Effect of low versus high frequency subthalamic deep brain stimulation on speech intelligibility and verbal fluency in Parkinson's disease: a double blind study

Timothy Grover[1], Dejan Georgiev[1,2,3,4], Rania Kaliola[1], Philipp Mahlknecht[1,5], André Zacharia[1], Joseph Candelario[1], Jonathan Hyam[1], Ludvic Zrinzo[1], Marwan Hariz[1], Thomas Foltynie[1], Patricia Limousin[1], Marjan Jahanshahi[1], and Elina Tripoliti[1]

[1]Unit of Functional Neurosurgery, Sobell Department of Motor Neuroscience and Movement Disorders, National Hospital of Neurology and Neurosurgery, Queen Square, London

[2]Department of Neurology, University Medical Centre Ljubljana, Slovenia

[3]Faculty of Medicine, University of Ljubljana, Slovenia

[4]Faculty of Computer and Information Sciences, University of Ljubljana, Slovenia

[5]Department of Neurology, Innsbruck Medical University, Innsbruck, Austria

Corresponding author:
Timothy Grover
Unit of Functional Neurosurgery, UCL Institute of Neurology
National Hospital for Neurology and Neurosurgery
Box 146, Queen Square,
London WC1N 3BG, U.K.
Tim.Grover@uclh.nhs.uk

Number of words – Abstract: 235; Article: 3661

Abstract

Background: Subthalamic Deep Brain Stimulation (STN-DBS) is an established treatment for late stage Parkinson's disease (PD). Speech intelligibility (SI) and verbal fluency (VF) have been shown to deteriorate following chronic STN-DBS. It has been suggested that speech might respond favourably to low frequency stimulation (LFS).

Objective: We examined how speech intelligibility, perceptual speech characteristics, phonemic and semantic VF and processes underlying it (clustering and switching) respond to LFS of 60 and 80Hz in comparison to high frequency stimulation (HFS) (110, 130 and 200 Hz).

Methods: In this double-blind study, 15 STN-DBS PD patients (mean age 65, *SD*=5.8, 14 right handed, three females), were assessed at five stimulation frequencies: 60Hz, 80Hz, 110Hz, 130Hz and 200Hz. In addition to the clinical neurological assessment of speech, VF and SI were assessed.

Results: Speech intelligibility and in particular articulation, respiration, phonation and prosody improved with LFS (all $p<0.05$). Phonemic VF switching improved with LFS ($p=0.005$) but this did not translate to an improved phonemic VF score. A trend for improved semantic VF was found. A negative correlation was found between perceptual characteristics of speech and duration of chronic stimulation (all $p<0.05$).

Conclusions: These findings highlight the need for meticulous programming of frequency to maximise speech intelligibility in chronic STN-DBS. The findings further implicate stimulation frequency in changes to specific processes underlying VF, namely phonemic switching and demonstrate the potential to address such deficits through advanced adjustment of stimulation parameters.

Keywords: subthalamic nucleus, deep brain stimulation, Parkinson's disease, speech intelligibility, verbal fluency, frequency

List of abbreviations:

DAB – Darley, Aronson and Brown scale

DD – Disease duration

DBS – Deep Brain Stimulation

FOG – Freezing of gait

HFS – High frequency stimulation

LFS – Low frequency stimulation

LFPs – Local field potentials

MON - Monologue

MONDAB – Monologue assessed by DAB scale

PD – Parkinson's disease

PVF – Phonemic verbal fluency

SI – Speech intelligibility

SIT – Speech Intelligibility Test

SITDAB – SIT sentences assessed by DAB scale

STN – Subthalamic Nucleus

SVF – Semantic verbal fluency

TSI – Time since implantation

TEED – Total electrical energy delivered

UPDRS-III – Unified Parkinson's Disease Rating Scale part III

VF – Verbal fluency

Introduction

Deep brain stimulation of the subthalamic nucleus (STN-DBS) is an established treatment for late stage Parkinson's disease (PD). Axial signs such as postural instability, freezing of gait (FOG) and dysarthria are less responsive and can even be adversely affected by STN-DBS[1, 2]. Clinical and surgical factors are known to affect speech presentation post STN-DBS, including longer disease duration [3], too medially placed left hemisphere active electrodes [3, 4], current spread laterally (to the corticospinal tract) or medially (to medial zona incerta or other, in proximity to STN, medially placed structures) [5], and time since implantation (TSI) [6]. In addition, speech can also be affected by changes of the stimulation parameters, such as amplitude of stimulation, which can considerably deteriorate speech [4]. Different strategies have been applied in order to alleviate speech deterioration after STN-DBS, such as the use of reduced stimulation frequency, interleaving mode or bipolar stimulation [7-9].

PD patients often perform poorly on tests designed to capture executive dysfunction such as tests of verbal fluency (VF) [10]. Additionally, the presence of VF deficits is thought to be predictive of dementia [11]. Neuropsychological studies [12-15] and meta-analyses have established that semantic verbal fluency (SVF) and phonemic verbal fluency (PVF) [16, 17] deteriorate following STN-DBS. Neither disease progression [18] nor reduction in dopaminergic medication are thought to be responsible, thus implicating surgery [12-15, 19-21], location of electrodes [21], high frequency stimulation (HFS) [22] or their combination [18] to be responsible for the fluency deterioration in these patients. There is also evidence that STN-DBS alters switching (the ability to disengage from a prior subcategory to a new one) [23], but not cluster size (the generation of words falling within subcategories) [23-25]. Again, low frequency stimulation might be helpful in improving VF after STN-DBS [22, 26]

The main aim of this study was to examine how articulation, respiration, phonation, resonance, prosody and rate respond to LFS (60Hz, 80Hz) in comparison to 110Hz, 130Hz and 200Hz and how this contributes to overall speech intelligibility. A further aim was to establish the effect of LFS and HFS on PVF and SVF and whether cluster size and switching are altered by stimulation frequency. The influence of clinical factors known to be instrumental in speech outcome such as disease duration (DD) and TSI was also examined.

Patients and Methods

The study included 15 English-speaking PD patients (14 right-handed, three females) diagnosed according to the Queen Square Brain Bank criteria [27]. All patients had been treated with bilateral STN-DBS for at least three years, had been reviewed by a neurologist, and identified as experiencing speech difficulties. Surgery had been performed as previously described [28] with patients asleep in general anaesthesia. Mean age at the time of surgery was 65, *SD*=5.8 years, mean disease duration prior to surgery was 10.6, *SD*=3.8 years and mean disease duration at the time of study was 18.5, *SD*=3.7 years. Mean duration of STN stimulation at time of study was 6 years, *SD*=3.5. All patients experienced axial problems (hypophonia ± dysarthria alone or in conjunction with gait, balance and/or postural difficulties). Patients had mixed speech presentation, ranging from mild to severe disturbance. The study was approved by the National Hospital for Neurology and Neurosurgery and the UCL Institute of Neurology joint research Ethics committee. Informed consent was obtained from all participants. Patients were assessed following overnight withdrawal of dopaminergic medication.

