Critical Review: Can sub-thalamic deep brain stimulation (STN-DBS) improve speech output in patients with Parkinson's Disease?

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This critical review examined the effects of subthalamic deep brain stimulation (STN –DBS) on speech in patients with Parkinson's disease. Study designs included: systematic reviews, randomized controlled trials, quasi-experimental designs, experimental designs, case studies, and cohort studies. Overall, research supports the effectiveness of STN-DBS in reducing motor symptoms associated with PD but strong evidence for its benefits on speech is lacking. Further optimization of the DBS system for speech is needed and further large scale studies in this area are warranted.

Introduction

Marsden (1994) defines Parkinson's Disease (PD) as "a progressive degeneration of dopamine producing cells in the substantia nigra, resulting in increased inhibitory output of the basal ganglia (BG) to the thalamus and the brainstem locomotive center." The subthalamic nucleus (STN) provides excitatory input to the BG, which in turn increases the inhibitory output of the BG to the thalamus, consequently resulting in more inhibition of the motor cortex. These changes in neural activity ultimately translate into disturbances in gait and facial expression, postural instability, akinesia, bradykinesia, rhythmic tremors, and rigidity of movement, which are the hallmarks of PD. In addition to the aforementioned characteristics, disturbances in speech and swallowing can also result and often co-occur in PD. Speech symptoms can include reduced perceptual loudness (hypophonia), a change in voice quality (i.e., breathiness, harshness, or tremor), monopitch, monoloudness, reduced stress, rapid speech rate, short rushes of speech, imprecise consonants, inappropriate silences, and reduced intelligibility overall (Duffy, 2005 p.189; pp.194-198).

Deep Brain Stimulation (DBS) has been documented in the literature to be a relatively recent and successful method of managing the overall gross motor symptoms associated with PD. The National Institute of Neurological Disorders and Stroke (NINDS) describes DBS as "a surgically implanted, battery operated device called a neurostimulator---similar to a heart pacemaker and approximately the size of a stopwatch---that delivers electrical stimulation to targeted areas of the brain that control movement, blocking the abnormal nerve signals that cause tremor and PD symptoms." The targeted areas of the brain for PD are usually the thalamus, subthalamic nucleus, and globus pallidus (NINDS deep brain stimulation for PD, 2006).

There are different parameter settings on the neurostimulator that can be adjusted to optimize treatment by changing the polarity, amplitude, pulse width, and frequency of the stimulation. Simply stated, these electrical pulses interfere with and block the neurotransmitter signals that cause the PD symptoms.

While there are a large number of reports describing the effectiveness of STN-DBS in reducing most motor symptoms associated with PD (i.e., tremors, rigidity, akinesia, and postural instability), the number of studies examining the effects of STN-DBS on the speech symptoms is limited (Hamani et al., 2005; Dromey et al., 2000).

Objectives

The primary objective of this paper was to outline and critically evaluate a few selected studies that have examined the effects of STN-DBS on the various speech characteristics of patients with PD. A secondary objective was to evaluate information related to what brain sites (left or right STN; lateral or ventral STN stimulation) are most effective in reducing speech symptoms associated with PD.

Methods

Search Strategy

Computerized databases, including PubMed, CINAHL, JNNP (online), Science Direct, CommDisDOME, PsycINFO, and the University libraries search engine were searched using the following search strategy:

(Parkinson's Disease) AND (Effects of Sub-thalamic Deep Brain Stimulation) AND (Speech).

This yielded very few results so my search strategy was then modified to:

(Parkinson's Disease) AND (Deep Brain Stimulation).

The search was limited to English language and journal articles or reviews.

Selection Criteria

Studies included in this critical review were required to examine the effects of subthalamic deep brain stimulation (STN-DBS) on speech in patients with Parkinson's disease. All patients studied suffered from levodopa-responsive PD. No limits were set on the demographics (age, gender, culture, race, or socioeconomic status) of research participants, type of speech parameter(s) (e.g., vocal intensity, intelligibility, intonation, respiration, phonation, etc.) investigated, nor on whether the authors looked at unilateral or bilateral stimulation, or both. Studies included those conducted in North America, as well as those conducted in Europe and Australia. Care was taken to ensure that those studies selected for this critical review were not duplicates or re-publications of one another.

Data Collection

Results of the literature search yielded seven (7) articles consistent with the selection criteria: 1 systematic review, 1 case study, 1 pre and post measure cohort study, 1 experimental design, 2 randomized controlled clinical trials, and 1 quasi-experimental design.

Results

Quasi-Experimental Designs

Gentil et al. (2003) quantitatively assessed various components of speech (i.e., articulation, phonation, and respiration) in 16 PD patients following bilateral stereotactic electrode implantation into each STN.

