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A Non-Invasive Imaging Approach to Understanding Speech Changes following Deep Brain Stimulation in Parkinson's Disease

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Abstract

Purpose—To explore the use of non-invasive functional imaging and "virtual" lesion techniques to study the neural mechanisms underlying motor speech disorders in Parkinson's disease. Here, we report the use of Positron Emission Tomography (PET) and transcranial magnetic stimulation (TMS) to explain exacerbated speech impairment following subthalamic nucleus deep brain stimulation (STN-DBS) in a patient with Parkinson's disease.

Method—Perceptual and acoustic speech measures as well as cerebral blood flow (CBF) during speech as measured by PET were obtained with STN-DBS on and off. TMS was applied to a region in the speech motor network found to be abnormally active during DBS. Speech disruption by TMS was compared both perceptually and acoustically with that resulting from DBS on.

Results—Speech production was perceptually inferior and acoustically less contrastive during left STN stimulation compared to no stimulation. Increased neural activity in left dorsal premotor cortex (PMd) was observed during DBS on. "Virtual" lesioning of this region resulted in speech characterized by decreased speech segment duration, increased pause duration, and decreased intelligibility.

Conclusions—This case report provides evidence that impaired speech production accompanying STN-DBS may be resulting from unintended activation of PMd. Clinical application of functional imaging and TMS may lead to optimizing the delivery of STN-DBS to improve outcomes for speech production as well as general motor abilities.

The primary aim of this clinical forum is to explore the role of modern, noninvasive, multimodality brain imaging in understanding motor speech disorders and demonstrate their

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utility by presenting a brain imaging case study of one patient with Parkinson's disease who underwent deep brain stimulation (DBS) of the subthalamic nucleus (STN). As with many individuals with Parkinson's disease and STN-DBS, stimulation in this patient resulted in speech deterioration while limb function improved (Pinto, Ozsancak, et al., 2004). We use this case as a proof-of-principle experiment that utilizes brain imaging to inform a clinical problem. We first present a brief literature review of DBS, including its mechanism of action and effects on speech in Parkinson's disease as well as a recently developed technique used in studying brain function, transcranial magnetic stimulation (TMS). Then we provide data from this case study of the speech changes associated with STN-DBS, as well as application of imaging technique to better understand the underlying reasons for such a change. Finally, we offer interpretation of the findings in this case and a more general discussion of how imaging may guide clinical decision-making and the development of new treatment approaches.

Literature Review: DBS and Parkinson's disease

Speech symptoms

Speech symptoms typically found in Parkinson's disease include voice problems (e.g. hypophonia), imprecise articulation, impaired intelligibility, and disrupted prosody (Duffy, 2005; Ramig, Fox, & Sapir, 2004). While levodopa is widely used in the pharmacologic treatment of Parkinson's disease to restore the balance of dopamine in the basal ganglia and reduce Parkinsonian symptoms, its effect on speech is mixed (Pinto, Ozsancak, et al., 2004). It has been shown to initially improve articulation and voice quality while phonatory parameters remain unchanged (Pinto, Ozsancak, et al., 2004). In a recent study, levodopa has been shown to increase the rate and intensity of speech parallel with limb movements in patients with Parkinson's disease (Ho, Bradshaw, & Lansek, 2008). However, these patients could not maintain speech intensity over the breath span while on levodopa. In a study examining handwriting and speech changes across the levodopa cycle in patients with Parkinson's disease, improvements were found only in handwriting but no changes were observed in speech across the medication cycle (Poluha, Teulings, & Brookshire, 1998). Over time, many individuals with Parkinson's disease develop levodopa-induced dyskinesias (LIDs), including uncontrolled choreiform movements.

Surgical interventions

Various surgical interventions are performed to alleviate the symptoms of Parkinson's disease as well as the unwanted side effects of pharmacological treatment (e.g., hyperkinesias). Among them, thalamotomy and pallidotomy (specifically globus pallidus) are common techniques (Schulz, Greer & Friedman, 2000; Scott et al., 1998). While limb motor function has been shown to improve following these surgical treatments, their effects on speech have been variable. Most patients continue to experience speech disorders post-operatively with only those with mild dysarthria showing significant improvements (Schulz et al., 2000; Schulz, Peterson, Sapienza, Greer, & Friedman, 1999; Scott et al., 1998). There are also reports of post-operative cognitive/linguistic deficits such as decreased verbal fluency that may further complicate the assessment of the speech motor system in these patients (Scott et al., 1998; Witjas et al., 2007). Deep brain stimulation of thalamus or pallidum has also been performed to alleviate symptoms of Parkinson's disease. Similar to dopaminergic replacement and surgical therapies, these procedures improve limb function but result in no improvement or worsening of speech (Pinto, Ozsancak, et al., 2004).

Deep brain stimulation

Recently, STN-DBS has emerged as a viable and common treatment for Parkinson's disease when drug therapies result in unacceptable side effects (Kleiner-Fisman et al., 2006). DBS is thought to act as a reversible and adjustable lesion to the targeted region (Obeso et al., 2000),

allowing for fine-tuning of settings to achieve the optimal outcome with regard to motor function (Moro, Poon, Lozano, Saint-Cyr, & Lang, 2006). To date, it is estimated that over 35,000 patients with Parkinson's disease have been implanted with STN-DBS worldwide (Benabid, Deuschl, Lang, Lyons, & Rezai, 2006; Kleiner-Fisman et al., 2006). In addition to treating the general motor symptoms of Parkinson's disease, STN-DBS has been found to ameliorate the drug related dyskinesias and motor fluctuations (Baron et al., 1996; Kumar, Lozano, Montgomery, & Lang, 1998). A meta-analysis of 22 studies of STN-DBS in Parkinson's disease found >50% improvement on the Unified Parkinson's Disease Rating Scale (UPDRS; Fahn et al., 1987) and of motor function and activities of daily living, and 69% reduction in dyskinesias (Kleiner-Fisman et al., 2006).

Although general motor function and dyskinesia in patients with Parkinson's disease improve following STN-DBS, motor speech abilities often do not respond or respond negatively to this treatment (D'Alatri et al., 2008; Pinto, Ozsancak, et al., 2004). Increased severity of speech impairment is reported as one of the most common side effects of this procedure. Reports of new or worsened dysarthria ranges widely from 5% (Krack et al., 2003), 20%, (Rodriguez-Oroz et al., 2005), 53%, (Gan et al., 2007) and up to 61% of implanted patients (Guehl et al., 2006). Specific motor speech symptoms associated with STN-DBS include decreases in speech intelligibility (Rousseaux et al., 2004), difficulty with speech initiation (Moretti et al., 2003) and greater impairment in prosody, articulation, and intelligibility (Santens, De Letter, Van Borsel, De Reuck, & Caemaert, 2003) in the presence of improved limb and body movements. The groups led by Gan (2007), Krack (2003), and Rodriguez-Oroz (2005) found that speech with STN-DBS declined or remained unchanged when assessed during on-medication cycles at follow-up sessions one year or more after implantation.

Unfortunately, speech performance measures in many studies have limitations. These include limited perceptual rating of speech (only a single perceptual dimension on UPDRS– item 18), and failure to assess speech with stimulation on *and* off (Gan et al., 2007; Krack et al., 2003; Rodriguez-Oroz et al., 2005) or assessment of speech during on-medication cycles as well as off-medication (Gentil, Chauvin, Pinto, Pollak, & Benabid, 2001; Gentil, Garcia-Ruiz, Pollak, & Benabid, 1999, 2000; Gentil, Pinto, Pollak, & Benabid, 2003). In these studies, the comparison measures for DBS off consisted of pre-surgical baseline performance measures, and therefore are confounded by possible variations due to disease progression or potential microlesions resulting from the surgical procedure.

There are reports of overall improvement in speech performance with DBS on compared to off in a series of four studies (during off-medication cycle only; Gentil et al., 1999, 2000, 2001, 2003). These researchers found speech improvements as measured with UPDRS Item 18 (perceptual rating of speech impairment), as well as changes in acoustic measures of voice with DBS on (e.g. increased vowel duration and pitch variation; Gentil et al., 2001). Finally, increased oral force measures also have been associated with DBS stimulation (Gentil et al., 1999, 2003).

Although these studies show that some improvements are possible in speech subsystems related to STN stimulation, the lack of measures during on-medication cycles precludes generalization to typical speaking situations in patients with Parkinson's disease, who generally continue dopaminergic replacement therapy along with STN stimulation for optimal clinical benefit. Furthermore, while the inclusion of quantitative measures (e.g. F0 variation and maximal phonation duration) are steps in the right direction for studies of speech with STN-DBS, oral force measures and the single dimension perceptual rating scale from the UPDRS provide little information about the nature of the functional speech deficit in speakers with Parkinson's disease and STN-DBS.

Existing studies examining speech effects of STN-DBS in Parkinson's disease highlight the need for more comprehensive measures of speech performance, including detailed multidimensional perceptual ratings as well as quantitative measures of acoustic parameters of speech production. One of the goals of the present work was to provide a more detailed picture of the speech consequences of STN-DBS. We used Darley, Aronson, and Brown's (1975) classical rating scheme with 38 perceptual dimensions of speech and voice characteristics, in addition to acoustic measures shown to be sensitive to speech characteristics in hypokinetic dysarthria secondary to Parkinson's disease (Rosen, Kent, Delaney, & Duffy, 2006). A clearer understanding of the nature of speech deficit in this population will help in making clinical decisions to improve functional outcomes.

Potential neural mechanisms

The neural mechanisms underlying the differential response of limb and body versus speech function in patients with Parkinson's disease who receive STN-DBS are not yet understood. Hypotheses include variations in electrode placement or an inadequate recruitment of surrounding neural structures and possible existence of separate motor programs for limbs and speech (Pinto, Thobois, et al., 2004). Farrell and colleagues (2005) hypothesized that the differences in speech response to DBS might relate to different innervation patterns in which cranial nuclei for laryngeal systems receive bilateral cortical input as opposed to primarily unilateral innervation of the limbs. In contrast to the dopaminergic imbalance that results in limb symptoms, a non-dopaminergic origin of speech disorder in Parkinson's disease has also been proposed (D'Alatri et al., 2008). This difference has been attributed as a reason for the differences in speech and limb motor response to levodopa and DBS treatments in Parkinson's disease (D'Alatri et al., 2008). Another interesting observation has been the differential effect of left and right-sided DBS on speech. Articulatory accuracy and syllable rates have been shown to decrease with active left STN stimulation when compared to pre-surgical measurements. Conversely, STN stimulation on the right side resulted in improved or no change in these speech parameters (Wang, Metman, Bakay, Arzbaecher & Bernard, 2003; Wang et al., 2006). These authors propose that motor asymmetry, that is, more damaged basal ganglia in the language dominant hemisphere (left hemisphere in 98% of population) may result in worse speech outcome in Parkinson's disease. It is important to further examine the causes of any differential effects on speech, especially if speech deterioration following STN-DBS can be minimized or avoided altogether.

