Neural Correlates of Efficacy of Voice Therapy in Parkinson’s Disease Identified by Performance–Correlation Analysis

Shalini Narayana, 1* Peter T. Fox, 1, 2 Wei Zhang, 1 Crystal Franklin, 1 Donald A. Robin, 1, 3 Deanie Vogel, 4 and Lorraine O. Ramig 5, 6

1 Department of Radiology, Research Imaging Center, University of Texas Health Science Center at San Antonio, Texas
2 Medical Services/Neurology, South Texas Veterans Administration Medical Center, San Antonio, Texas
3 Department of Neurology, University of Texas Health Science Center at San Antonio, Texas
4 Department of Speech, Language and Hearing Science, Our Lady of the Lake University, San Antonio, Texas
5 Communications Disorders Department, University of Colorado, Boulder, and National Center for Voice and Speech (NCVS), Denver, Colorado
6 Department of Biobehavior, Columbia University, New York, New York

Abstract: LSVT® LOUD (Lee Silverman Voice Treatment) is efficacious in the treatment of speech disorders in idiopathic Parkinson’s disease (IPD), particularly hypophonia. Functional imaging in patients with IPD has shown abnormalities in several speech regions and changes in these areas immediately following treatment. This study serves to extend the analysis by correlating changes of regional neural activity with the main behavioral change following treatment, namely, increased vocal intensity. Ten IPD participants with hypophonia were studied before and after LSVT LOUD. Cerebral blood flow during rest and reading conditions were measured by H215O-positron emission tomography. Z-score images were generated by contrasting reading with rest conditions for pre- and post-LSVT LOUD sessions. Neuronal activity during reading in the pre- versus post-LSVT LOUD contrast was correlated with corresponding change in vocal intensity to generate correlation images. Behaviorally, vocal intensity for speech tasks increased significantly after LSVT LOUD. The contrast and correlation analyses indicate a treatment-dependent shift to the right hemisphere with modification in the speech motor regions as well as in prefrontal and temporal areas. We interpret the modification of activity in these regions to be a top–down effect of LSVT LOUD. The absence of an effect of LSVT LOUD on the basal ganglion supports this argument. Our findings indicate that the therapeutic effect of LSVT LOUD in IPD hypophonia results from a shift in cortical activity to the right hemisphere. These findings demon-

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*Correspondence to: Shalini Narayana, Research Imaging Center, UT Health Science Center at San Antonio, San Antonio, Texas 78229. E-mail: narayana@uthscsa.edu

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Speech and voice disorders affect 90% of patients with idiopathic Parkinson’s disease (IPD) (Duffy, 2005). The dysarthria reported in IPD includes reduced loudness (hypophonia), monopitch, hoarseness, a breathy voice quality, and imprecise articulation (Duffy, 2005), likely related to the hypokinetic state (Ramig et al., 2001a,b, 2004; Sapir et al., 2002, 2007). Abnormalities in various measures of speech such as decreased maximum forces of the articulatory muscles, decreased force rise time, shorter duration of sustained phonation, longer pause duration, and decreased vocal sound pressure level (SPL), and an overall reduction in speech intelligibility have been reported (Gentil et al., 2001; Ramig et al., 2004; Sapir et al., 2007). In addition, abnormalities in the auditory system that also adversely affect speech production in IPD are reported. These include reduced ability to follow rapid intensity fluctuations (Guehl et al., 2008) and abnormal auditory-motor integration (Kofler et al., 2001; Sabate et al., 2008).

Although the neural correlates of speech have been studied extensively by functional imaging in healthy controls, only two neuroimaging studies have compared the speech motor areas in patients with IPD with healthy participants (Pinto et al., 2004a; Liotti et al., 2003). When compared to healthy participants, those with IPD demonstrated an increased regional cerebral blood flow (rCBF) in the premotor areas during speech tasks (Pinto et al., 2004a; Liotti et al., 2003). The rCBF response in the primary motor cortex and cerebellum appears variable with both decreases (Pinto et al., 2004a) and increases (Liotti et al., 2003) reported. The authors of both these studies interpret these findings as pretreatment abnormalities and hypothesize that an altered recruitment of the motor regions result in an increased involvement of the premotor and prefrontal cortices during speech (Liotti et al., 2003; Pinto et al., 2004a).

Dysarthria in IPD can be treated pharmacologically, surgically, and by behavioral speech therapy. A behavioral therapy that has been shown to be effective in treating hypophonia in IPD is LSVT® LOUD (Lee Silverman Voice Treatment). LSVT LOUD is organized around a simple but powerful therapeutic principle: increasing vocal loudness (targeting amplitude of respiratory-laryngeal movement) in individuals with IPD will retrain the sensory motor processes involved in disordered speech communication (Fox et al., 2002). The training mode of LSVT LOUD requires high effort (self-perceived effort) and intensive training (16 individual 60-min treatment sessions in 1 month) consistent with principles of motor learning, skill acquisition, and neural plasticity (Kleim and Jones, 2008; Schmidt and Lee, 1999; Verdolini et al., 1999). Treatment sessions consist of two parts: daily tasks and a speech hierarchy. Daily tasks increase vocal loudness through multiple repetitions of sustained vowels (“ah”), high/low-pitch range exercises, and functional phrases. The speech hierarchy systematically improves functional communication by training patients to maintain improved vocal loudness (achieved in daily tasks) for longer periods of speaking and in more complex speaking situations (e.g., progressing from words to conversational speech).