Force of the lips and tongue and the acoustic speech signal were measured under 2 conditions: during bilateral STN stimulation and 30 minutes after stopping stimulation. Speech tasks included: (1) sustained /a/ and /i/ vowels; (2) repetition of the phrase "Le petit chat joue avec la balle" without stopping for 30 seconds; (3) production of short sentences at a conversational speaking rate; and (4) repetition of nonsense words as fast as possible 10 times. In each condition, the motor disability of the patients was qualitatively assessed using the Unified Parkinson's Disease Rating Scale (UPDRS), and speech was estimated with item 18 of the UPDRS.

T-tests ($p < 0.01$) indicated significantly larger maximal forces of the upper lip, lower lip, and tongue in stimulated patients. The global motor UPDRS scores improved by 30-95% following stimulation, in the OFF-medication condition. The median speech score on item 18 of the UPDRS also improved from 2 before STN stimulation to 1 after STN stimulation (0-4 point scale). The authors also report that the ON-condition was associated with a longer maximal phonation time, shorter duration of the nonsense word /pataka/, and shorter pause durations, as well as a larger relative intensity. Fewer irregular changes in the f0 contours were found during the ON condition as indicated by a smaller coefficient of variability, and a weaker jitter factor. Analysis of relative intensity failed to reveal significant differences.

Pre-operative speech measures were not recorded and therefore do not allow comparison to baseline conditions. Individual scores were not provided and means and statistical results for maximal phonation time and pause duration were not reported.

Cohort study

Dromey et al. (2000) investigated the effects of STN-DBS on acoustic measures of voice in seven patients with PD who had been implanted with chronic STN-DBS circuits bilaterally. The authors report the pre-surgery and 6 month follow-up data for the seven patients.

UPDRS ratings were obtained in the OFF-medication, OFF-stimulation state. Speech recordings were made before surgery, in both the OFF-medication and ON-medication states. Patients produced sustained vowel phonation and gave a 30 second monologue on their topic of choice.

Mean and standard deviation of the fundamental frequency, speech intensity, and sustained vowels were analyzed with the Multi Dimensional Voice Program for the acoustic analysis of phonation. The Wilcoxon signed ranks test was used to compare performance across conditions. Intrameasurer reliability was calculated (0.9987 to 0.9997).

The stimulation effects on speech variables were limited to modest significant increases in vocal intensity and in fundamental frequency variability in the ON-medication condition for the monologue task. Pre-surgery and post-surgery OFF-medication and OFF-stimulation results were compared and no significant changes were found, thus controlling for micro lesion effects. The authors acknowledge that despite reaching statistically significant findings, the overall impact of these speech changes are not substantial and would not represent a functionally useful change in speech performance.

Case-study

Hoffman-Ruddy et al. (2001) looked at the effects of bilateral STN-DBS on voice and speech characteristics in a single male PD patient who had been living with PD symptoms for seven years.

The test protocol consisted of four conditions: (1) OFF-stimulation, OFF-medication; (2) ON-stimulation, OFF-medication; (3) OFF-stimulation, ON-medication; and (4) ON-stimulation, ON-medication. Clinical ratings were performed on the basis of the Unified Parkinson Disease Rating Scale (UPDRS) by a team of neurologists and an additional protocol for voice and speech measures was administered by a licensed speech language pathologist.

Phonatory tasks included three repetitions of maximum sustained vowel phonations, pitch glides, syllable repetition, short consonant-vowel-consonant (CVC) words and oral reading of a standardized passage. All recordings were analyzed using a Computerized Speech Lab (CSL) and Multi-Dimensional Voice Program (MDVP).

The most positive results occurred in the ON-stimulation, ON-medication condition across all speech parameters. The next most positive change occurred in the ON-stimulation, OFF-medication condition. The OFF-stimulation conditions produced the least amount of positive results. The results for standard deviation of VOT revealed the most dramatic change with an average standard deviation of 77ms for the /k/ phoneme in the OFF-stimulation, OFF-medication condition to an average standard deviation of 4ms in the ON-stimulation, ON-medication condition. The neurologists' clinical rating of motor disability for the ON-stimulation, ON-medication condition revealed only a mild speech impairment that resolved when the participant increased effort, and mild or no impairments in various motor symptoms.

Results of this study suggest that STN-DBS stimulation may be beneficial in reducing speech symptoms associated with PD, when combined with Parkinson medication. Pre-surgery motor and speech scores were not reported; therefore results cannot be compared to a baseline score. The results of this study need to be interpreted with caution, as they may only generalize to patients symptomatically similar to the one included in this study.