One way to gain an understanding of the mechanisms of action of motor and speech responses (positive or negative) to STN-DBS is to use non-invasive imaging to quantify the neurobiology of stimulation effects. While there are a few imaging studies examining the effect of STN-DBS on limb and executive functions (Asanuma et al., 2006; Carbon & Eidelberg, 2006; Trošt et al., 2006), there has been only one such study examining speech following STN-DBS (Pinto, Thobois, et al., 2004). We examined the neural mechanisms underlying the decreased capacity for speech production following STN-DBS in a single case by using Positron Emission Tomography (PET) and extended the investigation to include a "'virtual lesion"' study using TMS.

Imaging Techniques: An Overview

Of the many different approaches to brain imaging, some techniques focus on functional activity in the brain (e.g., PET), and others emphasize brain anatomy (structural imaging) such as magnetic resonance imaging (MRI). Here, PET was used to assess regional brain activity associated with STN stimulation. Specifically, while STN-DBS is intended to target the subthalamic nucleus, PET imaging was used to determine which brain regions were *actually* active during DBS stimulation. Anatomical MRI acquired prior to DBS implantation was used to register PET images and target TMS. For more details about imaging brain function with

PET and MRI the readers are referred to Cherry and Phelps (2002) and Mandeville and Rosen (2002), respectively. In this paper, we describe in detail a relatively new approach to study brain function, transcranial magnetic stimulation (TMS).

Transcranial magnetic stimulation

Transcranial magnetic stimulation (TMS) is a recent methodology that is being used to study neural function by introducing a localized magnetic field by applying coils of wire encased in plastic on a person's scalp. A magnetic field is induced in the orthogonal direction by passing current through the coils of wire. This magnetic field passes through the scalp and skull, and induces a secondary current in the underlying brain tissue. The neurons in the path of the secondary field depolarize and fire synchronously. When applied to a region such as the primary motor cortex, a single pulse of TMS can elicit an involuntary response from the target muscles.

TMS can be applied as a single pulse, paired pulses, or repetitively (rTMS). Single pulse TMS is used to study when the activity in the stimulated area contributes to the task (i.e. chronometric studies). Paired pulse TMS methodology explores the effects of the first TMS pulse on the second pulse and is used to examine corticocortical connectivity and interactions. rTMS has been used to modulate cortical excitability beyond the duration of the pulse application, and therefore has the potential to be a treatment tool (Pascual-Leone et al., 1998). rTMS has been applied to treat neuropsychiatric disorders such as depression, schizophrenia, tinnitus, Parkinson's disease, and stroke (Ridding & Rothwell, 2007). Both single pulse and rTMS can be used to transiently disrupt activity at the stimulated site, also termed as 'virtual lesions' (described below).

The immediate effects of TMS are observed when task performance is affected during TMS application. TMS applied to any cortical region will depolarize a mixture of excitatory and inhibitory neurons that lie in the path of the magnetic field, in both orthodromic (stimulation of the cell body and propagation of action potential along the axon) and antidromic (stimulation of axon and propagation of action potential towards the cell body) directions (Pascual-Leone & Walsh, 2002). The net effect of TMS is an outcome of complex interplay of several factors such as the cortical area being stimulated, the proportion of excitatory and inhibitory neurons in the stimulated area, the rate, the intensity, and the duration of TMS. For example, TMS can have an excitatory effect by synchronously firing neurons. Stimulation of the pyramidal cells in the primary motor cortex at rest results in involuntary contraction of muscles and a motor evoked potential (MEP). Another example of such an excitatory effect is production of phosphenes (perception of flashes of light) following TMS applied to the visual cortex. However, by injecting random or "out of phase" firing and resulting in de-synchronization of ongoing activity, TMS can also result in a disruption of the region's typical spontaneous activity. A single pulse or a train of rTMS can transiently disrupt normal brain activity by introducing 'out of phase' neural activity to the stimulated site, and result in a "virtual" lesion (Pascual-Leone, Walsh, & Rothwell, 2000). If the stimulated region is necessary for an ongoing task, virtual lesion with TMS results in disruption in the task performance. Such application of TMS enables researchers and clinicians to assess the functional significance of the stimulated region.

The major advantages of this method are (a) production of a focal lesion in a cortical region, (b) transient disruption of information processing, (c) absence of cortical reorganization that is seen following a lesion, and (d) assisting in establishing a chain of cause and effect between the activity of the brain and behavior. "Virtual" lesioning with TMS can also confirm the functional significance of a specific region that has been suggested through functional imaging using PET or functional MRI (fMRI). Virtual lesion studies using TMS have outlined the role of inferior frontal gyrus (Broca's area) in speech (Pascual-Leone, Gates, & Dhuna, 1991), and

the role of dorsal premotor cortex (PMd) in articulatory planning and execution (Stewart, Walsh, Frith, & Rothwell, 2001; Tandon et al., 2003). Most virtual lesion studies of speech motor system have focused on the disruptive effect of TMS, and the investigators induced a complete arrest of speech by applying TMS at high rates and intensities. In this study, we use stimulation rates and intensities that disrupt, but do not completely arrest speech, allowing for quantitative measurement of changes resulting from stimulation. In the case of DBS, a virtual lesion study using TMS is especially advantageous, as both techniques have a similar mechanism of action, that is, stimulation of a cortical region and disruption ongoing neural activity. For a more detailed review of principles and application of TMS, the readers are referred to Pascual-Leone and Walsh (2002) and Paus (2002).

Image-guided robotically positioned TMS

Use of anatomical and functional imaging for targeting has improved the accuracy of identifying the target sites for TMS (Brain Sight™, Rouge Research, Montreal, Canada; Krings et al., 2001). However many researchers continue to apply TMS by hand or using passive holding devices, resulting in positioning errors. Another factor that is important is the orientation of the magnetic field in relation to the neurons. Therefore, a system that includes image guided targeting, optimal orientation for individual sites, as well as a rigid holding mechanism is needed. For this reason, an image-based robotically positioned TMS system (irTMS) was developed at the Research Imaging Center (Lancaster et al., 2004). This system integrates the cortical-column cosine aiming theory for targeting and determining optimal orientation of the TMS coil (Fox et al., 2004) and holding capabilities of a robotic system. The positioning accuracy of the irTMS system, using a modified NeuroMate robot arm, was similar to that reported for the NeuroMate neurosurgical robot arm, 1.99±0.46 mm. The estimated maximum variation in planned delivery of E-field strength fell within the range of ±3–4%, demonstrating the high level of accuracy and precision of planned transcranial magnetic stimulation achievable by the irTMS system (Lancaster et al., 2004). The advantages of irTMS include precise localization of target, determining the correct orientation of the TMS coil for individual sites, as well as consistent delivery of TMS over long period of time and reproducibility across sessions.

Safety of TMS with DBS

Since TMS has a potential of inducing current in the wires, it is important to consider the safety of applying TMS on persons who have STN-DBS. The effects of TMS on scalp leads, and the implanted stimulator itself were examined in a phantom study (Kumar, Chen, & Ashby, 1999). They concluded that magnetic stimulation even at the maximum machine output directly over the scalp leads did not deliver damaging currents to the brain or to the implanted stimulator. They observed that the stimulator was no longer programmable only when TMS was applied directly over it or in close proximity (<2.5 cm). In the current study, the scalp leads were not near the scalp location of TMS application, and the location of stimulator was in the chest wall. In addition, the stimulator was turned off during TMS. With these precautions, we were confident that TMS application in this participant would be safe.

Study overview

Three experiments were conducted with a patient with Parkinson's disease who had electrodes implanted bilaterally in the STN and associated negative changes in speech function. In the first experiment, perceptual and acoustic measures of speech were used to document speech performance related to STN-DBS in four stimulation conditions (bilateral-on, left-on, right-on, and bilateral-off). Experiment 2 was a PET imaging study examining brain regions activated with the stimulators turned on or off (bilaterally). The information from this study allowed us to quantify the regions of the brain that were active during STN-DBS. We found

that left PMd (Brodmann Area [BA] 6) was overactive during STN-DBS while other activity patterns were typical based on known patterns of activity in Parkinson's disease and the location of the stimulator. To confirm that PMd is critical to this patient's speech difficulty, Experiment 3 was designed to induce a virtual lesion of this region (with DBS-off) using irTMS, and to determine if speech symptoms that emerged with irTMS paralleled those found with STN-DBS.

Method

Participant description

At the time of the case study, the patient was a 59 year-old, right-handed male who had Parkinson's disease for 11 years. He was implanted with DBS electrodes bilaterally in the STN two years prior to the study. While his general motor skills improved with STN-DBS, speech had deteriorated. We used the Hoehn and Yahr scaling system (Hoehn & Yahr, 1967) to assess the severity of Parkinson's disease. The Hoehn and Yahr scale is a commonly used system for describing how the symptoms of Parkinson's disease progress. The scale allocates stages from 0 (mild) to 5 (severe) to indicate the relative level of disability. The participant's Hoehn and Yahr level improved from level 3 to level 2 following implantation (symptoms on both sides of the body, and no impairment of balance). He was able to walk unassisted and had reduced resting tremor and bradykinesia on clinical examination. The DBS parameters were as follows bilaterally: amplitude 2.6 Volts, pulse width 90 μsec, and frequency of stimulation 185 Hz. The participant was on levodopa medication during the entire length of the study (Experiments 1, 2 and 3), in order to obtain the most representative speech behavior and to isolate the effects of DBS on speech. STN-DBS was turned off and on alternatively during experiments 1 and 2, but remained turned off during the entire duration of experiment 3. Written informed consent was obtained from the participant and all procedures were approved by the Institutional Review Board at the University of Texas Health Science Center.