LSVT LOUD has been shown to be effective in the short term and long term (up to 2 years) in improving hypokinetic dysarthria, especially hypophonia (Ramig et al., 2001a,b, 2004; Suchoworsky et al., 2006). A system-wide improvement across the speech production network, as well as improved self-monitoring, clinically referred to as recalibration of the auditory system have been documented following LSVT LOUD and are thought to contribute to the overall improvement in functional communication (Fox et al., 2006).

There exists yet another disparity between behavioral and imaging-based examination of the effect of treatment on speech disorders in IPD. Although many studies have examined the speech outcome following pharmacological, surgical, and behavioral treatments by perceptual and acoustic measurements [reviewed by Pinto et al. (2004b)], few have examined the changes in the speech motor areas by functional imaging. A significant improvement of variability in pitch and loudness, measures of respiration, and comprehensibility have been reported following pharmacological treatment (De Letter et al., 2007a,b; Pinto et al., 2004b). Although surgical interventions such as stimulation of the subthalamic nucleus (STN) have improved motor performances and vocal tremor, this procedure has also been shown to have either no effect or at times a worsening effect on perceptual and acoustic parameters related to prosody, articulation, vocal SPL, intensity, and intelligibility of speech (Pinto et al., 2004b; D’Alatri et al., 2008; Narayana et al., 2009).

Few functional imaging studies have reported on the changes that occur in the speech motor system in IPD immediately following various treatments (Rektorova et al., 2007; Pinto et al., 2004a; Liotti et al., 2003). A functional magnetic resonance imaging (fMRI) study of speech in females with IPD on levodopa, demonstrated significantly higher blood oxygen level dependent signal in the right primary sensorimotor cortex (SM1) compared to healthy individuals following the LSVT LOUD training program.
controls (Rektorova et al., 2007). This right-sided shift was attributed to the pharmacological treatment effect as well as compensatory mechanisms. By measuring rCBF with positron emission tomography (PET), the speech motor network in IPD was shown to become more similar to that of normal controls following STN stimulation (Pinto et al., 2004a), and a LSVT LOUD-dependent right-sided functional reorganization of brain activation pattern was also reported (Liotti et al., 2003). Our objective was to further examine the immediate mechanisms of action underlying the successful behavioral treatment such as LSVT LOUD. We were especially interested in identifying a possible neural mechanism for the auditory recalibration observed following LSVT LOUD (Fox et al., 2006).

Although within-subject conditional contrast analyses, used in previous studies, are powerful and widely used, they are not always an adequate image analysis strategy (Fox et al., 2000). Conditional contrast analysis is based on the assumption that only the brain regions that are activated differently during one task are isolated. Isolating desired behaviors during imaging presents a significant challenge. An alternative technique, called performance-correlation analysis using the principle that the intensity of brain activations is highly correlated with the frequency with which the neural elements are used during the imaging epoch was introduced for imaging (Silbersweig et al., 1995). It was further developed for speech motor studies (Braun et al., 1997; Fox et al., 2000; Ingham et al., 2004; Raboyeau et al., 2004; Jodzio et al., 2005; Rektorova et al., 2007), but thus far has not been applied to examine treatment outcomes. We therefore sought to apply performance correlation analyses to further investigate the brain correlates and the mechanisms of action characterizing successful LSVT LOUD treatment.

On this basis, this study had the following objectives: we sought to (1) replicate earlier findings of abnormalities in speech motor areas in individuals with IPD, (2) identify the neural correlates of a successful LSVT LOUD treatment by specifying the components of the speech system that directly correlate with the outcome of LSVT LOUD, and (3) propose a mechanism of action of LSVT LOUD based on the imaging findings reported below. Because the primary goal of LSVT LOUD is to increase vocal loudness, and loudness is a part of intonation and prosody that mainly activate speech motor areas in the right hemisphere (Ross and Monnot, 2008), we hypothesized that greater activation would be seen in the right hemisphere speech motor areas following LSVT LOUD. Loudness monitoring, another major component of LSVT LOUD, is predominantly regulated by the auditory cortices, especially in the right hemisphere (Ross and Monnot, 2008; Brancucci and San Martini, 2003; Brancucci et al., 2005). Therefore, we hypothesized that a voice treatment like LSVT LOUD would also target the auditory system, and such recruitment could indicate a possible neural mechanism for the auditory recalibration observed clinically following LSVT LOUD.

**METHODS**

**Participants**

Ten right-handed participants (8 men, 2 women; age 60 ± 11 years) with a diagnosis of IPD and speech and voice disorder were recruited for this study (see Table I for motor and speech characteristics). Symptom severity was mild to moderate with an average Unified Parkinson’s Disease Rating Scale (UPDRS) score of 51 ± 12, range, 36–78. The reported speech symptoms (item 5 of UPDRS) were an average of 2.2 (range, 2–3). The average score of a speech motor examination (item 18 of UPDRS) was 1.9 (range, 1–3) indicative of speech that is monotone, slurred but understandable. The more severe participants had poor intelligibility. Mean disease onset was 4.6 years (range, 1.5–7 years). The participants had no history of any hearing impairment or other neurologic or psychiatric

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Duration of PD (years)</th>
<th>UPDRS total</th>
<th>UPDRS (item 5)</th>
<th>UPDRS (item 18)</th>
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<tr>
<td>1</td>
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<td>78</td>
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<td>58</td>
<td>M</td>
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<td>6</td>
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<td>56</td>
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<td>46</td>
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<td>1</td>
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<tr>
<td>9</td>
<td>82</td>
<td>M</td>
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<td>M</td>
<td>1.5</td>
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</tbody>
</table>

UPDRS, Unified Parkinson’s Disease Rating Scale; UPDRS (Item 5), speech symptoms reported by the patients; UPDRS (Item 18), speech motor signs recorded by the clinician.
diseases. Individuals with IPD were considered for LSVT LOUD if they had significant hypophonia but could increase vocal loudness on command (5–10 dB SPL at 30 cm). All participants underwent a laryngeal examination to rule out abnormalities that might affect the participation and treatment outcomes (e.g., gastric reflux and vocal fold paralysis). All participants were on levodopa and the medication status was kept consistent throughout the period of the study. Written informed consent was obtained from all participants, and all procedures were approved by the Institutional Review Board at the University of Texas Health Science Center at San Antonio.