Study design and evaluations

This was a double-blinded study, as neither the patient nor the rater (TG) were aware of the stimulation parameters. Patients were assessed during a single morning session. A neurologist (DG/RK) changed stimulation settings. Five stimulation frequencies were tested and randomly assigned to conditions 1-5 for each patient; 60Hz, 80Hz, 110Hz, 130Hz and 200Hz. An interval of at least 20 minutes elapsed between changing of stimulation settings and repeat of testing. This interval was chosen based on previous studies [29-31] and also for practical reasons – sufficient time for effects of previous settings to elapse while not so long that it would be unfeasible to test patients in five different conditions. With frequency adjustments, voltage was increased or decreased and the pulse width held constant to maintain constant total electrical energy delivered (TEED) while also ensuring a tolerable stimulation level without the onset of (non-speech) side effect [32], according to the formula:

$$TEED = \frac{V^2 \times PW \times f}{I}$$

where V is the voltage, PW is the pulse width, f is the frequency and I is the impedance. However, if an intolerable (non-speech) side effect appeared with the calculated voltage of stimulation to maintain the same TEED, the next lower voltage, at which no (non-speech) side effect emerged, was used to stimulate at that frequency. The baseline stimulating parameters of all patients are presented in Table 1. The motor condition of the patients was assessed by the use of Unified Parkinson's Disease Rating Scale part III (UPDRS-III) [33].

The speech evaluation comprised of a reading and speaking task. For the reading task the Assessment of Intelligibility for Dysarthric Speech [34] was used, the computerised version of this test is termed the Speech Intelligibility Test (SIT). The SIT is a widely used standardized assessment of speech intelligibility. Patients are required to read 11 sentences of varying length from 5-15 words, totalling 110 words. Sentences are produced randomly from a pool of master sentences. An intelligibility score (SIT%) is derived from the number of

correct words transcribed following two exposures to the sentences by a native English speaker (TG). For speaking, patients were asked to produce a 60-second monologue (MON) on a topic of their choice.

The Darley, Aronson and Brown scale (DAB) (Darley, et al. [35] is the most widely used classification system of dysarthric speech and comprises 35 speech dimensions. Plowman-Prine, et al. [36] grouped the 35 speech dimensions under six speech clusters; articulation, respiration, phonation, resonance, prosody and rate. Each speech cluster is rated on a scale of 0-7 with a maximum score of 42 indicative of normal speech, whilst a score closer to 0 denotes pathological speech [36]. The SIT sentences (SITDAB) and 60-second monologue (MONDAB) were rated perceptually in this way. Perceptual analysis was performed independently for all patients with the same equipment to minimise any possible variability across tasks. The Computerised Speech Lab (CSL, Kay Pentax, 4150) was used to record all speech samples. Acoustic recordings were obtained using a Shure SM 48 dynamic microphone, with a 15cm mouth to microphone distance, at a 22 kHz sampling rate in a sound treated room [37]. The 15cm mouth-to-microphone distance was checked periodically throughout the assessments. In addition, the neurologist rated the speech during MONDAB and SITDAB evaluation according to item 18 of UPDRS-III [33].

At each frequency, patients were administered 3 PVF tasks and 1 SVF task. Protocol was as set out by Troyer [38]. To minimize practice effects the following letters and categories were used in the PVF and SVF tasks respectively: letters “FAS”, “BHR”, “CTL”, “PDW”, “NEK”, then Animals, Boy’s names, Furniture, Fruit and Vegetables, Drinks. In each condition, participants were given 60s to verbally generate words beginning with specific letters or belonging to specific categories. Participants had to follow specific rules, namely, that the words could not be names of people, places, or numbers and could not be repeated sequences (e.g., take, takes, taking, etc.). All words produced were recorded for

further analysis. The total number of correct words generated as well as measures of cluster size and switching were obtained using the procedures outlined by Troyer [38]. The overall duration of testing at each frequency lasted between 15 and 20 minutes.

Data analysis

Statistical analysis was performed with SPSS 22.0.0 (IBM Corp., Armonk, NY). The Shapiro-Wilk test was used to test for normality. A one-way within subjects repeated measures ANOVA with the single factor of frequency was carried out for each speech measure and for the individual perceptual measures of speech. The factor frequency had 5 levels (60, 80, 110, 130 and 200 Hz). Mauchly's test was used to test for sphericity; Greenhouse-Geisser correction was used if sphericity was not assumed. Paired *t*-tests were used for post-hoc comparison. Bonferroni correction was used to control for multiple comparisons. Pearson product-moment was used for correlation analysis. SITDAB and MONDAB perceptual characteristics for different frequencies were correlated to TSI and DD. The significance level was set at two-sided p-value of <0.05.

Results

Clinical data

STN-DBS significantly improved motor symptoms (mean UPDRS-III OFF medication before operation 48.7, SD=17.4, and OFF medication ON stimulation after operation 33.7, SD=9.3, $t(15)=3.025$, $p=0.009$).

In addition, change of DBS frequency significantly altered the UPDRS speech score (item 18) as assessed during MONDAB, $F(4,52)=6.615$, $p<0.0001$. The speech UPDRS score was the lowest for 60 Hz, $F(1,13)=13.542$, $p=0.003$, and 80 Hz $F(1,13)=16.059$, $p=0.001$.

The difference between UPDRS scores at 110 and 130 Hz compared to 200 Hz was not significant (p=0.336 and p=0.500 respectively) (Figure 1A).

Similarly, stimulation frequency significantly changed the UPDRS-III speech score as assessed during SITDAB, $F(4,52)=5.239$, p=0.001. The speech UPDRS-III score was the lowest for 60 Hz, $F(1,13)=10.947$, p=0.006. There was no difference in UPDRS speech scores between 80, 110, 130 Hz and 200 Hz (all *p values* >0.05) (Figure 1A).

Speech Intelligibility

SIT Score (%): There was an overall significant effect of DBS frequency on SIT%, $F(4,52)=2.700$, p=0.040. The post-hoc analysis, however, did not yield any significant differences between the five frequencies, with only a trend towards significance observed comparing the 60 Hz and the 200 Hz scores, $F(1,13)=4.262$, p=0.059.