Experiment 1: Perceptual and acoustic parameters of speech and voice

Stimuli and conditions—To examine changes in speech consequent to STN-DBS, the patient read a standard, phonetically balanced speech sample (The Rainbow Passage, Fairbanks, 1960) in each of four stimulation conditions (i.e. bilateral-on, left-on, right-on, bilateral-off). The speech samples were acquired 10 minutes after turning the DBS off or on.

Recording—Reading samples were recorded to a digital video camera with an external lapel microphone positioned 20 cm from the participant's mouth. Digital video and audio files were transferred to a PC for further analysis. Audio files were filtered using a noise reduction process from Adobe Audition (v. 1.5) to reduce background noise in the signal. Recordings were digitized at 44 kHz and low-pass filtered at 22 kHz.

Perceptual rating—Reading samples were rated for perceptual dimensions of speech and voice dysfunction by two SLPs experienced in the assessment of motor speech disorders (authors AJ and DAR). All stimuli across DBS and TMS conditions (see Experiment 3) were randomized and rated by the judges. A seven-point equal interval rating scale with 1 being most severely impaired and 7 being unimpaired (note that Darley et al. [1975] used the opposite weighting) was employed to rate the 38 perceptual dimensions developed by Darley and colleagues. Perceptual dimensions first were assigned individually, with the two raters blind to experimental condition and to the other's perceptual ratings. After completion of the task by each rater, perceptual ratings were compared to assess inter-rater agreement. The raters agreed on the same 8 aberrant dimensions across all conditions for 97% inter-judge agreement. This 97% inter-rater reliability reflects an agreement on the deviant dimensions, and not the actual rating values. Initial perceptual ratings of the two judges differed by an average of 1.2

points; values reported henceforth represent perceptual ratings determined by consensus following the initial rating.

Acoustic analysis—Acoustic measures also were obtained, including three parameters of acoustic contrastivity shown to be sensitive to differentiating speech of individuals with hypokinetic disorders from that of healthy, unimpaired speakers (Rosen et al., 2006) as well as broad durational measures of tone groups (similar to breath groupings, see below) and inter-group intervals. All acoustic analyses were performed using routines developed at the Research Imaging Center for Praat acoustic analysis software (Boersma & Weenink, 2008). First, reading passages were parsed into tone groups, a unit of segmentation similar to breath groups, defined as a group of words bounded by a single intonational contour (see Figure 1). Fast Fourier spectra and intensity contours with a minimum periodicity frequency of 50 Hz and a time step of 16 msec (one quarter of the effective window length) were created in Praat for each tone group.

The acoustic contrastivity measures reflect reduced spectral and temporal variation in the speakers with hypokinetic dysarthria and were designed to be used in various speaking conditions, including sentence production or conversation (Rosen et al., 2006). In that study, the three parameters most sensitive to differences in acoustic contrastivity include percentage pause time, intensity variation, and spectral range. The reported values of these measures, described in more detail as follows, represent mean values of the multiple tone groups within each stimulation condition.

For each tone group, an intensity contour was generated in Praat (see yellow trace in Figure 1). Speech and pause segments, respectively, were identified as periods in the intensity contour in which mean spectral energy was above or below a threshold of 15% of maximum spectral energy in the tone group. Percentage pause time (PPT, i.e. pause portion) was the percentage of time frames identified as pauses by the above criteria, thus reflecting extreme intensity drops in Parkinson's disease. Intensity variation (IV) was calculated as the standard deviation of intensity values of frames in the intensity envelope (i.e. root mean square energy contour) and reflects variation in prosody and articulatory closure. Spectral range (SR) was the range of acoustic energy occurring across frequency bandwidths in an utterance. Specifically, acoustic energy was measured in 28 consecutive 300 Hz frequency bands from the fast Fourier spectrum (0–8100 Hz). Spectral range was calculated as the difference in dB between maximum and minimum energy values across the spectrum. This measure is an indicator of homogeneity of acoustic energy distribution and is related to a reduction in the distinction between consonants and vowels frequently found in speakers with hypokinetic dysarthria (Rosen et al., 2006).

In addition to the acoustic contrastivity measures, broad durational analysis of tone group intervals and inter-group intervals was performed. Note that the acoustic contrastivity measures were based only on the acoustic signal within tone group boundaries, thus excluding large silent periods (i.e. intervals) between groups. Analysis of tone group duration and inter-group duration was used in order to better understand the timing of phrase groups more globally, particularly important for examining differences in speech in the TMS conditions (see Figure 1).

Experiment 2: Functional Imaging Study

PET Image Acquisition—The second experiment involved CBF measurements using PET (GE 4096 WB scanner, with 15 slices, each 6.5 mm) while the patient performed speech tasks or rested with DBS on and off. CBF was measured with ^{15}O labeled water with a half-life of 123 seconds. The isotope was administered as an intravenous bolus of 8–10 ml of saline containing 60 mCi. A 90 second scan was initiated at the point in time the tracer bolus entered the brain. A 10 minute inter-scan interval, sufficient for isotope decay (five half-lives), was

used. Two speech task conditions were employed, including reading aloud (Rainbow Passage, Fairbanks, 1960) and phonation (prolonged "ah"). The participant received a total of 12 injections of ^{15}O labeled water for the following conditions: two repetitions each of rest, reading, and phonation conditions during DBS on (6 scans with DBS on), and two repetitions each of rest, reading, and phonation conditions during DBS off (6 scans with DBS off), There was a 10 minute interval after turning DBS on and off prior to the subsequent imaging condition.

MRI—An anatomical MRI obtained prior to DBS implantation was used to optimize spatial normalization of PET images. MRI was performed using a 1.9 Tesla Elscint Prestige using high-resolution 3D Grass sequence: TR = 33 ms; TE = 12 ms; Flip angle = 60°; voxel size = 1 mm^3; matrix size = 256 × 192 × 192; acquisition time = 15 minutes.

Image Preprocessing—PET Images were reconstructed into 60 slices, with each of 2 mm thickness and an image matrix size of 60 ×128 × 128, using a 5 mm Hann filter, resulting in images with a spatial resolution of approximately 7 mm (full-width at half-maximum [FWHM]) and value normalized to a whole-brain mean of 1000. MRI and PET data were spatially normalized using Spatial Normalization (SN) software (Lancaster et al., 1995). This software performs "global" (9-parameter) spatial normalization, and registers the images to the target shape provided by the Talairach and Tournoux atlas (Talairach & Tournoux, 1988).

Image Analysis—Images were analyzed by creating voxel-wise statistical parametric images (SPIs) using the Medical Image Processing Station (MIPS, RIC, UTHSCSA) software validated for PET data analysis (Mintun, Fox, & Raichle, 1989). Z-score images (SPI{z}) with z-values above 1.96 and corrected for multiple comparisons by applying Bonferroni correction calculated from an image-wise standard deviation, were created by contrasting (a) all DBS off phonation conditions with DBS off resting conditions, (b) all DBS on phonation conditions with DBS on resting conditions, (c) all DBS off reading conditions with DBS off resting conditions, (d) all DBS on reading conditions with DBS on resting conditions, (e) all DBS on rest conditions with DBS off rest conditions, and (f) all DBS on conditions with all DBS off conditions. Images were displayed using MANGO (Multi-Image Analysis GUI) developed at our center (http://ric.uthscsa.edu/mango/).

Experiment 3: TMS Virtual Lesion Study

irTMS—In order to verify the outcome of Experiment 2, a TMS virtual lesion was induced in this patient with DBS off. The Cadwell High Speed Magnetic Stimulator (Cadwell Laboratories, Inc., Kennewick, WA) controlled by a pulse generator (Grass Technologies, West Warwick, RI, USA) was used. Image-guided robotic transcranial magnetic stimulation (irTMS) developed at the Research Imaging Center (Lancaster et al., 2004) was applied to the target site, namely left PMd corresponding to Brodmann area (BA) 6 (Talairach coordinates x = −46, y = 2, and z = 42). The irTMS system was used to: (a) determine target sites using co-registered anatomical (3D MRI) and PET images, (b) plan the TMS coil pose for the site of interest based on cortical columnar orientation (Fox et al., 2004), (c) register the participant's head to his 3D MRI image, (d) register the robot's coordinate system to the participant's head, and (e) robotically position the TMS coil to the planned pose.

TMS Delivery—The participant was seated in a dental chair and his head immobilized with a thermoplastic face mask. Resting motor threshold (rMT) was defined as the minimum level of stimulation that evoked a movement in the first dorsal interossii (FDI) muscle of the right hand in 50% of trials. In this case, with TMS applied to the left primary hand motor cortex, the rMT was determined to be 68% of the machine output. Once rMT was determined, the TMS coil was then positioned at the target site using the irTMS system. TMS stimulation then was applied to left PMd at 110% of the motor threshold (75% machine output) at a frequency

of 4 Hz. These parameters were based on a previous study in healthy volunteers while stimulating left PMd (Tandon et al., 2003). A TMS train consisted of a series of TMS pulses delivered over 5 seconds (4 pulses per second×5 seconds = 20 pulses), followed by no TMS for 5 seconds. The study consisted of 10 sessions, with 20 TMS trains applied in each session. The participant received a total of 4000 pulses during the study. The participant read either the *Grandfather* or *Rainbow passage* during TMS on and off conditions. As mentioned above, the deep brain stimulators were always off during this experiment. The entire session was videotaped.

Perceptual and acoustic analyses—Speech recordings were analyzed using the same perceptual and acoustic analytical methods described in Experiment 1. Prior to acoustic analysis, a custom software tool designed to remove the TMS "click" artifact was used to reduce the impact of TMS noise on acoustic measures (Ghosh, 2007). In addition, speech intelligibility during TMS on and off conditions was assessed perceptually as the percentage of produced words that were identifiable to listeners (authors AJ, DAR).