**Voice Therapy**

LSVT LOUD was administered according to the prescribed program (Ramig et al., 1995, 1996; Smith et al., 1995; Ramig et al., 2004) by a speech-language pathologist trained and certified in this method.

**Behavioral Data Acquisition**

Vocal SPL, the acoustic correlate of vocal loudness was measured for sustained vowel phonation, reading, and spontaneous conversation before, during and at the end of LSVT LOUD using a sound level meter (RadioShack®) placed at a distance of 30 cm from the participants’ mouth. Speech during PET sessions was recorded using a digital audiorecording system with microphone placed 20 cm from the participants’ mouth. Speech data were digitized at 44 KHz with a low-pass filter set at 22 KHz and filtered using a noise reduction process from Adobe Audition (v. 1.5) to reduce background noise in the signal and further analyzed using TF32 speech analysis tool (http://userpages.chorus.net/cspeak/) for loudness measurements.

**Imaging Method**

**PET acquisition**

PET data were acquired with a CTI EXACT HR+ scanner (Knoxville, TN). Sixty-three contiguous slices (2.5-mm thick) in a transaxial field of view of 15.5 cm were acquired. Images were corrected by measured attenuation using $^{18}$O PET data were acquired with a CTI EXACT HR+ scanner (Knoxville, TN). Sixty-three contiguous slices (2.5-mm thick) in a transaxial field of view of 15.5 cm were acquired. Images were corrected by measured attenuation using $^{18}$O/Water (H215O, half-life 122 s) was administered intravenously (555 MBq H215O dose/scan) and cerebral blood flow (CBF) was measured using a bolus technique (Fox et al., 2000, 2006). Participants’ heads were immobilized in the PET scanner using individually fitted, thermally molded, plastic face masks (Fox and Raichle, 1984). Each subject was studied in two sessions: before LSVT LOUD and immediately after completion of LSVT LOUD. During both sessions, the participants underwent four measurements of CBF during paragraph reading at habitual voice level and during eyes open rest (two repetitions each). The participants read standard passages used in speech and voice assessments: “The Rainbow” (Fairbanks, 1960) and “The Grandfather” (Darley et al., 1975) passages. The passages were displayed on a computer monitor screen placed in front of patients’ eyes. In the eyes open rest condition, patients were asked to lie still while looking at a crosshair on the monitor and maintain a relaxed state.

**MRI acquisition**

An anatomical MRI scan (Elscint 1.9T; Haifa, Israel) was also acquired for each subject for the purposes of spatial transformation of the PET data and parametric image display. A 3D-gradient recalled acquisition in a steady-state [GRASS] sequence was acquired with scan repetition time (TR) of 33 ms, an echo time (TE) of 12 ms, flip angle 60° as a 256 × 256 × 127 volume with a spatial resolution of 1 mm³.

**Image data preprocessing**

Image preprocessing was performed using previously validated methods and in-house software. PET images were corrected for head motion using the MCFLIRT tool in FSL 4.0 (http://www.fmrib.ox.ac.uk/fsl/) and PET and MRI images were spatially transformed relative to the stereotaxic atlas of Talairach and Tournoux (1988) (Lancaster et al., 1995, 1997). Regional tissue uptake of 15O-water was globally normalized to whole rCBF brain mean value with images scaled to a mean of 1,000 counts. These value and spatially normalized images were tri-linearly interpolated, re-sampled (60 slices, 8 mm³ voxels), and Gaussian filtered to a final resolution of 9.9 mm (FWHM). Further data analyses were performed using MIPS software (Medical Image Processing Station, Research Imaging Center, UT Health Science Center at San Antonio, TX) and MANGO (Multi Analysis GUI, Research Imaging Center, UT Health Science Center at San Antonio, TX).

**PET Analyses**

**Conditional contrast analysis**

For each subject and session, voxel-by-voxel pairwise contrasts were generated to identify regional changes present during overt paragraph reading relative to rest. Task-specific, within-subject regional changes were then averaged across individuals. A maxima and minima search (Fox et al., 1988; Fox and Mintun, 1989; Mintun et al., 1989) was then used to identify local extrema within a search volume measuring 1000 mm³. A gamma 1 statistic measuring skewness and gamma 2 statistic measuring kurtosis of the distribution of the extrema established before post hoc analyses were used as an
omnibus test to assess overall significance. We confirmed that for the reading versus rest contrasts, the gamma 2 statistic for all the masked voxels and for the extrema set were significant. The group-mean subtraction images from both sessions were then converted to statistical parametric images of \( z \) scores (SPI\( \{z\} \)). The Bonferroni correction was applied to correct for the number of positive extrema locations that were reported to have a \( P \) value <0.05. Laterality indices were calculated for pre- and post-LSVT LOUD sessions as the ratio of volumes of all reported significant activations in each hemisphere (after applying the Bonferroni correction) using the formula:

\[
\text{Laterality index} = \frac{\text{total volume of activation in left}}{\text{total volume of activation in right}}
\]

**Volume of interest analysis**

To further confirm the hemodynamic differences between pre- and post-LSVT LOUD conditions, the brain regions that appeared to change following LSVT LOUD were probed in the value normalized PET data. Cubic VOIs (side of 9 mm) were placed at the center-of-mass of bilateral primary motor cortices (MI), supplementary motor area (SMA), pre-SMA, dorsal premotor cortices (PMd), auditory cortices, globus pallidus (GP), right dorsolateral prefrontal cortex (DLPFC), and precuneus. The mean value normalized PET counts (VNC) were derived for the above locations during rest and reading conditions, both pre- and post-LSVT LOUD time points from each subject. A paired Student's \( t \)-test was performed to identify significant changes in CBF in these regions during reading condition contrasted with rest before and following LSVT LOUD.

