to the induction of stimulation-related speech deterioration as observed in the present study. However, little is known as regards the specific role of subcortical and brainstem structures, such as the STN and PPNa, on speech function. Thus, the effect of deep brain stimulation of these structures on speech in patients with Parkinson’s disease remains a challenging research area. Speech impairment after PPNa stimulation is a possible outcome that should be taken into account when considering such surgery, particularly as interactions between treatments rather than stimulation per se seem to determine speech outcome.

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Supplementary material

Supplementary material is available at Brain online.

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