Results

Experiment 1: Perceptual and acoustic parameters of speech and voice

Ratings for the eight aberrant perceptual dimensions are shown in Table 1 and Figure 2 for each of the four experimental conditions. As expected, findings indicate that this patient with long-standing Parkinson's disease had impaired speech production in all conditions. Lower perceptual ratings were found during conditions that included stimulation of the left STN (i.e. mean rating across dimensions for left stimulation = 2.65; bilateral stimulation = 3.1) as opposed to conditions when the right STN was stimulated as well as when there was no stimulation (i.e. mean rating across dimensions for right stimulation = 4.25; no stimulation= 3.98). Interestingly, right STN stimulation resulted in higher (less impaired) ratings than no stimulation for three dimensions (breathy, strained/strangled, short phrases). In the remaining five dimensions, right stimulation and no stimulation conditions were equivalent. With bilateral or left-only stimulation all scores dropped and generally ranged from two to three with none of the eight dimensions reaching a score of four.

Acoustic measures are shown in Table 2 for IV, PPT, and SR in the four DBS conditions, with comparison data from unimpaired speakers and those with hypokinetic dysarthria from Rosen et al. (2006). The mean values of these measures were compared across different conditions. Each of the three measures changed as a function of experimental condition. In particular, lower measures of IV and SR were evident in conditions with DBS on bilaterally or left only. In contrast, these measures were higher with DBS off or on only to the right side. These higher values are indicative of more normal production, although they are still below comparison measures from comparison speakers (unimpaired or those with HKD; see table 2). The pattern for PPT was less consistent, with lowest value for LH only condition (3.87), a moderate value of 5.99 for RH only, and similar PPT of 9.52 and 8.21 for bilateral on and off conditions, respectively.

The acoustic contrastivity measures were employed because they reflect articulatory closure and distinct inter-segment boundaries. Furthermore, they have been shown to be useful in differentiating speech of participants with hypokinetic dysarthria due to Parkinson's disease from that of healthy participants (Rosen et al., 2006). Our results indicate reduced acoustic contrastivity with STN-DBS on, particularly to the left hemisphere.

Additional acoustic measures included broad durational measures of tone groups compared with inter-group intervals as a means of assessing the global temporal structure of utterances (Figure 3). This analysis was particularly useful in contrasting the temporal structuring of

speech during TMS conditions in Experiment 3 (also shown in Figure 3). Findings indicated slightly shorter duration of tone group intervals in conditions with bilateral DBS or left hemisphere stimulation only, relative to DBS off or to the right hemisphere only. The findings for bilateral and left hemisphere only DBS are consistent with the results due to TMS, discussed in greater detail in Experiment 3. Inter-group interval durations were little affected by DBS condition, maintaining relatively stable at 600 ms across conditions.

In contrast to its effects on speech, STN-DBS improved the patient's general motor function, as judged by three authors (DAR, DV, HP) viewing videotapes of the patient. For example, turning the stimulators off bilaterally resulted in increased facial masking and the emergence of limb tremor. This worsening of general motor function with DBS turned off stands in marked contrast to the concomitant improvement in speech. A ten minute wait period between on and off conditions was sufficient to elicit the behavioral responses described above. Moreover, as the stimulator remained off during the TMS study reported below, facial masking, bilateral pill-rolling, and resting tremor worsened (see Table 1).

Experiment 2: Functional Imaging Study

Task related activation patterns for phonation contrasted with rest (both during DBS off and DBS on) primarily involved activation of the supplementary motor area (SMA, region 1 in Figure 4). Task related activation patterns for reading contrasted with rest (during DBS off) involved activation of SMA, bilateral primary motor cortices (M1, regions 2 and 3 in Figure 4), bilateral anterior cingulate cortices (regions 4 and 5 in Figure 4) and posterior cingulate cortex, insula, thalamus, basal ganglia, cerebellum, primary and secondary auditory and visual cortices. Similar activations were also seen during reading in DBS on condition, except in the primary motor cortices these did not reach significance during reading in the DBS on condition (Figure 4).

The contrast of DBS on and off conditions demonstrated significant blood flow increases in several brain regions (Tables 3 and Figure 5). Increase in blood flow was seen at the site of DBS (left STN) implant (Table 3, region 1 in Figure 5) and in the neighboring thalamus. The activation in the left STN was identified at Talairach coordinates of x=−10, y=−10, and z=−2, but the volume of activation was contiguous with the nearby thalamic activation centered at x=−6, y=−14, z=2 with a cluster size of 416 mm^3. In addition, increased blood flow was observed in bilateral lentiform nuclei of the putamen (regions 2 and 4 in Figure 5). Significant increase in blood flow was also seen in remote regions such as left PMd (BA 6, region 3 in Figure 5), frontal eye field (BA 8) and dorsolateral prefrontal cortex (BA 11), bilateral cingulate cortex (BA 32), and inferior frontal gyri (BA 44, 45, 46, and 47). The left PMd, which had the most significant increase in CBF, was chosen as a target site for TMS virtual lesion. Significant decreases in CBF in left M1-hand and SMA were noted during the DBS on condition (Table 4). We did not consider regions that showed decreases in CBF (such as SMA) as targets for TMS-induced virtual lesion. Contrast of DBS on and off during the rest condition revealed activations in the same regions. However, with smaller significance values and cluster sizes due to fewer number of scans (4 versus 12 scans used in all DBS on vs. all DBS off analysis), the areas had smaller significance values and cluster sizes. This indicates that the speech motor network can be identified using few scans, but the findings are more robust when more scans are included in the analysis. Therefore, including more scans assists in accurate targeting of a region with irTMS.

Experiment 3: TMS Virtual Lesion Study

The participant tolerated 4 Hz repetitive TMS (irTMS) without any adverse effects. While speech was affected by TMS, there were no overt effects on the oromotor system. The patient

did not demonstrate any abnormal tongue, jaw or lip movements during TMS. Further, no effects were observed on the limb motor system.

Complete speech arrest was observed in 60% of the trials. On the other trials speech production was possible but disrupted as shown in Figure 6. When TMS was applied, speech altered immediately with increased pause length between words (Figure 3). Specifically, average duration of tone group intervals was reduced from 1.1 s with TMS off to 0.6 s with TMS on. In accordance with this finding, average duration of inter-group intervals increased from 0.9 s (TMS-off) to 1.4 s (TMS-on). The average lengths of tone group durations and inter-group intervals with and with out TMS are shown in Figure 3, alongside durational data from Experiment 1. With TMS off, 97% of words were intelligible; when TMS was applied intelligibility dropped to 57%.

Perceptual analyses of speech data with TMS were performed to assess whether TMS stimulation of left PMd produces similar effects as bilateral or left STN stimulation (see Experiment 1; Figure 2). Critically, the same eight deviant perceptual dimensions found in Experiment 1 were also found to change as a result of TMS stimulation to the left PMd (See Table 1). It was also the case that three other aberrant perceptual dimensions consistently emerged with TMS stimulation, including reduced stress (rating of 2), inappropriate silences (rating of 1), and phoneme prolongation (rating of 1). The average rating across the eight perceptual dimensions hovered around 1 (the lowest possible score), showing that TMS stimulation of left BA 6 had devastating effects on speech production in the same perceptual dimensions as with left STN stimulation.

In addition to these perceptual measures, acoustic contrastivity measures also were obtained for purpose of comparison with effects due to DBS (see Experiment 1). Table 2 shows results of measures shown to be reduced in speakers with hypokinetic dysarthria (Rosen et al., 2006) and in left hemisphere STN stimulation, including intensity variation, pause percentage time, and spectral range. These measures did not show as great a difference due to TMS stimulation as was found for DBS conditions, with the exception of pause percentage time, which was much reduced with TMS on compared to off. This result may seem contradictory, as the previous section (Figure 6) described increased pause duration during TMS stimulation (which might be construed to correspond to *higher* PPT). Note, however, that PPT represents percentage of time *within* a tone group (see Figure 1) that is under 15% of the maximum spectral energy. Note also that the values of SR and IV for both TMS on and off conditions were similar to those found in DBS on condition. We speculate that these might reflect residual effects of TMS even during the off segments (also see discussion).

Discussion

In this report, we highlight the use of multimodality imaging to gain knowledge about speech deterioration following STN-DBS in a single participant with Parkinson's disease on levodopa medication. Unique in this report is the combination of objective measures of speech (perceptual and acoustic) with PET imaging and "virtual lesion" techniques to understand the underlying neural mechanisms responsible for speech impairment due to DBS.

Similar to previous studies (e.g. Pinto, Ozsancak, et al., 2004), speech was found to deteriorate with stimulation to the left STN in this patient. The use of Darley et al.'s (1975) multidimensional rating system in this study provided greater specificity to the nature of the speech impairment than that has been previously reported, revealing deficits characteristic of hypokinetic dysarthria in Parkinson's disease (e.g. short phrases, monopitch, monoloud, imprecise consonants, intelligibility) as well as others that are not typically found in individuals with Parkinson's disease (harsh, strained/ strangled vocal quality). Multidimensional

perceptual ratings may provide clues to the nature of the mechanism underlying speech deterioration sometimes found in Parkinson's disease patients with STN-DBS. For example, harsh and strained/strangled vocal qualities typically are associated with spastic dysarthria. These perceptual findings suggest that STN-DBS in this patient is stimulating not only the subthalamic nucleus and connected basal ganglia, but may be inadvertently stimulating fibers in the corticospinal tract as well (Figure 7).

Speech changes associated with STN-DBS were assessed with acoustic measures previously used in speakers with hypokinetic dysarthria due to Parkinson's disease (Rosen et al., 2006). These measures provided evidence of STN effects on speech, resulting in blurred acoustic boundaries (pause percentage time), reduced differentiation between consonant and vowel sounds (spectral range), and decreased acoustic contrastivity (i.e. variation in the intensity envelope, important for normal prosody). In contrast, with DBS off or on only to the right side, acoustic contrastivity measures were more similar to reported data from speakers with Parkinson's disease and hypokinetic dysarthria (Rosen et al.). Overall, this pattern of acoustic results indicates a loss of acoustic contrastivity when DBS was applied to the left STN, while absence of stimulation or stimulation to the right STN resulted in a higher degree of contrast. Similar differential effects of left and right DBS on speech has been previously reported (Wang et al., 2003, 2006), where the intensity of maximally sustained vowel phonation was shown to be improved only during right DBS on when compared to both baseline and left DBS on.

Furthermore, it might be expected that spectral contrast measures during DBS off and TMS off should be more similar than found (Table 2). However, IV, PPT, and SR for TMS off did not vary appreciably compared to TMS on, and were generally more comparable with the DBS on conditions. This pattern of effects may indicate that the disrupted articulatory plans generated in left PMd during TMS on were carried out by the motor cortex during TMS off and resulting in a "spillover" of TMS-induced disruption into the TMS off period.