**Performance correlation analysis**

A statistical parametric image of \( r \) values (SPI\( \{r\} \)) was computed as a voxel-wise correlation of CBF with the loudness measure during reading using previously described method (Fox et al., 2000). Pre-LSVT LOUD-reading was contrasted with post-LSVT LOUD reading and the CBF difference image was correlated with respective change in vocal SPL. SPI\( \{r\} \) was analyzed for speech performance effects first by an omnibus (whole-brain) test and, if omnibus significance was proven, then a post hoc (regional) test was done and local extrema were identified. The SPI\( \{r\} \) was converted to SPI\( \{z\} \), and \( P \) values were assigned from the \( Z \) distribution and corrected for the number of positive extrema. The volumes of significant correlations in various brain regions in both the hemispheres meeting the above criteria were calculated and graphed. A laterality index was calculated as the ratio of volumes of all significant positive correlation of CBF with vocal SPL during reading in each hemisphere using the formula:

\[
\text{Laterality index} = \frac{\text{total volume of correlating voxels in left}}{\text{total volume of correlating voxels in right}}
\]

<table>
<thead>
<tr>
<th>Pre-LSVT</th>
<th>Post-LSVT</th>
</tr>
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<tbody>
<tr>
<td>Phonation</td>
<td>85</td>
</tr>
<tr>
<td>Reading</td>
<td>85</td>
</tr>
<tr>
<td>Conversation</td>
<td>85</td>
</tr>
</tbody>
</table>

Figure 1. Behavioral data: changes in measure of loudness as sound pressure level (SPL) in decibels (dB) during sustained phonation, reading, and conversation pre and post-LSVT LOUD. *Post-LSVT LOUD loudness was significantly different (\( P < 0.0005 \)).

**RESULTS**

**Behavioral Effects of LSVT LOUD**

Voice and speech measures acquired immediately before and after LSVT LOUD (SPL at 30 cm) showed highly significant improvement (see Fig. 1). An ANOVA revealed significantly higher post-LSVT LOUD SPL for all the three speech conditions: sustained phonation pre- (\( M = 84.9 \pm 1.7 \) dB) versus post-LSVT LOUD (\( M = 74.6 \pm 4.9 \) dB), \( P = 0.0005, F = 51.75 \), paragraph reading pre- (\( M = 76 \pm 1.7 \) dB) versus post-LSVT LOUD (\( M = 68.3 \pm 2.5 \) dB), \( P = 0.0002, F = 64.72 \), and spontaneous conversation pre- (\( M = 73.7 \pm 1.3 \) dB) versus post-LSVT LOUD (\( M = 66.7 \pm 2.7 \) dB), \( P = 0.00001, F = 74.37 \). No significant change was observed in the duration of sustained phonation between post-LSVT LOUD (\( M = 20.1 \pm 8.3 \) s) versus pre-LSVT LOUD (\( M = 16.3 \pm 11.2 \) s), \( P = 0.37, F = 0.88 \). The treatment related increase in vocal SPL confirmed perceptual judgments of the LSVT clinician regarding improved hypophonia and intelligibility. ANOVA of SPL measurements during paragraph reading in PET sessions showed significant increase following LSVT LOUD similar to out of scanner changes (pre-LSVT LOUD \( M = 65.6 \pm 3.2 \) dB vs. post-LSVT LOUD \( M = 73.6 \pm 2.5 \) dB) \( P = 0.0007, F = 16.55 \).

**PET Results**

**Conditional contrast**

Table II and Figures 2–4 identify the brain regions showing a significant change during paragraph reading compared with rest both before and after LSVT LOUD. After correcting for multiple positive extrema, only maxima
<table>
<thead>
<tr>
<th>Lobe</th>
<th>Region</th>
<th>Pre-voice treatment</th>
<th>Post-voice treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>X</td>
<td>Y</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Frontal</td>
<td>M1-mouth (BA 4)</td>
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<td>-16</td>
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<tr>
<td></td>
<td>Dorsal premotor cortex (BA 6)</td>
<td>-42</td>
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<td></td>
<td>Supplementary motor cortex (BA 6)</td>
<td>-4</td>
<td>-6</td>
</tr>
<tr>
<td></td>
<td>Pre-SMA/rostral SMA (BA 6/8)</td>
<td>-3</td>
<td>12</td>
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<tr>
<td></td>
<td>Cingulate cortex (BA 24)</td>
<td>-8</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>Inferior frontal gyrus (BA 47)</td>
<td>48</td>
<td>-6</td>
</tr>
<tr>
<td>Right</td>
<td>M1-mouth (BA 4)</td>
<td>54</td>
<td>-12</td>
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<tr>
<td></td>
<td>Dorsal premotor cortex (BA 6)</td>
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<td>Pre-SMA/rostral SMA (BA 6/8)</td>
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<td>14</td>
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<td>Middle frontal gyrus (BA 9/10)</td>
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<td>38</td>
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<td>Lingual gyrus (BA 17)</td>
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<td>Lobule IV/V (culmen)</td>
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<td></td>
<td>Lobule IV/V (culmen)</td>
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<td>-60</td>
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M1, primary motor cortex; BA, Brodmann area; x, y, z, talairach co-ordinate system; SMA, supplementary motor area.
Activation pattern during paragraph reading in individuals with IPD hypophonia. Top panel A: Pre LSVT LOUD and bottom panel B: Post-LSVT LOUD. (1) Bilateral SMA, (2) right PMd, (3) left primary motor cortex (M1-mouth), (4) right primary motor cortex (M1-mouth), (5) right parietal cortex (BA 7), (6) right dorsolateral prefrontal cortex (BA 9), and (7) right superior temporal cortex. The figures in the last column are coronal sections (at $x = 52$) show increased right M1 activation, as well as appearance of right superior temporal gyrus activation post-LSVT LOUD during a speech task.