Overall SITDAB score: There was a significant effect of frequency on the overall SITDAB score, $F(4,52)=5.069$, p=0.002. The overall SITDAB score was the highest for 60 Hz reflecting closer to normal speech at LFS and conversely the score was lowest for 200 Hz, (60 Hz vs. 200 Hz comparison) $F(1,13)=6.545$, p=0.024 (Figure 1B) reflecting less intelligible speech. There was no difference in the overall score either between the 110 and the 200 Hz $F(1,13)=1.708$, p=0.214, or between the 130 and 200 Hz $F(1,13)=0$, p>0.05 The difference between 60 and 80 Hz was also not significant, $F(1,13)=1.087$, p=0.295.

Overall MONDAB score: There was a significant effect of frequency on overall MONDAB score, $F(4,52)=4.222$, p=0.005. The overall MONDAB score was highest for 60 Hz, and lowest for 200Hz, (60 Hz vs. 200 Hz comparison) $F(1,13)=7.694$, p=0.016. There

was no significant difference between MONDAB scores at intermediate frequencies (all *p values*>0.05).

Individual SITDAB and MONDAB scores: The results for the individual SITDAB and MONDAB scores are presented in Table 2. For SITDAB, there were significant differences in the Group comparisons for Articulation, Phonation, Prosody and Rate. The articulation, $F(1,13)=10.426$, $p=0.007$, phonation, $F(1,13)=7.759$, $p=0.015$ and prosody scores, $F(1,13)=5.026$, $p=0.043$ were all significantly different in the ANOVA with the highest scores for 60 Hz compared to 200 Hz. There were no significant differences in SITDAB articulation, phonation and prosody scores between other frequencies. The rate score was the highest for 60 Hz and the lowest for 200 Hz, although the difference only approached trend levels of significance $F(1,13)=3.427$, $p=0.085$.

For MONDAB, there were significant effects of frequency on articulation, respiration, phonation and prosody.. The post hoc comparison of 60 Hz vs. 200 Hz confirmed significant differences for articulation, $F(1,12)=14.190$, $p=0.003$, respiration, $F(1,12)=9.561$, $p=0.009$, phonation, $F(1,12)=5.333$, $p=0.040$, and prosody scores, $F(1,12)=5.660$, $p=0.035$, all with higher values for 60 Hz and lowest for 200 Hz. There was a significant difference in phonation score between 80 and 200Hz $F(1,12)=5.672$, $p=0.035$.

Correlation analysis

There was a negative correlation of TSI with Articulation for both MONDAB and SITDAB for all frequencies (60, 80, 110, 130 and 200 Hz, all p values<0.05) (Table 3). TSI negatively correlated with Phonation MONDAB for 60, 80 and 130 Hz and Phonation SITDAB for 60 and 130 Hz (all p values<0.05), as well as with Prosody SITDAB for all

frequencies and Prosody MONDAB for 60, 80 and 130 Hz (all p values<0.05). There was a negative correlation between TSI and Rate MONDAB 130 Hz, and Rate SINDAB 80 and 130 Hz (p<0.05). No perceptual characteristics for either MONDAB or SITDAB significantly correlated with disease duration.

Verbal fluency

Phonemic verbal fluency: There was, a significant effect of frequency for the switching score $F(4,52)=2.798$, $p=0.035$, which was highest for 60 Hz and gradually declined for higher frequencies (60hz vs. 200hz comparison) $F(1,13)=11.410$, $p=0.005$ (Table 4).

Semantic verbal fluency: The effect of DBS frequency approached significance for the total number of correct words generated again with highest scores for the lowest frequency (60hz vs. 200hz comparison) $F(4,52)=2.316$, $p=0.069$ (Table 4).

Discussion

To our knowledge, this is the first double blind study to systematically evaluate the effect of different frequencies of stimulation on speech intelligibility and verbal fluency. Speech intelligibility was improved at LFS in comparison to HFS; this is accounted for by improvements seen in articulation, phonation, respiration and prosody. PVF switching was improved with LFS compared to HFS, but neither the number of words generated in PVF or SVF nor the measure of cluster size for either fluency task was significantly altered by frequency.

Speech intelligibility

As was predicted for the speech intelligibility score (SIT%), a significant frequency effect was found for the overall perceptual score of the SIT sentences (SITDAB) and the overall perceptual score of the 60-second monologue (MONDAB). These improvements are best understood in respect of the frequency effect for the perceptual speech measures of articulation, phonation, respiration and prosody that were observed.

Our findings are consistent with Tornqvist, et al. [39] who found that divergence from normal articulation was less with a lower frequency setting (70 Hz) compared to the higher settings (130 and 185 Hz). Studies have proposed that STN-DBS results in a reduced vowel space in speech subsequent to restricted articulatory range [40]. This is attributed to spasticity resulting from current spread to neighbouring fibres [5, 40]. Sidtis, et al. [41] proposed that STN-DBS alters the internal mapping of the articulators and the afferent feedback regarding their state and in doing so disrupts the co-ordination of articulatory, laryngeal and respiratory components. Studies using acoustic and aerodynamic measures demonstrate improved co-ordination of phonation and respiration with LFS [42]. While it is generally accepted that disturbance to speech results from current spread to neighbouring fibres instrumental to the control of speech, it remains to be seen why LFS alleviates this disturbance. Blumenfeld, et al. [43] demonstrated that in contrast to HFS at 130Hz which attenuates STN alpha/beta band neural synchrony, LFS of 60Hz was found to amplify resting state neural synchrony. Furthermore the effect of 60Hz on neural synchrony could not be attributed to lower total power delivered as the effects were counter to those produced by equivalent DBS settings at 130Hz and therefore the effects of 60Hz were likely frequency specific. The authors suggested this was support for the theory that different frequencies have different effects on underlying neural circuitry. Moreau, et al. [42] also found improvements in dysarthria and FOG with LFS. They proposed that prolonged HFS could induce chronic side effects due to

the involvement of mesencephalic locomotor area, cerebellar tracts and in particular the fasciculus cerebellothalamicus resulting in paradoxical inhibition of these areas which are involved in the regulation of orofacial movements during speech. As expected there was a negative correlation between articulation (for all frequencies), phonation, prosody and rate (mainly for lower frequencies) and TSI, such that as time has progressed, these speech features have deteriorated. This effect was not frequency specific (e.g. correlations of articulation for all frequencies to TSI was significant), meaning that stimulation at different frequencies did not completely remove the net detrimental effect of chronic DBS. Moreover, disease duration was not significantly correlated to any of the perceptual characteristics for different frequencies, further confirming that the chronic effects of DBS on deterioration of the speech, are distinct from natural disease progression. Fasano, et al. [6] also found TSI to be instrumental in speech deterioration. Regarding the possible mechanisms behind the effect of TSI on worsening of speech abilities, Tripoliti and Limousin [44] proposed that the delayed onset of speech difficulties following STN-DBS was due to the involvement of the cerebellothalamic tracts and pallidothalamic tracts when the active electrode was positioned medial to the STN in the proximity of these tracts.

