Changes in Brain Activity Following Intensive Voice Treatment in Children With Cerebral Palsy

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Abstract: Eight children (3 females; 8–16 years) with motor speech disorders secondary to cerebral palsy underwent 4 weeks of an intensive neuroplasticity-principled voice treatment protocol, LSVT LOUD®, followed by a structured 12-week maintenance program. Children were asked to overtly produce phonation (ah) at conversational loudness, cued-phonation at perceived twice-conversational loudness, a series of single words, and a prosodic imitation task while being scanned using fMRI, immediately pre- and post-treatment and 12 weeks following a maintenance program. Eight age- and sex-matched controls were scanned at each of the same three time points. Based on the speech and language literature, 16 bilateral regions of interest were selected *a priori* to detect potential neural changes following treatment. Reduced neural activity in the motor areas (decreased motor system effort) before and immediately after treatment, and increased activity in the anterior cingulate gyrus after treatment (increased contribution of decision making processes) were observed in the group with cerebral palsy compared to the control group. Using graphical models, post-treatment changes in connectivity were observed between the left supramarginal gyrus and the right supramarginal gyrus and the left precentral gyrus for the children with cerebral palsy, suggesting LSVT LOUD enhanced contributions of the feedback system in the speech production network instead of high reliance on feedforward control system and the somatosensory target map for regulating vocal effort. Network pruning indicates greater processing efficiency and the recruitment of the auditory and somatosensory feedback control systems following intensive treatment. *Hum Brain Mapp 38:4413–4429, 2017.*

Key words: cerebral palsy; intensive voice and speech therapy; functional connectivity; fMRI; activity-dependent neuroplasticity

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INTRODUCTION

Cerebral Palsy (CP) refers to a movement disorder resulting from damage to motor areas of the brain before, during, or shortly after birth, with a prevalence of 2.11 per 1000 live births [Bax et al., 2005; Oskoui et al., 2013]. Dysfunctions of speech and language are common in this condition, affecting education, and social participation [Boliek and Fox, 2014; Nordberg et al., 2013]. CP motor speech disorders involve one or more subsystems including: respiratory, laryngeal, velopharyngeal, oral-articulatory, or coordination among them [Hodge and Wellman, 1999; Redstone, 2004; Wang et al., 2012].

Perhaps due to the wide range of subsystems affected, there has been no unitary, standardized therapy proven effective for targeting motor speech in CP. Recently, Lee Silverman Voice Treatment (LSVT LOUD), a single-system treatment approach, has been found to positively influence speech motor control in children with CP [Boliek and Fox, 2016; Boliek and Fox, 2014; Fox and Boliek, 2012; Levy et al., 2012]. Initially designed for adults with Parkinson's disease [Fox et al., 2006; Ramig, 2001], it also has been found effective for individuals with stroke [Mahler & Ramig, 2012], multiple sclerosis [Sapir et al., 2001], and traumatic brain injury [Mahler and Ramig, 2012; Sapir et al., 2001; Solomon et al., 2004]. LSVT LOUD focuses on establishing healthy vocal loudness with demonstrated spreading effects to velopharyngeal and articulatory control [Fox et al., 2006] and engages Adkins et al.'s [2006] three elements of training (i.e., skill, strength, and endurance). Moreover, LSVT LOUD follows the principles of activity-dependent neuroplasticity including: intensive treatment delivery, repetitive practice, sensory feedback, and saliency [Garvey et al., 2007; Kleim et al., 2003; Schertz and Gordon, 2009]. Furthermore, Adkins et al. [2006] demonstrated that acquisition of skilled movement induces motor cortex reorganization and alters brain connectivity patterns that support skilled movement sequences, such as voice and speech. Moreover, in their review, Adkins et al. [2006] showed correlations between behavioral changes that occur within the treatment phase (fast-phase changes) to underlying mechanisms associated with protein synthesis whereas continued practice of a skill was related to synaptogenesis and map reorganization (slow-phase changes) (Fig. 1, p. 1778). Evidence for this has been shown in adults with Parkinson's disease following LSVT LOUD [Liotti et al., 2003; Narayana et al., 2010]. The literature provides insight into activity-dependent neuroplasticity [Adkins et al., 2006] specific to gross and fine motor control of limbs. However, little is known about activity-dependent neuroplasticity as it relates to voice and speech motor control and what is known comes from the adult literature [Liotti et al,. 2003; Narayana et al., 2010]. To our knowledge, no other study to date, reports on treatment-based neuroplasticity of the speech mechanism in children. Moreover, there are only a handful of speech production models available to help guide specific inquiry about the underlying neural mechanisms of change in the voice and speech production network following intensive treatment.