Pre LSVT LOUD conditional contrast (reading-rest)

Bilateral activations were observed in the primary mouth motor cortex (M1-mouth, Brodmann area (BA 4), supplementary motor cortex (SMA, BA 6), dorsal premotor cortex (PMd, BA 6), visual areas [lingual (BA 17), middle and inferior occipital (BA 18), and fusiform (BA 19) gyri], and cerebellum (lobules 1V, V, and V1). In the left hemisphere, activations in anterior cingulate cortex (ACC, BA 24), rostral SMA (BA 6/8), superior temporal (BA 22), and middle temporal gyri (BA 21) were observed. In addition, activation in the right precuneus (BA 7) was also observed. The laterality index measured as the ratio of volume of activation in each hemisphere was 0.23, indicating a slightly greater volume of activation in the left hemisphere.

Post-LSVT LOUD conditional contrast (reading-rest)

Following LSVT LOUD, bilateral activations were still present in SMA, PMd, visual areas, and cerebellum. In addition, bilateral activations were observed in superior and middle temporal gyri. Left-sided activations were observed in inferior frontal gyrus (BA 47). Left-sided activations that were present pre-LSVT LOUD in the M1-mouth, rostral SMA, and ACC did not reach significance post-treatment. However, several right-sided activations were present following LSVT LOUD in areas such as middle frontal gyrus (BA 9 and 46), rostral SMA and notably in superior and middle temporal gyri. The activated volumes in various brain regions in the two hemispheres showed a rightward shift, which is reflected in the laterality index of −0.13.

Volume of interest analysis

VOI analysis comparing the pre- versus post-LSVT LOUD contrasts of reading with rest showed significantly ($P < 0.05$) increased hemodynamic response in right DLPFC, PMd, and the auditory cortex following the voice treatment. Right M1 and left rostral SMA showed trends ($P \leq 0.01$) of increased CBF (see Fig. 4). Following LSVT LOUD, there was also a significant decrease in CBF in left globus pallidus.

Performance correlation

Brain regions with an $r$-value $\geq 0.5$, $z$-score $\geq 2.8$, and $P \leq 0.0025$ (after correcting for multiple positive extrema) are reported (Figs. 5 and 6 and Table III). Brain regions were predominantly on the right side with M1-mouth, M1-hand, PMd, middle frontal gyrus (BA 9), inferior frontal gyrus (BA 44/45), middle and inferior temporal gyri (BA 22, 21), primary sensory cortex (S1-BA 3), precuneus...
Comparison of activation patterns during paragraph reading in individuals with IPD hypophonia pre and post-LSVT LOUD. Green: activations during paragraph reading pre LSVT LOUD; red: activations during paragraph reading post-LSVT LOUD; yellow: overlap of activations between two imaging sessions. L, left hemisphere; R, right hemisphere. (1) SMA, (2) rostral or pre-SMA, (3) dorsal premotor cortex, (4) left primary motor cortex (M1-mouth), (5) right primary motor cortex (M1-mouth), (6) right dorsolateral prefrontal cortex (BA 9), (7) left thalamus, (8) right superior temporal cortex, (9) right superior temporal sulcus, and (10) bilateral visual cortices. Notice no change in SMA, left M1, and visual areas following LSVT LOUD.

Volume of interest analysis: value normalized counts from speech conditions contrasted with rest in select brain regions that showed significant changes following LSVT LOUD. Post-LSVT LOUD changes were significant in RPMd, RDLPC, R Aud, and LGP areas. L and RM1, left and right primary mouth motor cortex; SMA, bilateral supplementary motor area; L and R preSMA, left and right rostral SMA; L and RPMd, left and right dorsal premotor areas; RDLPC, right dorsolateral prefrontal cortex; L and R Aud, left and right auditory cortices; RPrecuneus, right precuneus; L and RGP, left and right globus pallidus.

**Means \( P < 0.05 \) and * indicates \( P < 0.01 \).

Positive correlation of cerebral activity with treatment outcome (SPL) following LSVT LOUD in individuals with IPD. L, left hemisphere; R, right hemisphere. (1) Right dorsal premotor cortex, (2) right M1-hand, (3) LEFT precuneus (BA 7), (4) right M1-mouth, (5) right DLPFC, and (6) right superior temporal gyrus.
volumes in the right hemisphere were seen corresponding to a laterality index of −0.50 that once again indicates a shift to the right hemisphere.