Verbal fluency

Our findings provide tentative evidence that stimulation contributes to changes in VF and that frequency has a role to play. Phonemic switching was found to improve with LFS relative to HFS but this did not translate into an overall improvement in the number of words generated during the PVF test. A trend towards improved SVF at LFS was found. Frequency had no effect on cluster size for either PVF or SVF. Wojtecki, et al. [22] found SVF and PVF to be better at LFS (10Hz) and worst at HFS (130Hz). They attributed this to activation of neural pathways projecting to the inferior frontal cortex providing evidence of frequency

dependent tuning of cognitive circuits interconnected with the STN, where DBS of the STN at 10 Hz might have an inhibitory effect on the motor circuit and yet a facilitatory effect on the cognitive circuit. Fagundes, et al. [26] also found that, PVF, but not SVF responded favourably to LFS, proposing that due to frontocortical impairment in PD, a frequency effect would manifest to a greater extent in tasks that make demands on frontocortical functions such as PVF.

Vonberg, et al. [25] found stimulation increased the number of switches and a trend towards reduced switch times, however, this did not increase the number of words produced. They drew a distinction between the executive process of switching and the lexico-semantic process of clustering during VF and as such proposed that STN-DBS could influence the procedural/executive aspect of VF as opposed to the lexical. In doing so they proposed that STN-DBS modulation of the basal ganglia was occurring that permitted disengagement from prevailing cognitive states through suppression of excessive beta-oscillations thought to be associated with symptoms of static motor behavior such as rigidity and bradykinesia. Improved switching as a consequence of stimulation could result from an enhanced 'antistatic' mental drive that facilitates disengagement from a prevailing lexical concept (cluster) towards a new one [25]. In the first study of its type, Anzak, et al. [45] recorded Local field potentials (LFPs) from externalized electrodes in the STN bilaterally while patients performed PVF, SVF or control word repetition tasks. They found that compared to the control tasks, which controlled for motor output, word generation during the VF tasks was associated with a significant increase in gamma band activity in the LFPs recorded from the STN. Of particular interest to the present results is their finding that gamma changes recorded from contacts lying in the left hemisphere (dominant in verbal fluency) correlated with the average number of correct responses generated ($r = 0.81$ $p = 0.015$) and measures of 'switching' ($r = 0.79$ $p = 0.020$). These gamma band specific power changes observed during

task performance are consistent with involvement of the subthalamic nucleus in switching during verbal fluency. Wojtecki, et al. [46] combined LFPs in the STN through externalised DBS electrodes with EEG scalp recordings during a phonemic verbal generation task and demonstrated enhanced coherence between the STN and frontal cortex in lower frequency bands (alpa-theta Hz). It was proposed that improved VF during LFS was a result of enhancement of alpha-theta oscillatory network activity.

Limitations of the study and future research

A limitation of the present study was the omission of repeat whole UPDRS-III in each condition; this would have enabled assessment of whether improvements in speech intelligibility achieved with LFS were to the detriment of benefits to other (axial) motor symptoms, especially swallowing. Recent studies have shown that low frequency (60 Hz) stimulation has a good effect on reducing aspiration frequency, perceived swallowing difficulty, freezing of gait severity, bradykinesia and overall axial and motor symptoms, although the overall effect decreases over time [47, 48]. This would be challenging however in view of patient fatigue. In addition, the main objective of the present study was to specifically explore the effect of changing frequencies on speech. Another limitation of the study might be the relatively short time between changing of frequencies (20 minutes). According to the available data, switching the DBS off leads to a progressive deterioration of symptoms such that tremor worsens in a couple of minutes, followed by worsening of bradykinesia and rigidity and then axial symptoms. However, the rate of improvement of symptoms after switching DBS on again seems to be much faster, especially the improvement of axial symptoms [29]. A longer time period in-between frequency change might have been physiologically plausible; however, considering the fact that the patients were off medication,

a prolongation of the “wait” period would have been too unpleasant for the patients. In addition, we have clearly seen changes of the speech characteristics with the change of frequencies. A previous pilot study [49] has established that articulation can further deteriorate with the addition of medication to stimulation. In the present study patients were off medication in all conditions. This might have affected the results of the study at the end of the visit. However, frequencies were randomly assigned across patients thus this possibility should not represent a systematic bias. In a future study we plan to establish whether specific speech parameters are affected with the addition of medication and whether this was as marked with LFS. In addition, it would be interesting to explore the duration of the beneficial effect of LFS on speech.

Conclusion

The present double blind study has demonstrated that certain characteristics of speech, namely articulation, phonation, respiration, and prosody are sensitive to HFS and contribute to decreased intelligibility. These difficulties have been found to deteriorate as TSI increases. We found that with LFS, HFS-induced pathological speech presentation is partially reversible, resulting in improved speech intelligibility. The study further demonstrates that stimulation and in particular, frequency of stimulation influences specific VF processes, namely switching during PVF. Both speech intelligibility and VF should be considered during routine parameter adjustments and frequency of the stimulating current is a viable parameter to adjust/alter to address issues in these domains.

Acknowledgements: The Unit of Functional Neurosurgery is supported by the Parkinson Appeal UK, and the Monument Trust with support from the National Institute of Health Research University College London Hospitals Biomedical Research Centre and the Edmond J Safra Philanthropic Foundation.

Conflicts of Interest: MH has received honoraria and / or travel expenses from Medtronic, St Jude, and Boston Scientific for speaking at meetings. TF has received honoraria for speaking at meeting sponsored by BIAL, Britannia, and Profile Pharma. He has served on Advisory boards for Abbott, Oxford Biomedica, and Celgene, and received grant support from Michael J Fox Foundation, Cure Parkinson's Trust, John Black Charitable Foundation and European Union FP7.

References

[1] Deuschl G, Herzog J, Kleiner-Fisman G, Kubu C, Lozano AM, Lyons KE, Rodriguez-Oroz MC, Tamma F, Troster AI, Vitek JL, Volkmann J, Voon V (2006) Deep brain stimulation: postoperative issues. *Mov Disord* **21 Suppl 14**, S219-237.