The *Directions into Velocities of Articulators* (DIVA) model of speech acquisition and production [Guenther and Vladusich, 2012; Guenther, 2006; Tourville and Guenther, 2011] provides a framework for exploring activity-dependent neuroplasticity. The DIVA model comprises a feedforward subsystem involved in initiating motor commands for well-learned motor sequences, and a feedback subsystem, including auditory and somatosensory systems, involved in corrective iteration for less familiar motor sequences [Guenther, 2006]. Development of the DIVA model was guided by functional brain imaging studies (see Price [2012] for a review) and has been computationally tested [Guenther and Vladusich, 2012].

The brain regions defined in the DIVA model—supplementary motor area (SMA), superior temporal gyrus (STG), supramarginal gyrus (SMG), precentral gyrus (PCG), inferior frontal gyrus (IFG), and cerebellum—are well-documented speech and/or language regions [Price, 2012]. The SMA, part of DIVA's feedforward network, is involved in coordinating sequential movements [Gerloff, 1997; Lee and Quessy, 2003] and speech initiation [Alario et al., 2006; Ziegler et al., 1997]. The STG, attributed to the auditory feedback control system, is assumed to contain auditory target, error, and state maps, with the right STG being involved in speech prosody [Obleser et al., 2008; Zhang et al., 2010]. The SMG, responsive to phonological decisions [Price, 2012], is thought to contain DIVA's somatosensory target and error maps. According to the DIVA model, the PCG controls motor output and contains articulator velocity and position maps in the feedforward control system, and feedback control maps in the feedback control system. In the DIVA model, the IFG works as the feedback control map and the speech sound map, which is

Abbreviations

ACG	anterior cingulate gyrus
BOLD	blood oxygen level-dependent
CP	cerebral palsy
dB SPL	decibels in sound pressure level
DDK	diadochokinetic
f_o	fundamental frequency
fMRI	functional MRI
IFG	inferior frontal gyrus
MTG	middle temporal gyrus
PSC	percentage signal change
PCG	precentral gyrus
ROI	region of interest
SMA	supplementary motor association cortex
SMG	supramarginal gyrus
STG	superior temporal gyrus

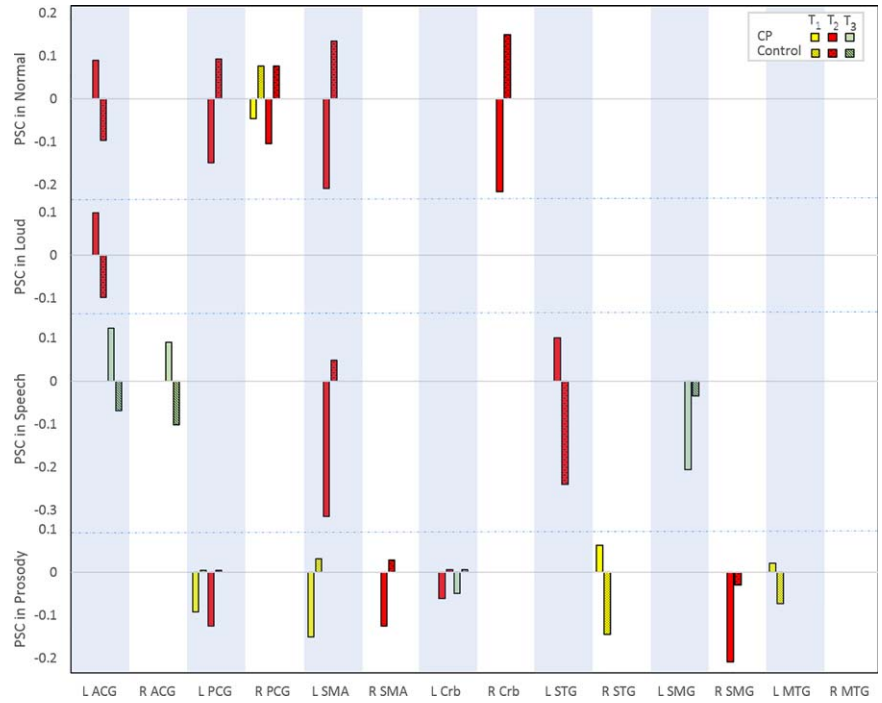

Figure 1.

ROIs with significant PSC differences between the control and the CP groups for the normal phonation, loud phonation, speech, and prosody conditions in the each session (T_1 (yellow), T_2 (red), and T_3 (green). Solid color shows PSC in the CP group, while the respective patterned color shows PSC in the control group. [Color figure can be viewed at wileyonlinelibrary.com]

the repository of learned speech motor programs in the feedforward control system. It is known to be involved in syntactic and semantic processing, verbal working memory, and decision making [Price, 2012]. The cerebellum provides feedback and feedforward motor commands based on afferent sensory error and efferent motor area projections.