**DISCUSSION**

Data presented above replicate earlier reports of abnormal activations in the speech motor areas in individuals with IPD. Our data demonstrate, for the first time, the use of performance correlation as a powerful analytical tool to identify the components of the speech motor system directly involved in a successful behavioral treatment. Successful treatment with LSVT LOUD resulted in a rightward shift in the cortical speech motor and premotor systems as well as in the association areas mediating multimodal integration. We interpret the modification of activity in these regions during speech to be a top–down effect of LSVT LOUD. This deduction is further supported by the absence of a direct effect of LSVT LOUD on the basal ganglion (BG). These effects of LSVT LOUD are discussed under two sections: (1) neural correlates of successful voice treatment and (2) brain regions that remained unchanged following treatment.

**Neural Correlates of Successful Voice Therapy**

Previous neuroimaging studies of speech in IPD that examined the speech motor regions (Pinto et al., 2004a; Liotti et al., 2003; Rektorova et al., 2007) have reported abnormal increases or decreases in neural activity in several areas of the speech system and interpreted these findings as pretreatment abnormalities. Consistent with previous studies, our data show that in the pretreatment session, the conditional contrasts revealed similar

<table>
<thead>
<tr>
<th>Lobe</th>
<th>Region</th>
<th>X</th>
<th>Y</th>
<th>Z</th>
<th>Cluster size (mm³)</th>
<th>Z score</th>
<th>r value</th>
<th>P value</th>
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<tr>
<td>Frontal</td>
<td>Pre-SMA/rostral SMA (BA 6/8)</td>
<td>−14</td>
<td>12</td>
<td>54</td>
<td>240</td>
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<td>Right</td>
<td>M1-mouth (BA 4)</td>
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<td>−10</td>
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<td>384</td>
<td>3.71</td>
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<td></td>
<td>Dorsal premotor cortex (BA 6)</td>
<td>34</td>
<td>0</td>
<td>52</td>
<td>600</td>
<td>3.26</td>
<td>0.59</td>
<td>0.00056</td>
</tr>
<tr>
<td></td>
<td>M1-hand (BA 4)</td>
<td>34</td>
<td>−22</td>
<td>50</td>
<td>504</td>
<td>3.01</td>
<td>0.54</td>
<td>0.00130</td>
</tr>
<tr>
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<td>Middle frontal gyrus (BA 9)</td>
<td>26</td>
<td>30</td>
<td>32</td>
<td>672</td>
<td>2.90</td>
<td>0.52</td>
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<td></td>
<td>Interior frontal gyrus (BA 44/45)</td>
<td>48</td>
<td>14</td>
<td>20</td>
<td>472</td>
<td>3.13</td>
<td>0.56</td>
<td>0.00087</td>
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<td>Temporal</td>
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<td>46</td>
<td>−2</td>
<td>−11</td>
<td>392</td>
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<td>Middle temporal gyrus (BA 22)</td>
<td>50</td>
<td>−34</td>
<td>2</td>
<td>552</td>
<td>3.37</td>
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<td></td>
<td>Middle temporal gyrus (BA 21)</td>
<td>49</td>
<td>−54</td>
<td>6</td>
<td>656</td>
<td>3.64</td>
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<td>Parietal</td>
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<td>2.88</td>
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<td>posterior cingulate (BA 31)</td>
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<td>Sub cortical</td>
<td>Thalamus</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>Ventral posterior lateral nucleus (VPLN)</td>
<td>−2</td>
<td>−2</td>
<td>10</td>
<td>768</td>
<td>3.50</td>
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<td>Right</td>
<td>Ventral anterior nucleus (VAN)</td>
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<td>18</td>
<td>512</td>
<td>2.96</td>
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SMA, supplementary motor area; BA, Brodmann area; x, y, z, talairach co-ordinate system; M1, primary motor cortex.
significant activations in the motor, premotor, and subcortical areas as well as the sensory areas such as the superior temporal gyrus (STG), parietal cortex, and visual cortices. The data presented here indicate that the primary effect of LSVT LOUD broadly consists of two major components: (1) recruitment of right-sided regions during speech and (2) a top–down mechanism of action of voice therapy. The right-sided shift is evident from the laterality indices calculated on the conditional contrast as well the performance correlation data. Pre-LSVT LOUD, the activations were predominantly in the left hemisphere as indicated by the laterality index of 0.23 and post-LSVT LOUD, the laterality index during speech was −0.13, indicating greater volumes of activated cortical and subcortical areas in the right hemisphere. The CBF in regions correlating with vocal SPL also showed a strong rightward shift with a laterality index of −0.5.

The right-sided regions that were mainly modified by treatment were M1-mouth, DLPFC, PMd, and auditory cortices (Figs. 4 and 6). Consistent with our hypothesis, we attribute this right shift to be a direct result of motor and sensory loudness training during LSVT LOUD. Such an effect is thought to result in an increased modulation of prosody and the gain processing of speech sounds. Loudness along with tone and pitch are nonsegmental parts of speech and are elements of speech prosody (Seddoh and Robin, 2001). Both lesion and imaging studies have shown right hemispheric dominance in overall comprehension and production of speech as well as in comprehension and expression of global aspects of prosodic speech such as tone, pitch, and loudness (Belin et al., 1998a; Riecker et al., 2002; Borod et al., 2002; Mitchell and Crow, 2005; Hesling et al., 2005; Nakhitina et al., 2006; Ross and Monnot, 2008). Frontal lobes (M1, PMd, insula) and parietal lobes, as well as inferior, middle, and superior temporal sulci have been shown to be activated by prosody. Similarly, the right hemispheric frontal-parietal-temporal cortical network has been shown to be involved in selective attention to auditory stimuli (Paus et al., 1997; Belin et al., 1998a,b). Indeed, consistent with our hypothesis, these were the regions that showed significant right shift in this study.