[2] Weaver FM, Follett K, Stern M, Hur K, Harris C, Marks WJ, Jr., Rothlind J, Sagher O, Reda D, Moy CS, Pahwa R, Burchiel K, Hogarth P, Lai EC, Duda JE, Holloway K, Samii A, Horn S, Bronstein J, Stoner G, Heemskerk J, Huang GD, Group CSPS (2009) Bilateral deep brain stimulation vs best medical therapy for patients with advanced Parkinson disease: a randomized controlled trial. *JAMA* **301**, 63-73.

[3] Tripoliti E, Limousin P, Foltynie T, Candelario J, Aviles-Olmos I, Hariz MI, Zrinzo L (2014) Predictive factors of speech intelligibility following subthalamic nucleus stimulation in consecutive patients with Parkinson's disease. *Mov Disord* **29**, 532-538.

[4] Aström M, Tripoliti E, Hariz MI, Zrinzo LU, Martinez-Torres I, Limousin P, Wardell K (2010) Patient-specific model-based investigation of speech intelligibility and movement during deep brain stimulation. *Stereotact Funct Neurosurg* **88**, 224-233.

[5] Mahlknecht P, Akram H, Georgiev D, Tripoliti E, Candelario J, Zacharia A, Zrinzo L, Hyam J, Hariz M, Foltynie T, Rothwell JC, Limousin P (2017) Pyramidal tract activation due to subthalamic deep brain stimulation in Parkinson's disease. . *Movement Disorders* **32**, 1174-1182.

[6] Fasano A, Romito LM, Daniele A, Piano C, Zinno M, Bentivoglio AR, Albanese A (2010) Motor and cognitive outcome in patients with Parkinson's disease 8 years after subthalamic implants. *Brain* **133**, 2664-2676.

[7] Picillo M, Lozano AM, Kou N, Puppi Munhoz R, Fasano A (2016) Programming Deep Brain Stimulation for Parkinson's Disease: The Toronto Western Hospital Algorithms. *Brain Stimul* **9**, 425-437.

[8] Sidiropoulos C, Walsh R, Meaney C, Poon YY, Fallis M, Moro E (2013) Low-frequency subthalamic nucleus deep brain stimulation for axial symptoms in advanced Parkinson's disease. *J Neurol* **260**, 2306-2311.

[9] Zibetti M, Moro E, Krishna V, Sammartino F, Picillo M, Munhoz RP, Lozano AM, Fasano A (2016) Low-frequency Subthalamic Stimulation in Parkinson's Disease: Long-term Outcome and Predictors. *Brain Stimul* **9**, 774-779.

[10] Henry JD, Crawford JR, Phillips LH (2004) Verbal fluency performance in dementia of the Alzheimer's type: a meta-analysis. *Neuropsychologia* **42**, 1212-1222.

[11] Levy G, Marder K (2003) Prevalence, Incidence, and Risk Factors for Dementia in Parkinson's Disease In *Mental and Behavioral Dysfunction in Movement Disorders.*, Bédard MA, Agid Y, Chouinard S, Fahn S, Korczyn AD, Lespérance P, eds. Humana Press, Totowa, NJ.

[12] Morrison CE, Borod JC, Perrine K, Beric A, Brin MF, Rezai A, Kelly P, Sterio D, Germano I, Weisz D, Olanow CW (2004) Neuropsychological functioning following bilateral subthalamic nucleus stimulation in Parkinson's disease. *Arch Clin Neuropsychol* **19**, 165-181.

[13] Pillon B, Ardouin C, Damier P, Krack P, Houeto JL, Klinger H, Bonnet AM, Pollak P, Benabid AL, Y. A (2000) Neuropsychological changes between "off" and "on" STN or GPi stimulation in Parkinson's disease. *Neurology* **55**, 411-418.

[14] Witt K, Granert O, Daniels C, Volkmann J, Falk D, van Eimeren T, Deuschl G (2013) Relation of lead trajectory and electrode position to neuropsychological outcomes of subthalamic neurostimulation in Parkinson's disease: results from a randomized trial. *Brain* **136**, 2109-2119.

[15] Okun MS, Fernandez HH, Wu SS, Kirsch-Darrow L, Bowers D, Bova F, Suelter M, Jacobson CEt, Wang X, Gordon CW, Jr., Zeilman P, Romrell J, Martin P, Ward H, Rodriguez RL, Foote KD (2009) Cognition and mood in Parkinson's disease in subthalamic nucleus versus globus pallidus interna deep brain stimulation: the COMPARE trial. *Ann Neurol* **65**, 586-595.

[16] Parsons TD, Rogers SA, Braaten AJ, Woods SP, Troster AI (2006) Cognitive sequelae of subthalamic nucleus deep brain stimulation in Parkinson's disease: a meta-analysis. *Lancet Neurol* **5**, 578-588.

[17] Wyman-Chick KA (2016) Verbal Fluency in Parkinson's Patients with and without Bilateral Deep Brain Stimulation of the Subthalamic Nucleus: A Meta-analysis. *J Int Neuropsychol Soc* **22**, 478-485.

[18] Højlund A, Petersen MV, Sridharan KS, Ostergaard K (2017) Worsening of Verbal Fluency After Deep Brain Stimulation in Parkinson's Disease: A Focused Review. *Comput Struct Biotechnol J* **15**, 68-74.

[19] Halpern CH, Rick JH, Danish SF, Grossman M, Baltuch GH (2009) Cognition following bilateral deep brain stimulation surgery of the subthalamic nucleus for Parkinson's disease. *Int J Geriatr Psychiatry* **24**, 443-451.

[20] Lefaucheur R, Derrey S, Martinaud O, Wallon D, Chastan N, Gérardin E, Hannequin D, Maltête D (2012) Early verbal fluency decline after STN implantation: is it a cognitive microlesion effect? *J Neurol Sci* **321**, 96-99.

[21] Mikos A, Bowers D, Noecker AM, McIntyre CC, Won M, Chaturvedi A, Foote KD, Okun MS (2011) Patient-specific analysis of the relationship between the volume of tissue activated during DBS and verbal fluency. *Neuroimage* **54**, S238-246.

[22] Wojtecki L, Timmermann L, Jorgens S, Sudmeyer M, Maarouf M, Treuer H, Gross J, Lehrke R, Koulousakis A, Voges J, Sturm V, Schnitzler A (2006) Frequency-dependent reciprocal modulation of verbal fluency and motor functions in subthalamic deep brain stimulation. *Arch Neurol* **63**, 1273-1276.

[23] Troyer AK, Moscovitch M, Winocur G (1997) Clustering and switching as two components of verbal fluency: evidence from younger and older healthy adults. *Neuropsychology* **11**, 138-146.