The speech-related functional activation patterns for reading contrasted with rest (DBS on and off) found in this participant are similar to the previously reported pattern in Parkinson's disease (Liotti et al., 2003; Narayana et al., in review; Pinto, Thobois, et al., 2004). Local and remote increases in CBF with DBS on that were found in this participant are also consistent with published literature (Haslinger, Kalteis, Boecker, Alesch, & Ceballos-Baumann, 2005; Hershey et al., 2003). Unilateral activity at the site of stimulation even when both stimulators are on as seen in this participant has been reported in other STN-DBS studies (Asanuma et al., 2006; Hershey et al.). Further, decreases in CBF seen in the primary motor cortex (M1), and the supplementary motor areas (SMA) following STN stimulation with DBS is consistent with the published literature (Haslinger et al.; Hershey et al.). These studies also report decreased CBF in left PMd when DBS is on. The neural mechanism of these CBF changes is not well characterized. However, we found that the DBS on vs. off contrast revealed an unexpected area of hyperactivation in the left PMd (see Figure 5). Therefore, we investigated the role of left PMd in speech production and whether the abnormal activation of this region could explain the speech disorder in this participant.

Various functional studies also have shown activation of PMd in normal speech (Bookheimer, Zeffiro, Blaxton, Gaillard, & Theodore, 2000; Petersen, Fox, Posner, Mintun, & Raichle, 1988; Price, Moore, & Frackowiak, 1996; Schulz, Varga, Jeffires, Ludlow & Braun, 2005; Watkins, Gadian, & Vargha-Khadem, 1999; Wise et al., 1991; Wise, Greene, Büchel, & Scott, 1999), as well as in motor speech disorders such as stuttering (Brown et al., 2005) and Parkinson's disease (Narayana et al., in review). Several lesion studies indicate that PMd is important in speech programming (Fox et al., 2001; Robin, Jacks, & Ramage, 2008; Watkins, Dronkers, & Vargha-Khadem, 2002), phonemic speech production (Larner et al., 2004), and phonetic perceptual processing (Demonet et al., 1992; Zatorre, Evans, Meyer, & Gjedde,

1992; Zatorre, Myer, Gjedde, & Evans, 1996). Previous work in our center has also shown that TMS stimulation to this area disrupts speech in healthy, unimpaired speakers (Robin, Guenther, et al., 2008; Tandon et al., 2003). The role of PMd in normal speech production is thought to involve working memory storage of units/programs for speech production (Mass et al., 2008; Robin et al., 2007, Wright et al., in press). The increased blood flow in PMd during normal speech therefore can be thought to be a result of neurons firing in a temporal hierarchical and a synchronous pattern. However during DBS-on the neurons in left PMd are stimulated continuously also resulting in an increased blood flow. Functional imaging method such as PET do not have the temporal resolution to differentiate the timing of cortical processes involved in speech that usually occur in milliseconds. Therefore in PET, neuronal firing during normal speech (i.e. periodic firing of neurons) and DBS-on (i.e. continuous firing of neurons) neuronal firing appears as activations. Further, continuous stimulation or 'out of phase' firing resulting from direct antidromic stimulation from DBS (or TMS) and the resulting de-synchronization of ongoing activity, disrupts the normal function of left PMd. Therefore speech disruption seen during DBS as well as TMS are a direct result of de-synchronization of ongoing activity in the left PMd. Verification of left PMd as critical to the worsening of speech in this patient was obtained with irTMS when the stimulators were turned off. As noted, stimulation of this area in this patient produced a speech deficit that was perceptually similar to that found with STNDBS.

It is not well understood how STN-DBS increases CBF in PMd. Recently, using MR tractography, connections have been shown between STN and several cortical areas such as PMd, SMA, M1-hand, M1-trunk and M1-fore upper limb (Aravamuthan et al., 2007). An upstream antidromic (i.e. propagation of action potential from the axon to the cell body) modulating effect of STN stimulation on these direct cortico-subthalamic projections has been proposed (Haslinger et al., 2005). High frequency stimulation within the STN has been shown to induce negative frontal cortical potentials, further supporting the direct antidromic stimulation of cortico-subthalamic axons (Ashby et al., 2001). Therefore, one potential explanation of this finding is that bilateral or left-sided stimulation of STN in this participant resulted in antidromic activation of left PMd, thereby causing speech to deteriorate with STN-DBS. This is depicted in Figure 7. Stimulation of STN by DBS results in orthodromic (i.e., the propagation of action potential from cell body to the axon) disruption of excitatory effect of STN on the internal segment of globus pallidus (GPi). The net outcome of this disruption is the release of inhibition on the thalamus and motor cortex and improvement in limb motor symptoms of Parkinson's disease. However, at the same time, stimulation of STN can propagate in the antidromic direction along the cortico-subthalamic fibers and could result in speech impairment.

The notion of Farrell and colleagues (Farrell et al., 2005) that speech motor planning/programming may be disrupted as a result of STN-DBS is in line with our findings, as stimulation of PMd only disrupts speech attempts and not silent reading (Tandon et al., 2003). Thus, we hypothesize that DBS disrupts ongoing processes in left PMd (for example during speech) by adding noise to the system vis-à-vis antidromic stimulation. Virtual lesioning by TMS also resulted in such disruption of ongoing activity in left PMd during overt speech. This finding points to the role of PMd in speech motor programming. Furthermore, DBS could result in speech deficit not only by direct disruption of PMd activity, but also indirectly by interfering with the interactions between PMd and the primary motor cortex. Excitability of PMd has been shown to directly modulate the primary motor cortex (Reis et al., 2008).

As noted in the introduction, explanations for the differential responses to stimulation observed for speech versus general motor behavior are speculative, ranging from hypotheses about electrode placement to differential neural organization of speech and limb motor systems. Relative to electrode placement, appropriate increases in CBF in STN, thalamus and basal

ganglia were demonstrated bilaterally using PET imaging with DBS on (Table 3). Further, improvement in limb motor performance when DBS was on indicates appropriate positioning of electrodes. However, the exact site of stimulation in this patient is not known as post-operative MRI was not performed.

Topographically, there is evidence that the STN regions connected to the cortex (i.e. motor cortex, SMA and PMd) are located in close proximity and are more lateral and anterior to the STN regions connected to other brain regions (i.e. basal ganglia and thalamus; Aravamuthan et al., 2007). Therefore, DBS can directly stimulate areas in STN connected to the premotor cortices as well as the primary hand, trunk and upper limb motor areas. In the superior-inferior dimension (z plane) STN regions connected to PMd and SMA were segregated from those parts of STN connected to the motor cortex (Aravamuthan et al.). Thus, even a small displacement of the DBS in the z direction can stimulate not only regions in STN connected to the primary motor cortex but also areas of STN connected to SMA and PMd. Therefore, while improving motor function by lesioning the connections of STN to the motor cortex, DBS might incidentally lesion its connections to the premotor areas. This can also explain the speech disturbances found in our participant with Parkinson's disease and STN-DBS. Such differences in the location of the implanted electrodes can explain why some patients with DBS do have speech problems.

Farrell and colleagues (2005) have argued that disruption of speech due to STN-DBS results from activation differences in local neuronal population responses and fundamental differences in their role in the regulation of speech and limb movements. The argument that speech planning and execution are driven by different neural organization schemes than other motor systems has been challenged in the literature, particularly for high-level motor organization and programming (Ballard, Robin, & Folkins, 2003). Another point made by Farrell et al. is that limb systems receive unilateral (contralateral) innervation via corticospinal inputs whereas speech structures, which project to corticobulbar systems, include bilateral innervation patterns of some muscle groups. It is unclear how these differences in innervation patterns would lead to poorer or no response of speech to DBS in the face of positive limb responses, particularly given our finding that right-sided stimulation has minimal or no detrimental effects on speech. Our findings support similar findings by others (Wang et al., 2003, 2006) and their argument about motor asymmetry.

In summary, one patient with long-standing Parkinson's disease who was implanted bilaterally with STN-DBS was studied. Unique in this report was the combination of objective measures of speech (perceptual and acoustic) with PET and MRI imaging as well as "virtual lesion" methods using TMS to understand the underlying neural mechanisms responsible for speech impairment due to DBS. Although these data are based on only one patient, they provide a strong direction for future research efforts. We have provided preliminary evidence to explain the neural mechanism underlying speech deterioration in patients with Parkinson's disease and STN-DBS. The finding that right-sided stimulation resulted in speech that was in many ways perceptually better than when the stimulators were off, might allow for balancing the intensity of stimulation between hemispheres as a successful treatment strategy. If these findings hold for other patients with STN-DBS, then image-guided adjustment of STN-DBS parameters may promote improvement in ALL motor functions.