A finding of specific interest in this study is the increased activation seen in the auditory cortices, especially in the right hemisphere after LSVT LOUD. It is well documented that patients with IPD have difficulty integrating sensory information into the motor commands and show a mismatch between internal sense of effort (calibration of sensory signals internally) and motor output (Solomon et al., 2000; Solomon and Robin, 2005). This has been shown to be true in the somatosensory (Solomon and Robin, 2005) as well the auditory (Kühn et al., 2004; Sabate et al., 2008) systems in IPD. Existence of such abnormal sensory-motor integration can easily explain the altered self-assessment of loudness that is frequently observed in individuals with IPD (Fox et al., 2006). Through loudness training, LSVT LOUD is thought to recruit the auditory cortex, especially on the right side and result in sensory calibration particularly of the auditory system. Such targeted increase in activity in the auditory cortex and improved communication of this region with other speech motor areas is thought to augment sensory motor integration and improve feedback. Such a phenomenon supports the hypothesis that the auditory calibration that is observed following treatment is a result of increased recruitment of right auditory cortex.

This study provides evidence that the main effect of LSVT LOUD is to directly modify the cortical motor, auditory, and prefrontal areas during speech. These areas, in turn, are thought to modulate the activity of subcortical regions during speaking tasks. In this aspect, LSVT LOUD can be considered to be a speech motor treatment paradigm resulting in a top–down treatment effect. Differential effects of pharmacotherapy (from the limbic system to the cortex, i.e., bottom–up) and psychotherapy (from the cortical areas to the limbic system, i.e., top–down) on the cortico-limbic system have been demonstrated by neuroimaging in depression (Mayberg, 2003; Mayberg et al., 1999; Petersen, 2006). In contrast to the cortical or top–down modulation of speech motor system by behavioral treatment such as LSVT LOUD, the surgical and pharmacological treatments in IPD can be thought to be effective via a direct effect on the subcortical speech regions, that is, a bottom–up effect. In this case, the subcortical regions in turn modify activity of cortical regions such as M1, SMA, and PMd during speech. The top–down modulation of the speech motor system by LSVT LOUD can also explain the distributed effects of improved articulation (Fox et al., 2006; Sapir et al., 2007), facial expression (Spelman et al., 2003), and swallowing (El Sharkawi et al., 2002) that are reported following LSVT LOUD. Similarly, positive effects of LSVT LOUD that are documented in disorders other than IPD, such as ataxic dysarthria (Sapir et al., 2003), stroke, and cerebral palsy (Fox et al., 2006) can be explained on the basis of top–down therapeutic effect of LSVT LOUD.

The following discussion will examine the individual speech motor, auditory, and multimodal association areas directly modified by LSVT LOUD and will also examine the role of the thalamus in increasing loudness.

**Major Cortical Areas Modified by LSVT LOUD**

**Primary motor areas**

In our study, the right M1-mouth showed significantly greater activation during speech post-LSVT LOUD (Figs. 3 and 4) and a strong correlation with treatment outcome (Figs. 5 and 6). Such a change in M1-mouth region is likely a direct effect of LSVT LOUD. Similar findings have been found in IPD following STN stimulation where improvements in clinical, acoustic, and biomechanical parameters of dysarthria were demonstrated following restored activation of bilateral M1-mouth area during speech (Pinto et al., 2004a). Such compensatory changes in the non-dominant primary motor areas have been demonstrated in other neurological disorders as well, such as stuttering (Fox...
et al., 2000; Ingham et al., 2004), and stroke (Riecker et al., 2002). We conclude that the vocal exercises of LSVT LOUD directly modulate the activity of primary mouth motor cortices, especially on the right side.

**Primary and secondary auditory areas**

Another cortical area that was significantly altered following LSVT LOUD was the right auditory region (BA 21, 22). Although the role of left auditory areas (BA 22) appears to be related mainly to discriminating linguistic components of speech, the right auditory regions have been shown to have more diverse functions. Price et al. (1992, 1996) showed a linear increase in activity in the right anterior STG with increased word rate. Right auditory cortex has been shown to have a role in pitch judgement, processing complex harmonic structures, and timbre discrimination (Zatorre and Binder, 2000; Perry et al., 1996, 1999). Right STG has been shown to be active in conjunction with right prefrontal and premotor areas in working memory tasks of pitch (Zatorre et al., 1994) and auditory tones (Perry et al., 1993). Increased bilateral activation of primary auditory cortices has been shown in IPD individuals under both DBS-off and DBS-on conditions and is thought to be associated with the auditory feedback perception (Pinto et al., 2004a). In stuttering, right temporal lobe (BA 21, 22) activity has been shown to correlate negatively with stuttering rate (Ingham et al., 2004; Brown et al., 2005) and is thought to be a result of an increased inhibition from the primary motor cortices, an abnormal efference copy (Brown et al., 2005). Such data indicate the existence of connections between primary motor and auditory cortices. This supports our conclusion that compensatory or plastic connections exist between the motor cortical areas and auditory areas and that these connections can be activated during speech motor training programs such as LSVT LOUD.

**Dorsolateral prefrontal cortex**

The right DLPFC also showed significant increase in activity during speech and correlated with treatment outcome (Figs. 4–6). A previous DBS study in IPD has shown abnormal hyperactivity in bilateral DLPFC in participants with IPD during speech tasks that was reversed following stimulation of STN (Pinto et al., 2004a). The authors conclude that the combined hyperactivity of DLPFC and the rostral SMA to be a compensatory phenomenon due to the disease process, which becomes normalized following STN-DBS. In the previous LSVT LOUD imaging study (Liotti et al., 2003), the DLPFC activation was seen in speech tasks only post treatment. Here, the authors concluded that the DLPFC activation post-LSVT LOUD undergoes normalization similar to the limb motor system in IPD, due to reestablishment of BG-thalamic inputs to the prefrontal cortex.