[24] De Gaspari D, Siri C, Di Gioia M, Antonini A, Isella V, Pizzolato A, Landi A, Vergani F, Gaini SM, Appollonio IM, Pezzoli G (2006) Clinical correlates and cognitive underpinnings of verbal fluency impairment after chronic subthalamic stimulation in Parkinson's disease. *Parkinsonism Relat Disord* **12**, 289-295.

[25] Vonberg I, Ehlen F, Fromm O, Kuhn AA, Klostermann F (2016) Deep Brain Stimulation of the Subthalamic Nucleus Improves Lexical Switching in Parkinsons Disease Patients. *PLoS One* **11**, e0161404.

[26] Fagundes VC, Rieder CR, da Cruz AN, Beber BC, Portuguez MW (2016) Deep Brain Stimulation Frequency of the Subthalamic Nucleus Affects Phonemic and Action Fluency in Parkinson's Disease. *Parkinsons Dis* **2016**, 6760243.

[27] Hughes AJ, Daniel SE, Kilford L, Lees AJ (1992) Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. *J Neurol Neurosurg Psychiatry* **55**, 181-184.

[28] Foltynie T, Zrinzo L, Martinez-Torres I, Tripoliti E, Petersen E, Holl E, Aviles-Olmos I, Jahanshahi M, Hariz M, Limousin P (2011) MRI-guided STN DBS in Parkinson's disease without microelectrode recording: efficacy and safety. *J Neurol Neurosurg Psychiatry* **82**, 358-363.

[29] Temperli P, Ghika J, Villemure JG, Burkhard PR, Bogousslavsky J, Vingerhoets FJ (2003) How do parkinsonian signs return after discontinuation of subthalamic DBS? *Neuology* **60**, 78-81.

[30] Keresztenyi Z, Valkovic P, Eggert T, Steude U, Hermsdorfer J, Laczko J, Botzel K (2007) The time course of the return of upper limb bradykinesia after cessation of subthalamic stimulation in Parkinson's disease. *Parkinsonism Relat Disord* **13**, 438-442.

[31] Cooper SE, Driesslein KG, Noecker AM, McIntyre CC, Machado AM, Butson CR (2014) Anatomical targets associated with abrupt versus gradual washout of subthalamic deep brain stimulation effects on bradykinesia. *PLoS One* **9**, e99663.

[32] Koss AM, Alterman RL, Tagliati M, Shils JL (2005) Calculating total electrical energy delivered by deep brain stimulation systems. *Ann Neurol* **58**, 168; author reply 168-169.

[33] Fahn S ER, Members of the updrs Development Committee. (1987) Unified Parkinson's Disease Rating Scale In *Recent Developments in Parkinson's Disease*, Fahn S, Marsden CD, Calne DB, Goldstein M, eds. Macmillan Health Care Information, Florham Park, NJ, pp. 1 53-51 63.

[34] Yorkston KM, Beukelman DR (1984) *Assessment of Intelligibility of Dysarthric Speech.*, CC Publications, Tigard Oregon.

[35] Darley FL, Aronson AE, Brown JR (1969) Clusters of deviant speech dimensions in the dysarthrias. *J Speech Hear Res* **12**, 462-496.

[36] Plowman-Prine EK, Okun MS, Sapienza CM, Shrivastav R, Fernandez HH, Foote KD, Ellis C, Rodriguez AD, Burkhead LM, Rosenbek JC (2009) Perceptual characteristics of Parkinsonian speech: a comparison of the pharmacological effects of levodopa across speech and non-speech motor systems. *NeuroRehabilitation* **24**, 131-144.

[37] Tripoliti E, Zrinzo L, Martinez-Torres I, Tisch S, Frost E, Borrell E, Hariz MI, Limousin P (2008) Effects of contact location and voltage amplitude on speech and movement in bilateral subthalamic nucleus deep brain stimulation. *Mov Disord* **23**, 2377-2383.

[38] Troyer AK (2000) Normative data for clustering and switching on verbal fluency tasks. *J Clin Exp Neuropsychol* **22**, 370-378.

[39] Tornqvist AL, Schalen L, Rehncrona S (2005) Effects of different electrical parameter settings on the intelligibility of speech in patients with Parkinson's disease treated with subthalamic deep brain stimulation. *Mov Disord* **20**, 416-423.

[40] Dromey C, Bjarnason S (2011) A preliminary report on disordered speech with deep brain stimulation in individuals with Parkinson's disease. *Parkinsons Dis* **2011**, 796205.

[41] Sidtis JJ, Alken AG, Tagliati M, Alterman R, D. V-L-S (2016) Subthalamic Stimulation Reduces Vowel Space at the Initiation of Sustained Production: Implications for Articulatory Motor Control in Parkinson's Disease. *J Parkinsons Dis* **6**, 361-370.

[42] Moreau C, Pennel-Ployart O, Pinto S, Plachez A, Annic A, Viallet F, Destee A, Defebvre L (2011) Modulation of dysarthropneumophonia by low-frequency STN DBS in advanced Parkinson's disease. *Mov Disord* **26**, 659-663.

[43] Blumenfeld Z, Velisar A, Miller Koop M, Hill BC, Shreve LA, Quinn EJ, Kilbane C, Yu H, Henderson JM, Bronte-Stewart H (2015) Sixty Herz Neurostimulation Amplifies Subthalamic Neural Synchrony in Parkinson's Disease. *PLoS ONE* **10**, e0121067.

[44] Tripoliti E, Limousin P (2010) Electrical Stimulation of deep brain structures and speech. In *Speech Motor Control: In normal and Disordered Speech*, Maassen B, Pascal HHM, Van Lieshout P, eds. Oxford University Press, Oxford.

[45] Anzak A, Gaynor L, Beigi M, Limousin P, Hariz M, Zrinzo L, Foltynie T, Brown P, Jahanshahi M (2011) A gamma band specific role of the subthalamic nucleus in switching during verbal fluency tasks in Parkinson's disease. *Exp Neurol* **232**, 136-142.

[46] Wojtecki L, Elben S, Vesper J, Schnitzler A (2017) The rhythm of the executive gate of speech: subthalamic low-frequency oscillations increase during verbal generation. *Eur J Neurosci* **45**, 1200-1211.

[47] Xie T, Bloom L, Padmanaban M, Bertacchi B, Kang W, MacCracken E, Dachman A, Vigil J, Satzer D, Zadikoff C, Markopoulou K, Warnke P, Kang UJ (2018) Long-term effect of low frequency stimulation of STN on dysphagia, freezing of gait and other motor symptoms in PD. *J Neurol Neurosurg Psychiatry*.