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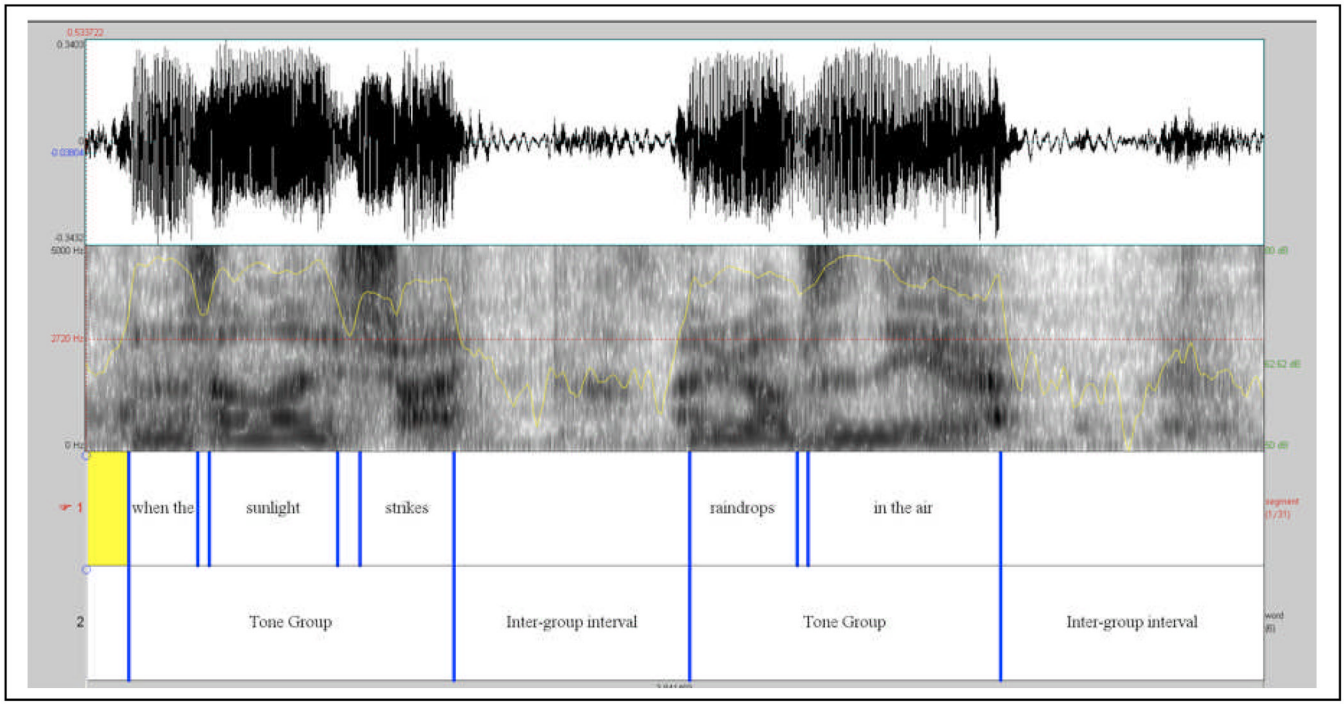

Figure 1.
Visual depiction of the acoustic signal and parsing method in Praat (Boersma & Weenink, 2008). The first two rows show the acoustic signal, including the acoustic waveform and a broad band spectrogram. The third row shows speech and pause segment intervals. The fourth row shows the demarcation among tone groups and intergroup intervals.

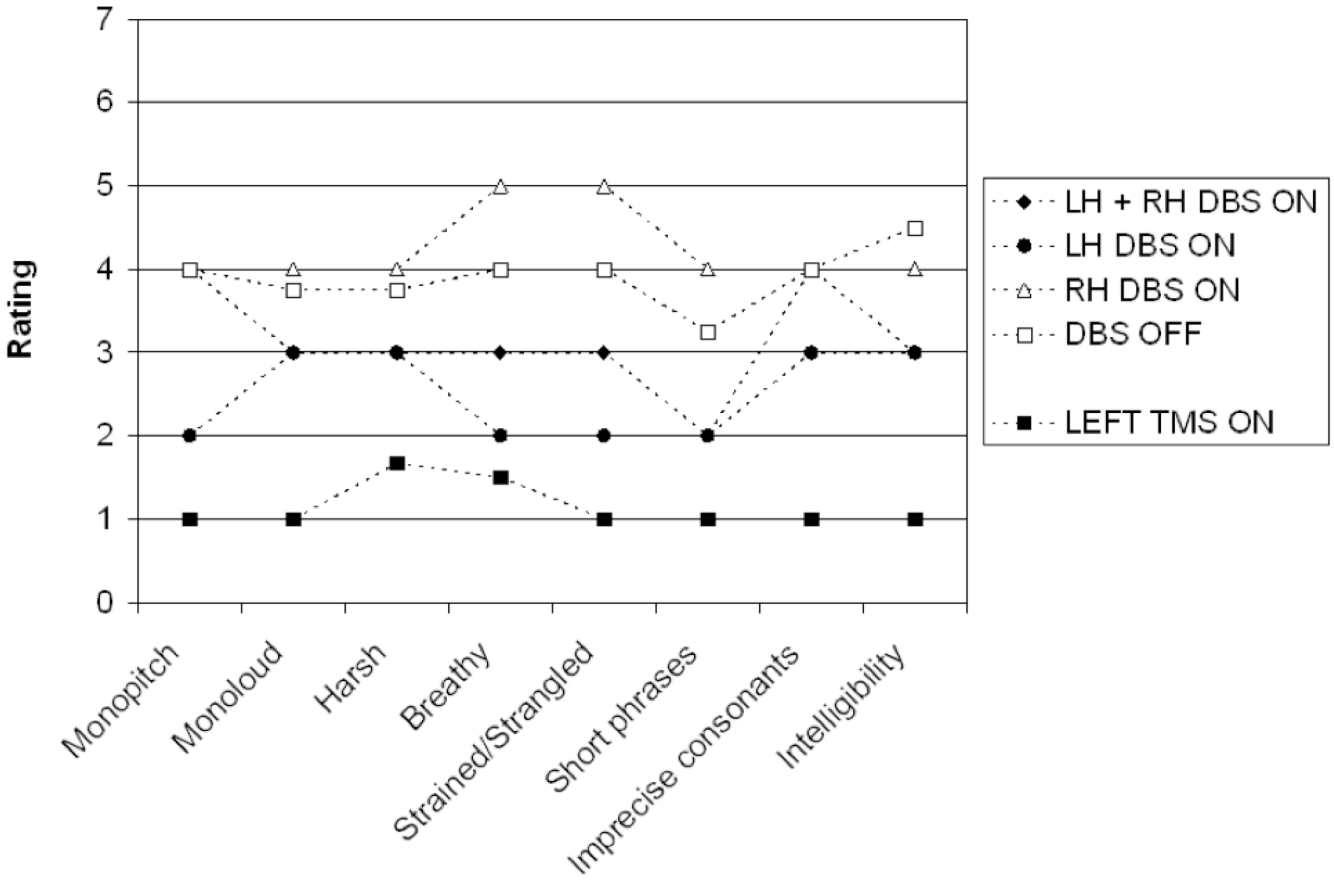

Figure 2.
Perceptual ratings for each of the eight aberrant speech dimensions for each experimental condition. Lower values reflect greater impairment.

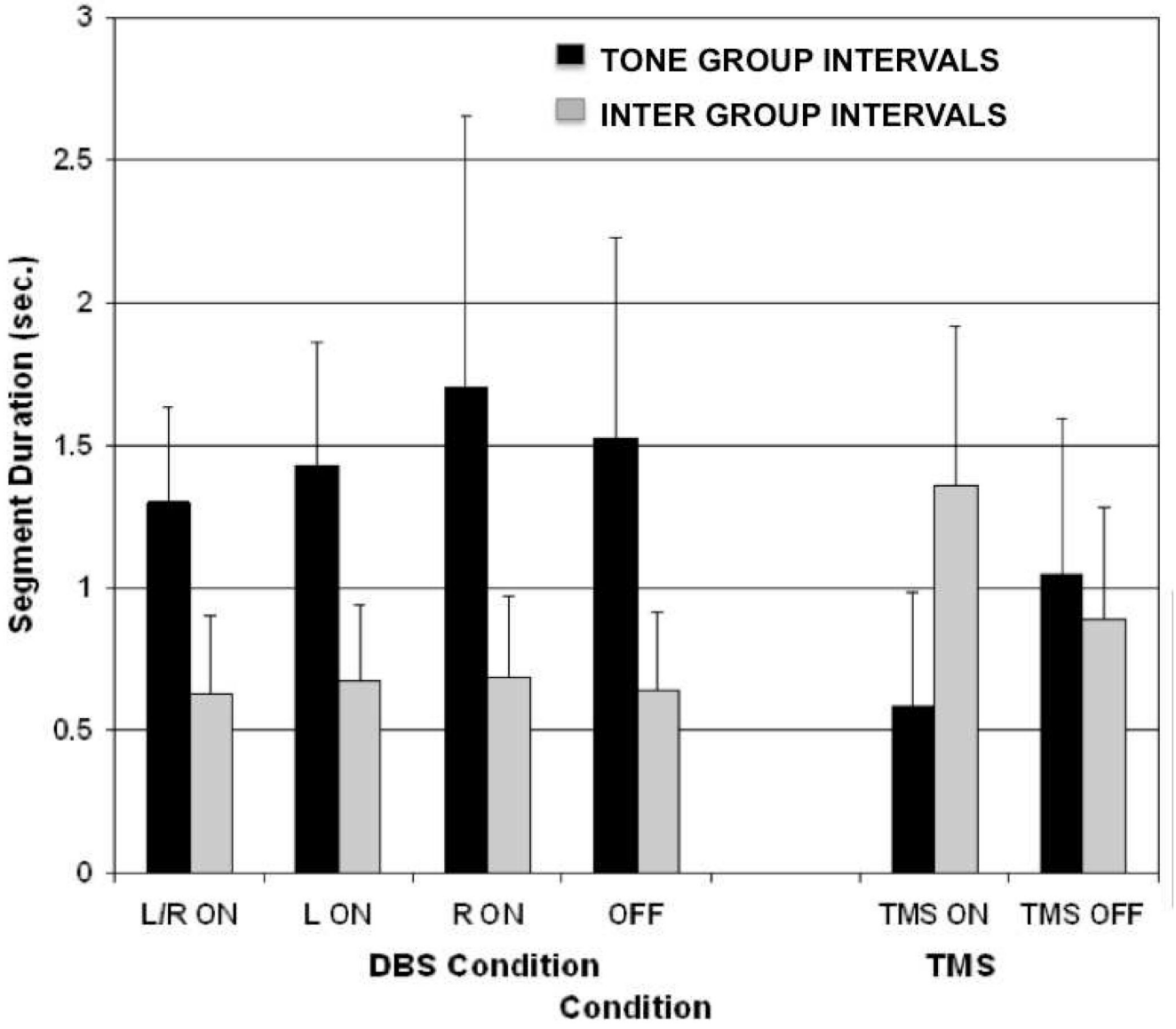

Figure 3.
Acoustic measures: Average speech and pause interval durations with TMS ON and OFF during paragraph reading.