In both these studies, the primary effect of treatment was thought to be at the level of the BG. However, DLPFC is not usually active in healthy participants during speech motor tasks. Furthermore, behavioral correlation in our study indicates that as speech became more normal, CBF in the right DLPFC increased. Thus, our data indicate that the recruitment of an alternative fronto-striatal loop able to affect pallidal output (Alexander et al., 1986; Liotti et al., 2003) is a more reasonable explanation. This effect of LSVT LOUD can be viewed as a component of the top-down modulation of the speech motor network. Thus, LSVT LOUD modifies the activity in DLPFC, which, in turn, activates motor and subcortical connections (basal ganglia-thalamic inputs) for an effective speech outcome. The absence of correlation between the activity in the basal ganglia and the treatment (see below) supports this conclusion. Through its connection to the parietal and temporal areas (Passingham, 1997), DLPFC can augment somatosensory and auditory feedback and improve communication of these regions with motor areas. Such a top-down effect on sensory systems can explain not only the auditory recalibration seen following LSVT, but also the distributed effects of LSVT LOUD (see above).

**Thalamus**

In this study, activity in ventroposterior lateral nucleus on the left side and VAN on the right hemisphere during speech correlated positively with treatment. Thalamus is a major component of the extrapyramidal motor system connecting the cortical motor areas with the BG, the cerebellum, and the thalamocortical pathway and is involved in movement initiation. The effects of LSVT LOUD on thalamic nuclei can be considered to be secondary downstream modulation by cortical areas such as the DLPFC and premotor cortices.

**Brain Regions That Remained Unchanged Following Treatment**

Regions of the speech motor network such as left primary motor, premotor, auditory cortices, and right GP continue to show activation during speech after LSVT LOUD. Bilateral parietal association areas (BA 7 and 31), visual cortices, and cerebellum were also active during speech after treatment. These findings indicate that the left motor cortex continues to be specialized for the control of movements of face and support higher order aspects of speech production. Following stimulation of STN, the abnormal activation in left PMd during speech are reported to be normalized (Pinto et al., 2004a). However, our data suggest that even after successful outcome following LSVT LOUD, individuals with IPD continue to show activation during speech after LSVT LOUD. Bilateral parietal association areas (BA 7 and 31), visual cortices, and cerebellum were also active during speech after treatment. These findings indicate that the left motor cortex continues to be specialized for the control of movements of face and support higher order aspects of speech production. Following stimulation of STN, the abnormal activation in left PMd during speech are reported to be normalized (Pinto et al., 2004a). However, our data suggest that even after successful outcome following LSVT LOUD, individuals with IPD continue to activate left PMd during speech. Caudal SMA (Talairach coordinate $y \leq 0$), thought to be a premovement sensory integration and articulatory planning area (Loucks et al., 2007; Passingham, 1997; Passingham et al., 1989), was active bilaterally during speech tasks after LSVT LOUD.
However, there was no correlation between CBF in caudal SMA and the behavioral outcome. Parietal association areas (BA 5, 7, and 40) that play a crucial role in the processing of somatosensory and visual information required for motor movement (Deiber et al., 1991; Jenkins et al., 2000; Playford et al., 1992) continued to be active during speech in IPD after voice treatment. The above findings support our conclusion that bilateral parietal association areas (both superior and inferior) continue to be important in speech production in patients with IPD following the voice treatment.

Another main finding in this study is the absence of correlation of activity in BG with treatment outcome. Although activation of BG has been shown to be important in motor preparation, execution (Chesselet and Delfs, 1996), and rescaling movement dimensions in limb-motor tasks, including velocity, strength, and force (Turner and Anderson, 1997; Turner et al., 1998), there is evidence that it does not primarily mediate motor learning (Boecker et al., 1996; Grafton et al., 1992; Jenkins et al., 1994). Basal ganglia activity has been shown not to correlate with increasing movement frequency (Blinkenberg et al., 1996; Jenkins et al., 1997) or force (Dettmers et al., 1995). In earlier studies in IPD, BG activation was absent during speech tasks both with DBS-on and DBS-off conditions (Pinto et al., 2004a). This was thought to be due to presence of activity in BG during all conditions, therefore suppressed during intergroup contrasts. As pointed out earlier, this is a major drawback of contrast analysis. In the previous LSVT LOUD study, a treatment-specific effect was found in right putamen and caudate nucleus in the phonation task, and it was speculated that LSVT LOUD might restore function in the BG (Liotti et al., 2003). Our finding is consistent with both IPD speech studies. Basal ganglia activation reported during speech post-LSVT LOUD indicates its direct role during speech tasks such as phonation and paragraph reading. But its activity is modified posttreatment, not directly as speculated by Liotti et al. (2003), but rather indirectly via alternate fronto-striatal loop that modify pallidal output.

In conclusion, speech appears to be a complex motor task in individuals with IPD requiring several motor and prefrontal areas. Even after a successful behavioral treatment (e.g., LSVT LOUD), speech continues to be a complex and challenging task requiring these areas, especially in the right hemisphere. The changes reported here are immediately following the completion of treatment. It is important to follow up with imaging to see if the right-sided shift is also a marker of long-lasting therapeutic effect of LSVT LOUD.

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