[48] Xie T, Padmanaban M, Bloom L, MacCracken E, Bertacchi B, Dachman A, Warnke P (2017) Effect of low versus high frequency stimulation on freezing of gait and other axial symptoms in Parkinson patients with bilateral STN DBS: a mini-review. *Transl Neurodegener* **6**, 13.

[49] Hartinger M, Tripoliti E, Hardcastle WJ, Limousin P (2011) Effects of medication and subthalamic nucleus deep brain stimulation on tongue movements in speakers with Parkinson's disease using electropalatography: a pilot study. *Clin Linguist Phon* **25**, 210-230.

Figure 1A. Item 18 assessing Speech from the Unified Parkinson’s disease rating Scale–part III for different frequencies (60, 80, 110, 130 and 200 Hz) are presented. Error bars represent standard errors of the mean.

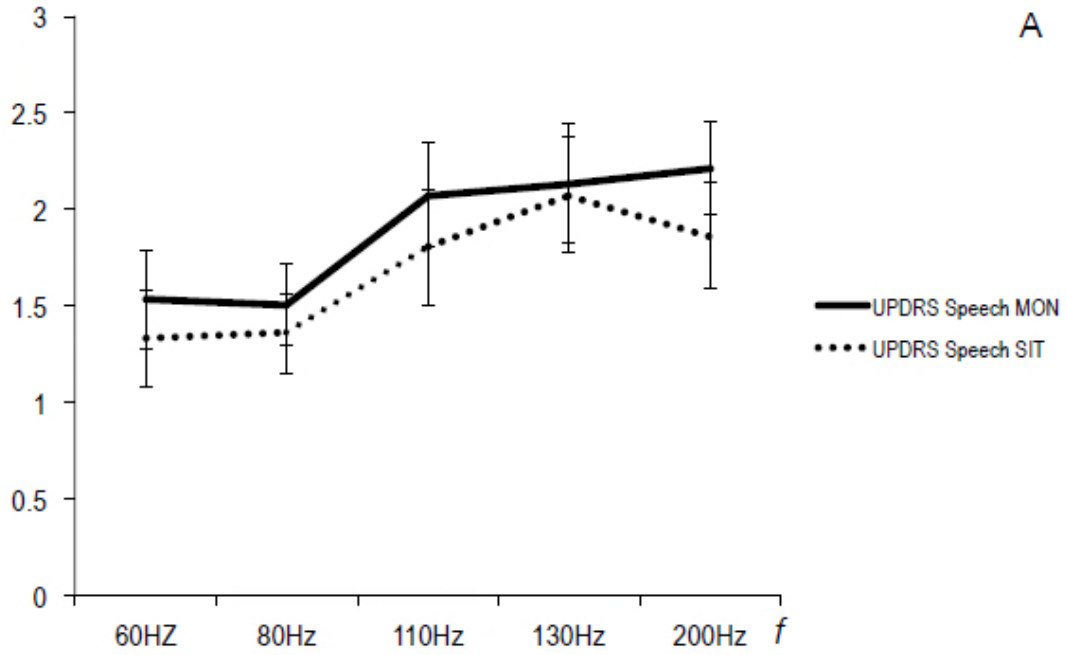

Figure 1B. Total Darley, Aronson and Brown rating of SIT sentences (SITDAB) and Darley, Aronson and Brown rating of minute monologue (MONDAB) scores for different DBS frequencies (60, 80, 110, 130 and 200 Hz,) are presented. Error bars represent standard errors of the mean.

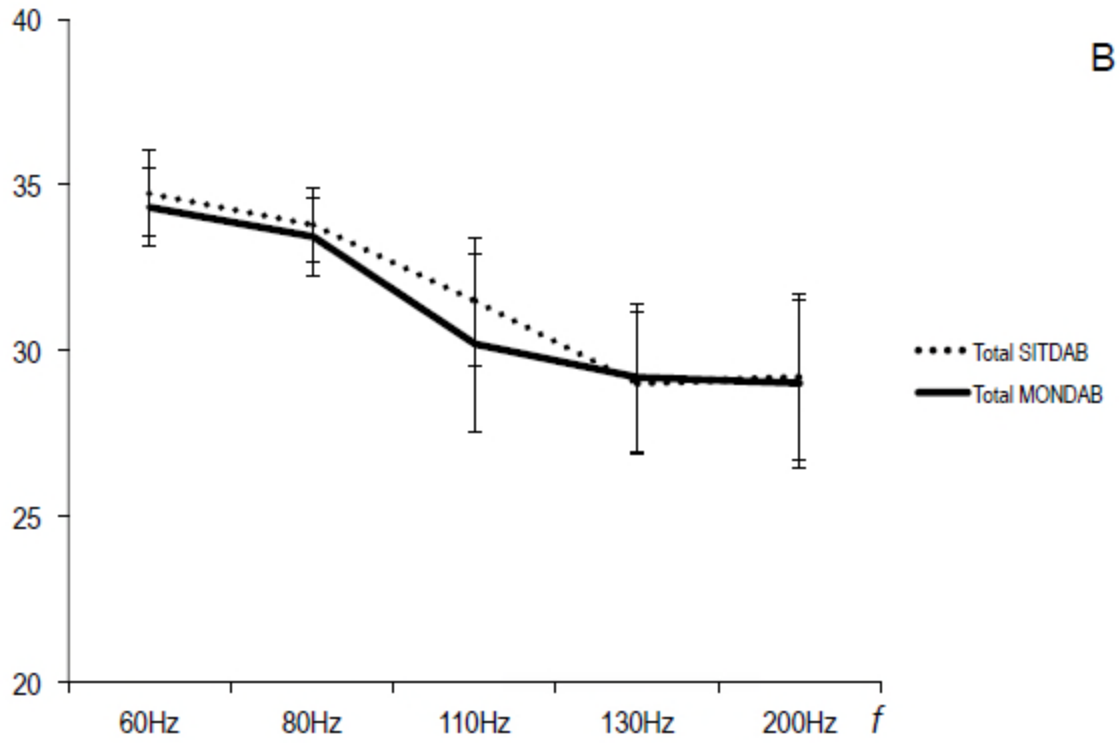

Table 1. Baseline stimulation parameters of the patients included in the study.