Experimental Design

Wang et al. (2003) investigated the effect of unilateral stimulation of the STN on respiratory and phonatory subsystems of speech production in six right-handed PD patients with mild to moderate dysarthria. Three patients received implantation of the STN-DBS stimulator in the right STN, and three in the left STN. Speech recordings were made in the OFF-medication state at baseline pre-surgery, and three months post-surgery with and without stimulation. Evaluators and patients were blinded to the stimulator conditions until after the data were analyzed. Tasks included six maximally sustained vowel phonations (MSVP), three diadokinetic rates, reading sentences with varying stress, and a structured monologue. Performance on non-speech motor tasks was rated by a movement disorder neurologist, using the motor section of the UPDRS-III.

A mixed two-factor analysis of variance with repeated measures was used to assess the significance of the changes in both, non-speech motor and speech tasks. The alpha level of 0.05 was used for all tests except for the post-hoc tests. Group means were reported.

STN-DBS significantly improved the UPDRS-III scores regardless of the side of stimulation. The post-hoc comparisons by the Scheffe test indicated that all pairwise comparisons were significant. There was a reduction in the UPDRS-III scores in the OFF-stimulation condition as well, which may possibly be due to a micro lesion effect. A significant improvement in the respiratory/phonatory subsystems of speech (intensity and duration) was only observed in right-sided STN stimulation. Left-sided stimulation actually worsened voice quality when comparing to the baseline condition. Furthermore, small increases in the performance in these measures were observed for the right STN and further losses were observed for the left STN in the OFF-stimulation condition, suggesting more evidence for micro lesion effects. There were no consistent changes in f0 associated with the DBS in either side of the STN across the three testing conditions. There was no indication of controlling for gender differences in f0.

Randomized Control Clinical Trials

Santens et al. (2003) analyzed the effects of left and right STN stimulation separately on different aspects of speech in seven PD patients who had been implanted with a bilateral STN-DBS system.

In all patients, STN stimulation resulted in a substantial reduction of motor symptoms and a total disappearance of dyskinesia. Levodopa dosage was reduced in all patients.

The speech evaluation consisted of the patients' performance on two tasks: 1) a 200 word reading passage, and 2) sustained "ah" vowel phonation in four different STN stimulation conditions: (1) left ON, right OFF; (2) right ON, left OFF; (3) bilateral stimulation OFF; and (4) bilateral stimulation ON. The four conditions were randomized within patients to avoid order effects. All speech samples were videorecorded and randomized for further analysis. Each videotaped reading passage was subjectively rated (VAS) on six different aspects of speech production in a single session by 22 qualified SLPs, who were blinded for the respective stimulator conditions.

Inter-rater reliability was calculated using Chronbach's α test, ranging from 0.86 to 0.97, which is acceptable. Effects of stimulation conditions on different characteristics were estimated using Friedman's non-parametric testing for related samples. Post-hoc Wilcoxon signed ranks test were performed. For all statistical analyses, a p-value of less than .05 was considered significant.

Results of this study indicate that speech is differentially affected by left and right STN stimulation. Right STN stimulation had little effect compared to bilateral stimulation OFF, irrespective of the status of the left-sided stimulation. There were no significant differences in speech characteristics when comparing bilateral stimulation OFF with bilateral stimulation ON. Selective stimulation of the left STN had a significant negative effect, especially on prosody, when compared to bilateral stimulation OFF. Duration of the maximal phonation time of the "ah" vowel did not differ significantly between the four stimulation conditions.

Limitations include the use of subjective ratings, lack of intra-rater reliability measurement, and videotaped samples, which are not necessarily representative of the true real-time sample and may have created learning effects if they were played more than once. Visual cues such as lip-reading also may have aided interpretation of the samples and could have resulted in have an overall inflated intelligibility rating.

Tornqvist et al. (2005) were the first to examine the effects of different electrical parameter settings on the intelligibility of speech in ten PD patients treated with bilateral STN-DBS stimulation.

The speech recordings were done with 11 different parameter settings in random order for each patient, following withdrawal of all anti-parkinsonian drugs. For each parameter setting, the patients were required to read a standard running text in Swedish and then five syntactically correct nonsense sentences originating from the dysarthria test described by Lillvik and collegues. The coded speech recordings were copied to another mini-disc in random order, mixing both, patients and test situations and played through free-field loudspeakers. A randomly selected listener panel blinded for the conditions and patient numbers were required to orthographically transcribe the words in the nonsense sentences and evaluate the overall intelligibility, precision of articulation, and quality of voice for all readings using a 10cm (0-10) visual analog scale (VAS). Rate of speech was calculated as syllables per second from the readings of the standard running text, using the automatic time counter of the mini-disc recorder.