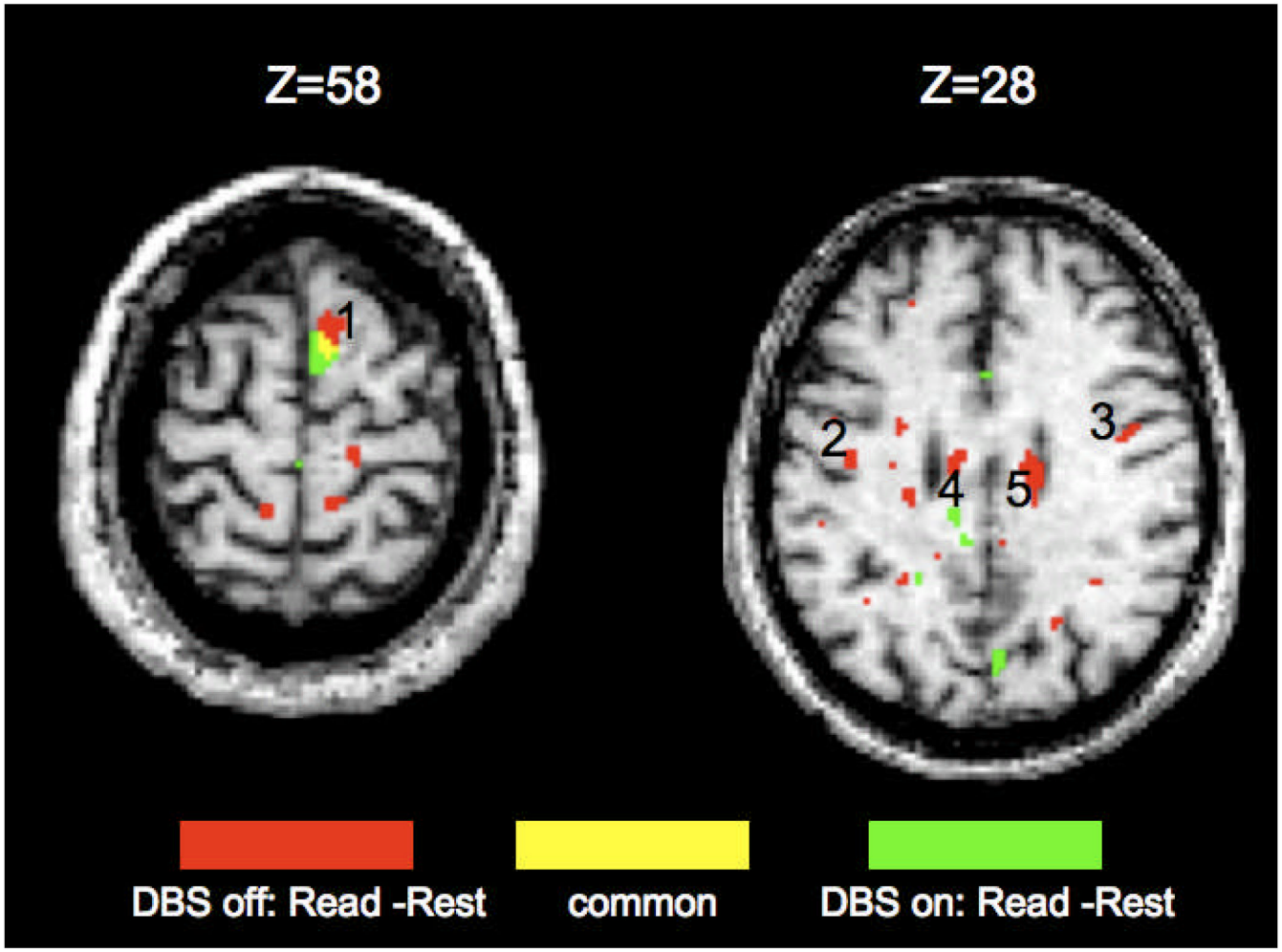

Figure 4.
Activations during speech tasks contrasted with rest during DBS on and off conditions. Activations during reading in DBS off condition are shown in red; activations during reading with DBS on are in green, and activations common across both conditions are shown in yellow. Numerals indicate the following specific locations: 1. Supplementary motor cortex (SMA); 2. Left primary motor cortex mouth; 3. Right primary motor cortex mouth; 4. Left cingulate cortex; and 5. Right cingulate cortex.

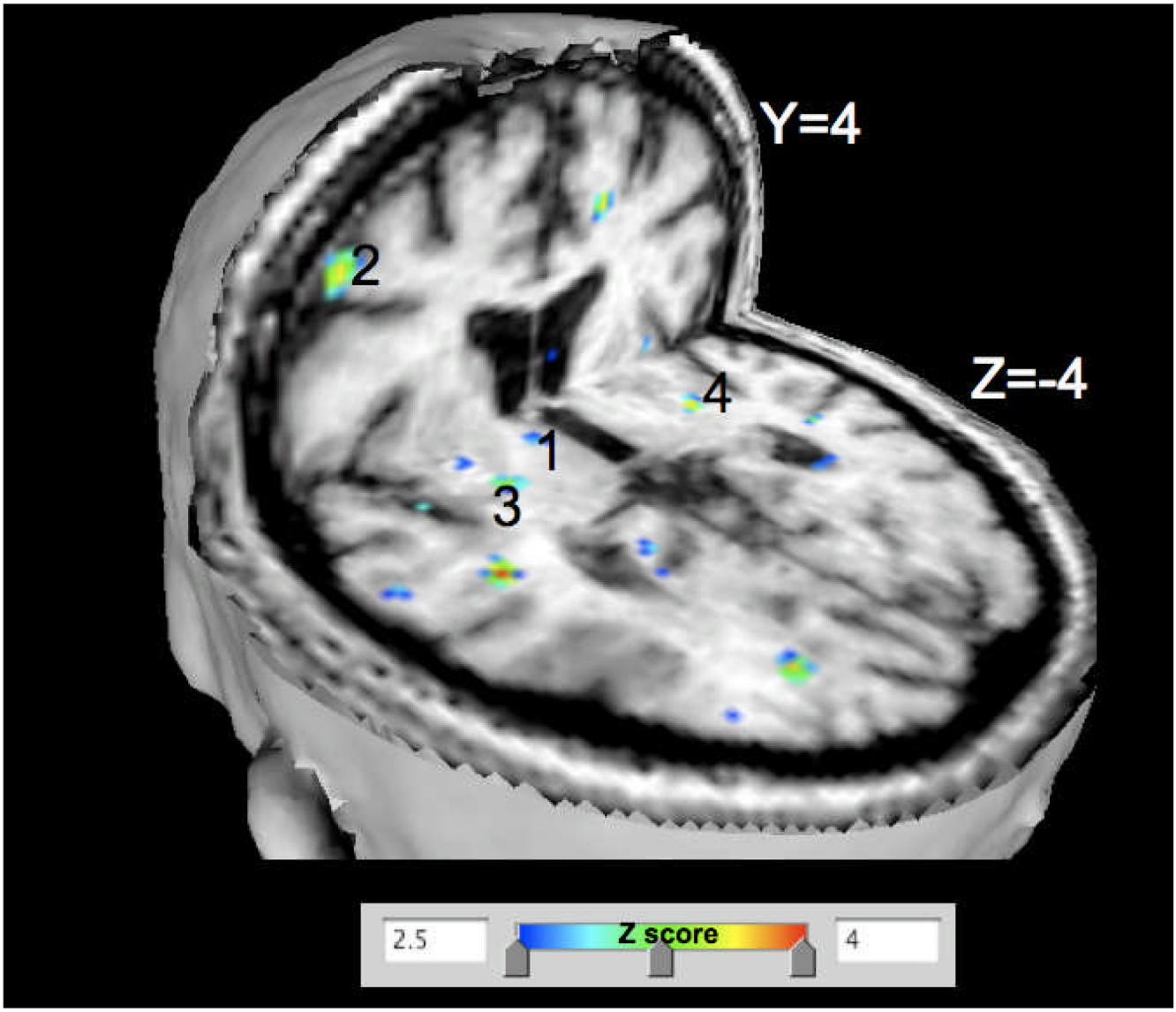

Figure 5.
Activation of local (z plane) and remote (y plane) brain regions by DBS. Marker 1 corresponds to left STN/ventral posterior nucleus of the thalamus (VPN), 2 corresponds to left PMd (BA 6), 3. the left putamen, and 4. Corresponds to right putamen.