(f = frequency of stimulation, AC = active contact, PW = pulse width, µs = microseconds, V = volt).

	f (Hz)	Left STN AC	Right STN AC	PW (µs)	Voltage Left STN (V)	Voltage Right STN (V)

P1	80	2-	6-	60	2.80	2.80
P2	80	1-2-	4-	60	5.00	4.40
P3	130	1-2-	4-5-	60	4.50	4.50
P4	80	0-1-	8-9-	60	2.30	3.00
P5	80	1-	5-	60	3.60	3.40
P6	80	1-	5-	60	4.50	4.00
P7	80	1-2-	6-7-	60	4.20	4.00
P8	80	1-	5-	60	4.30	2.70
P9	130	2-	3-	60	0.70	2.95
P10	80	1-2-	10-	60	3.65	4.25
P11	130	1-	9-	60	1.90	1.95
P12	130	1-	9-	60	3.10	2.20
P13	130	1-	9-	60	2.40	2.20
P14	80	2-	5-	60	3.60	3.70
P15	80	1-	5-	60	4.00	3.00

Table 2. SITDAB and MOTDAB mean scores ± standard deviation for different stimulation frequencies (60, 80, 110, 130, 200 Hz) and *p*-values (after Bonferonni correction for multiple comparisons) for different aspects of speech intelligibility. Significant results are written in **bold**.

	60 Hz	80 Hz	110 Hz	130 Hz	200 Hz	*p*

SITDAB						
Articulation	**5.53±1.06**	5.42±1.05	4.73±1.53	4.13±1.73	**4.29±1.81**	**.005**
Respiration	5.67±1.18	5.60±1.12	5.07±1.49	4.93±1.39	4.86±1.66	.066
Resonance	6.33±0.81	6.27±0.96	6.00±1.13	5.80±1.42	5.71±1.89	.349
Phonation	**5.40±1.12**	5.03±1.20	4.80±1.47	4.33±1.49	**2.29±1.54**	**.002**
Prosody	**5.67±0.97**	5.40±1.06	5.20±1.42	4.80±1.66	**4.86±1.83**	**.035**
Rate	6.40±0.74	6.33±0.72	5.87±1.30	5.60±1.68	5.64±1.87	**.039**
MONDAB						
Articulation	**5.67±1.04**	5.43±1.39	4.80±1.94	4.13±1.85	**4.29±1.85**	**.001**
Respiration	**5.60±0.98**	5.29±1.07	4.93±1.94	4.67±1.79	**4.50±1.61**	**.028**
Resonance	6.47±0.74	6.50±0.76	5.73±1.94	5.80±1.61	5.79±1.93	.109
Phonation	**5.20±1.15**	**5.00±0.96**	4.53±1.66	4.40±1.35	**4.29±1.64**	**.017**
Prosody	**5.60±0.74**	5.43±1.09	5.13±1.87	4.87±1.55	**4.93±1.69**	**.037**
Rate	6.13±0.73	6.14±0.95	5.53±2.03	5.60±1.59	5.64±1.86	.242

Table 3. Pearsons correlation coefficients (r) of Time Since Implantation (TSI) to *Artic* (articulation), *Resp* (respiration), *Reson* (resonance), *Phon* (phonology), *Prosod* (prosody) and *Rate* (rate) for 60, 80, 110, 130 and 200 Hz for Darley, Aronson and Brown rating of minute monologue (MONDAB) and Darley, Aronson and Brown rating of SIT sentences (SITDAB). Statistically significant results ($p \leq .05$) are marked in **bold**.

MONDAB		*TSI*	*Artic60*	*Artic80*	*Artic110*	*Artic130*	*Artic200*	*Resp60*	*Resp80*	*Resp110*	*Resp130*	*Resp200*
r	*TSI*	1	-0.482	-0.484	-0.495	-0.609	-0.57	-0.213	-0.19	-0.321	-0.42	-0.434
Sig. (1-tailed)		.	**.048**	**.047**	**.043**	**.014**	**.021**	.242	.267	.143	.076	.069
SITDAB												
r	*TSI*	1	-0.509	-0.537	-0.595	-0.666	-0.548	-0.149	-0.169	-0.332	-0.403	-0.171
Sig. (1-tailed)		.	**.032**	**.024**	**.012**	**.005**	**.021**	.306	.282	.123	.077	.280

MONDAB		*TSI*	*Reson60*	*Reson80*	*Reson110*	*Reson130*	*Reson200*	*Phon60*	*Phon80*	*Phon110*	*Phon130*	*Phon200*
r	*TSI*	1	-0.169	-0.108	-0.36	-0.324	-0.368	-0.556	-0.615	-0.237	-0.501	-0.274
Sig. (1-tailed)		.	.291	.363	.114	.14	.108	**.024**	**.013**	.218	**.041**	.182
SITDAB												
r	*TSI*	1	-0.157	0.025	-0.364	-0.291	-0.287	-0.484	-0.434	-0.264	-0.482	-0.07
Sig. (1-tailed)		.	.296	.467	0.100	.156	.160	**.040**	.061	.181	**.040**	.405

MONDAB		*TSI*	*Prosod60*	*Prosod80*	*Prosod110*	*Prosod130*	*Prosod200*	*Rate60*	*Rate80*	*Rate110*	*Rate130*	*Rate200*
r	*TSI*	1	-0.628	-0.704	-0.43	-0.487	-0.441	-0.380	-0.452	-0.45	-0.476	-0.42
Sig. (1-tailed)		.	**.011**	**.004**	.071	**.046**	.066	0.100	.061	.061	**.050**	.077
SITDAB												
r	*TSI*	1	-0.702	-0.613	-0.514	-0.513	-0.546	-0.327	-0.409	-0.506	-0.517	-0.255
Sig. (1-tailed)		.	**.003**	**.010**	**.030**	**.030**	**.022**	.127	.073	**.032**	**.029**	.189

Table 4. Phonemic and semantic fluency total number, cluster size, and switching score mean values ± standard deviations and *p*-values (after Bonferonni correction for multiple comparisons) for different frequencies (60, 80, 110, 130, 200 Hz) are presented. Significant results are presented in **bold.**

	60 Hz	80 Hz	110 Hz	130 Hz	200 Hz	*p*

Phonemic fluency						
Total number	33.40±14.58	30.33±13.08	33.00±15.09	34.67±15.54	28.07±13.14	.171
Cluster size	1.40±0.57	1.40±0.42	1.67±0.92	1.56±0.81	1.77±0.77	.842
Switching score	26.13±9.79	22.27±7.58	21.93±8.71	19.07±9.66	17.43±8.38	**.005**
Semantic fluency						
Total number	11.40±6.23	12.33±4.42	14.07±6.34	11.20±5.96	11.36±5.05	.069
Cluster size	2.02±1.17	1.79±0.99	1.85±1.36	1.69±1.86	1.65±1.14	.989
Switching score	4.53±3.52	6.27±3.92	8.00±6.02	5.33±3.89	6.14±3.76	.146