Intra and inter-rater reliability of the judges were calculated with the Spearman rank correlation coefficient ($r > 0.75$). For each patient and each tested parameter setting, the mean value of the 10 listeners' evaluations was calculated for further statistical analysis ($p < 0.05$; $r > 0.70$).

Results indicated that different parameter settings can affect the intelligibility of speech. High amplitudes and high frequencies tended to negatively affect speech. The rate of speech was unaffected by the different parameter settings tested. The VAS assessments of overall intelligibility and articulation also tended to worsen with stimulation-ON using the patients' normal parameter settings, compared with the stimulation-OFF condition. Patients judged their speech as divergent from normal with all parameter settings (including DBS-off) when asked to self-evaluate their speech for each parameter setting.

This study included 3 patients who had previously been treated with PD ablation surgery and possible microlesion effects from these surgeries were not controlled for. The quality of the speech recordings may be questionable as a 20 to 80cm distance between the mouth and microphone is quite variable and can affect the intensity of the speech signal. Lastly, a patient selection criterion on the basis of self-perceived speech disturbances does not represent a random sample from the PD population.

<u>Systematic Review</u>

Hamani et al. (2005) conducted a systematic review on the effects of bilateral STN-DBS stimulation for Parkinson's disease. The outcomes for a total of 471 patients with PD who had been treated with bilateral STN-DBS were assessed according to the UPDRS in ON-medication and OFF-medication conditions.

The statistical analysis included tabulating the mean values and standard deviations from each published study. UPDRS motor scores improved consistently in the OFF-medication condition at 6 months, 12 months, 2 year, 5 year follow-ups compared with pre-operative OFF-medication scores. The ON-medication, ON-stimulation condition produced the most significant improvement in UPDRS motor scores when compared with pre-surgery OFF-medication sub-scores. ON-medication dyskinesias were reduced by 94% after 12 months of stimulation. L-dopa intake was reduced by 52% following 12 months of stimulation.

There were mild to moderate adverse effects of stimulation and a 1% to 2% incidence of severe adverse effects of stimulation resulting in death or permanent neurological deficits.

Hypophonia occurred as a side effect of stimulation in 5.8% of patients and dysarthria scores were not quantified by most studies included in this review. The authors identify weaknesses in the literature including a large number of open label studies, small, non-standardized case reports, data corruption, and a high number of duplicate publications.

This article provides support for the benefits of STN-DBS in reducing the motor symptoms associated with PD but strong statistical evidence is lacking and speech is not specifically addressed. This article also demonstrates that adverse effects can occur in a substantial number of patients and the need for further optimization of the procedure to reduce adverse effects is warranted.

Discussion

The results of these studies need to be interpreted with caution as all deal with small sample sizes and many provide conflicting reports as to how effective the DBS-STN system is for speech in Parkinson's patients. While the motor benefit of the system is widely reported, the benefits on speech have yet to reach a consensus in the literature. Part of the discrepancy in the findings may be related to the patient selection criteria. Those studies demonstrating a positive effect of STN-DBS stimulation on speech often selected participants on the basis of a significant speech impairment (Gentil et al, 2003; Hoffman-Ruddy et al., 2001). Also, the fact that STN-DBS stimulation actually led to adverse effects on speech in some patients (Hamani et al., 2005; Dromey et al., 2000; Santens et al., 2003) is an important finding for SLPs working with this population. The study by Tornqvist et al. (2005) indicates the need for additional studies to investigate the precise stimulation parameters needed to optimize speech while still allowing for a substantial reduction of motor symptoms in PD.

The studies by Santens et al. (2003) and Wang et al., (2003) provide insight into the neural substrates modulating speech and language and how speech is differentially affected by left versus right stimulation of the STN. Indeed, most studies have suggested that bilateral stimulation of the STN is optimal for speech, but additional studies comparing unilateral and bilateral procedures are required.

The discrepancy in findings between speech and motor benefits has led some researchers to hypothesize that differently modulated pathways are involved in the regulation of speech and limb control (Santens et al., 2003). Further knowledge of the neural substrates that modulate speech should lead to an optimization of speech and limb treatment for deficits while minimizing adverse effects of stimulation.

Recommendations

Further well-controlled empirical studies examining the precise effects of STN-DBS on speech in a larger number of randomized Parkinson's patients using both quantitative and qualitative measurement tools are needed. More longitudinal studies are needed to investigate the long-term effects of STN-DBS in the later stages of the disease.

Future research should consider:

- different sites within the STN;
- evaluating the effect of STN-DBS on spontaneous conversational speech ;
- the stage of the disease;
- determining the frequency settings that are optimal for the treatment of speech symptoms.

Subthalamic DBS for Parkinson's disease is still a relatively new treatment and perhaps we will better understand its effects on speech in Parkinson's patients as it becomes more widely used.

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