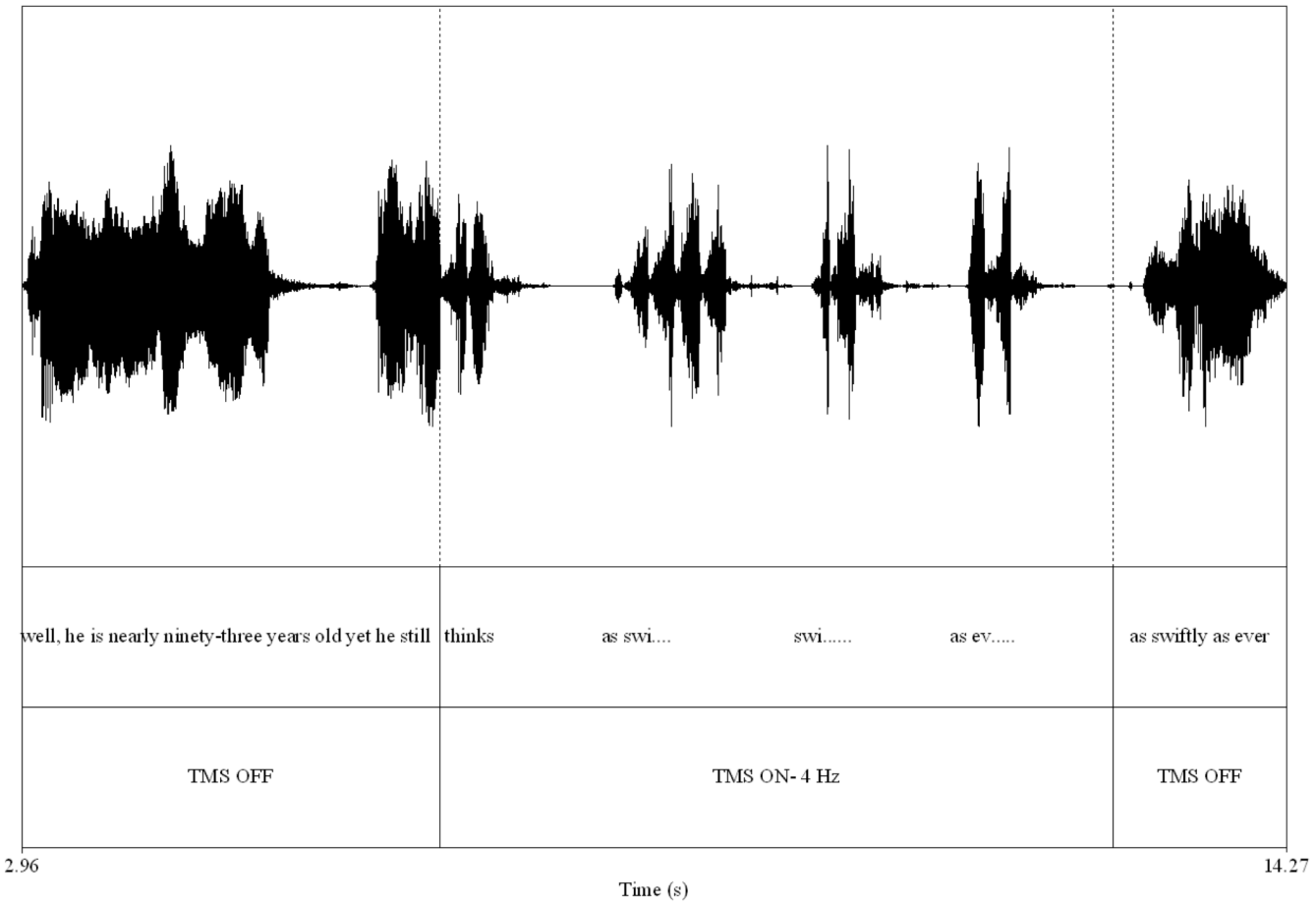

Figure 6.

Real time representation of speech acoustic signal and TMS stimulation in Praat (Boersma & Weenink, 2008). The first row shows the acoustic waveform, with vertical boundaries marking the segments with and without TMS. The second row includes a gloss transcription of the participant's speech, and the third row indicates the TMS condition.

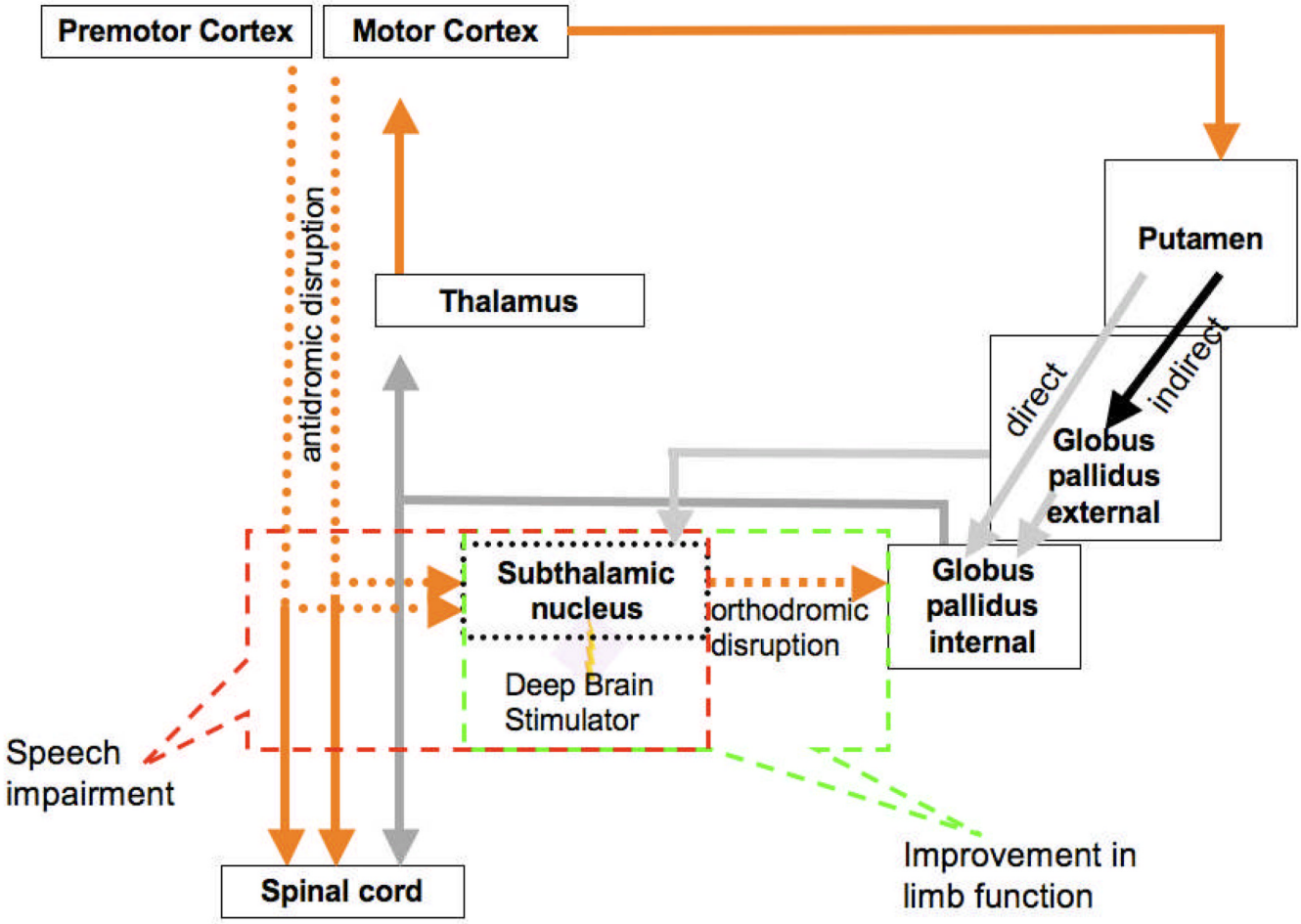

Figure 7.

Schematic representation of effects of STN-DBS in Parkinson's disease. Orange lines represent excitatory connections and grey and black lines represent inhibitory connections. Direct and indirect stimulation of STN by DBS is indicated by box with dashed lines. The dash lines indicate disrupted connections following STN-DBS. Orthodromic disruption of globus pallidus by STN is shown in the green box and antidromic propagation along the cortico-subthalamic fibers is shown in the red box.

Table 1

Perceptual speech and limb measurements during DBS on and off conditions

	Measures	DBS on	LH DBS	RH DBS	DBS off
Limb Measures	Hoehn and Yahr level	2			3
	Facial masking	−			+
	Tremor	−			+
	Pill rolling movement	−			+
Perceptual speech measures	Monopitch	4	2	4	4
	Monoloud	3	3	4	4
	Harsh	3	3	4	4
	Breathy	3	2	5	4
	Strained/Strangled	3	2	5	4
	Short phrases	2	2	4	4
	Imprecise consonants	4	3	4	4
	Intelligibility	3	3	4	4

Note: LH = left hemisphere; RH = right hemisphere; perceptual measures: 7= normal; 1 = profoundly impaired; + = present; - = absent.

Table 2

Spectral contrast measures in four STN-DBS conditions and TMS conditions

	DBS CONDITION				TMS CONDITION		COMPARISON DATA (Rosen et al., 2006)	
	LH + RH ON	LH ON	RH ON	OFF	TMS ON	TMS OFF	Healthy Controls	Hypokinetic Dysarthria
INTENSITY VARIATION (dB)	3.92 (0.42)	3.63 (0.24)	4.54 (0.30)	4.47 (0.29)	3.09 (0.25)	3.82 (0.22)	6.5	5.4
PAUSE PERCENTAGE TIME (%)	9.52 (4.16)	3.87 (2.38)	5.99 (1.80)	8.21 (2.37)	2.72 (0.12)	9.92 (1.35)	25.0	14.0
SPECTRAL RANGE (dB)	46.93 (3.10)	39.46 (3.06)	67.03 (6.02)	62.18 (5.54)	40.28 (2.02)	40.56 (1.77)	94.0	84.0

Note: LH = left hemisphere; RH = right hemisphere; TMS= transcranial magnetic stimulation. Values represent means, with standard errors in parentheses.

Table 3

Coordinates of significant cerebral blood flow increases during DBS-ON contrasted with DBS-OFF

Site of stimulation and vicinity						
X	**Y**	**Z**	**Brain Region**	**Cluster size (mm^3)**	**Z score**	**p value**
−24	−16	2	left lateral globus pallidus	704	3.99	0.00003
−16	−19	7	left VPMN thalamus	400	3.87	0.00005
−24	−8	6	left Putamen	528	3.6	0.00016
−6	−14	2	left STN/Thalamus	416	3.48	0.00025
−10	−34	2	left Thalamus (Pulvinar)	280	3.43	0.0003
32	−20	0	right Putamen	528	4.14	<0.00003

Note: x, y, and z represent brain coordinates in Talairach Atlas (Talairach & Tourneux, 1988). STN = sub thalamic nucleus; VPMN = ventral posterior medial nucleus

Table 4

Coordinates of significant cerebral blood flow increases in remote sites during DBS-ON contrasted with DBS-OFF

Remote Sites						
X	**Y**	**Z**	**Brain Region**	**Cluster size (mm^3)**	**Z score**	**p value**
−22	36	40	left frontal eye field (BA 8)	360	4.31	<0.00003
−46	2	42	left PMd (BA 6)	480	3.67	0.00012
−5	48	−18	left middle frontal gyrus (BA 11)	400	3.36	0.00039
−6	32	−8	left anterior cingulate cortex (BA 32)	656	3.35	0.00041
−39	38	0	left inferior frontal gyrus (BA 45/46)	272	3.28	0.00052
35	28	−6	right inferior frontal gyrus (BA 47)	328	3.65	0.00013
20	2	40	right anterior cingulate cortex (BA 24/32)	296	3.63	0.00014
58	18	2	right inferior frontal gyrus (BA 44/47)	224	3.62	0.00015
10	19	42	right anterior cingulate cortex (BA 32)	200	3.38	0.00036
7	−20	42	right BA 24/SMA	240	3.26	0.00056
−36	−26	42	left M1 hand (BA 4)	280	−2.65	0.004
−3	−14	62	left SMA (BA 6)	240	−3.02	0.001

Note: x, y, and z represent brain coordinates in Talairach Atlas (Talairach & Tourneux, 1988). BA = Brodmann area; M1 = primary motor cortex; SMA = supplementary motor area; PMd = dorsal premotor cortex