Within the context of speech motor control treatment, the anterior cingulate gyrus (ACG) and middle temporal gyrus (MTG) are also important regions to consider. Dorsal ACG, which is reciprocally connected with prefrontal cortex [Delorme et al., 2007; Williams et al., 2004], facilitates action selection through information integration, initiation, and decision making [Arikuni et al., 1994]. Because LSVT LOUD encourages participants to continuously monitor and modulate their own loudness, the ACG would likely be engaged for this continuous decision making and for initiating appropriate laryngeal motor actions, especially in the early phase of learning. Improvements in speech intelligibility have been shown in children with dysarthria and CP following LSVT LOUD [Boliek and Fox, 2014, 2016; Fox and Boliek, 2012; Levy et al., 2012], which entails improvements in the control across speech subsystems (e.g., respiratory, laryngeal, and articulatory). Moreover, observed improvements in pitch range and variation enhance the prosodic features of speech and its intended meaning [Fox and Boliek, 2012]. As such, MTG, which is involved in semantic processing [Price, 2012] should be included as an ROI when evaluating LSVT LOUD.

There is much evidence that the language network is typically left-lateralized in adults [Gaillard et al., 2003] and, to some extent in children (Gaillard et al. [2003]; see also Tzourio-Mazoyer et al. [2017] for a recent review on hemispheric specialization for language), there are unique contributions to processing from both the right and left hemispheres [Gaillard et al., 2001; Price, 2012], and recent research suggests a bilateral network in children for certain aspects of language processing [Goto et al., 2015]. Furthermore, previous researchers found a right-hemisphere shift in speech motor control following LSVT LOUD in adults with Parkinson's disease [Liotti et al., 2003; Narayana et al., 2010]. Therefore, we consider both hemispheres in our analysis.

Graphical modeling is a recently developed approach for fMRI and EEG data that is used to investigate functional connectivity networks and to make inferences regarding the underlying integration mechanisms [Smith et al., 2011]. In graphical modeling, the amount of connectivity within a predefined set of brain regions is estimated

using statistical approaches such as correlation and partial correlation. The results are presented in a graphical model framework in which links between regions represent the statistical dependencies between those regions. The resulting graph can be undirected, which does not provide information on causality between regions. Undirected graphical models can be used as an exploratory device, which is useful when there are no specific hypotheses about the structure of the network or when the number of ROIs is large. Functional connectivity estimation via graphical modeling has previously been used to discriminate between healthy controls and patient groups, including autism [Pollonini et al., 2010], Parkinson's disease [Liu et al., 2012], depression [Rosa et al., 2015], Alzheimer's disease [Huang et al., 2009], schizophrenia [Ma et al., 2011], and stroke [Gorrostieta et al., 2013].

Previous studies have provided behavioral evidence of positive outcomes following LSVT LOUD in children with CP [Boliek and Fox, 2014, 2016; Fox and Boliek, 2012; Levy et al., 2012]. However, the underlying neural mechanisms of change have not yet been investigated. Therefore, in this study, we used fMRI and graphical modelling to investigate neural changes during phonation and speech immediately following LSVT LOUD and again after a 12-week structured maintenance program in a group of children with motor speech disorders secondary to CP. Based on the literature described above, we predefined our ROIs, applied graphical modelling analysis, and hypothesized that LSVT LOUD would induce immediate (fast-phase) changes associated with treatment-based skill, strength, and endurance and longer term (slow-phase) changes based on continued everyday practice and use (beyond the therapeutic dose) of skills targeted in treatment [Adkins et al., 2006; Kleim et al., 2004].

MATERIALS AND METHODS

Participants

Eight children with motor speech disorders secondary to CP (mean age ± SD: 11.6 ± 2.7 years, range: 8–16, 3 females) participated in this study. All participants were medically stable and seizure-free, had basic oral communication skills, and did not use alternative or augmentative communication. For detailed participant demographics and lesion sizes and/or ventricle enlargement information, see Supporting Information, Tables 1 and 2. Eight sex- and age-matched typically developing children served as controls, with average or above average cognitive level and no history of speech or language problems, based on teacher and parent report. Control children did not receive treatment or any similar training throughout the course of the study. Consent and assent were obtained according to the Declaration of Helsinki (2013, http://www.wma.net/en/10home/index.html), and the study was approved by the institution's Health Research Ethics Board.

For the CP group, behavioral and MRI data were acquired immediately pre-(Time 1; T_1) and post-(Time 2; T_2) treatment and after 12 weeks of maintenance (Time 3; T_3), with the same time intervals used for controls. Treatment provided was LSVT LOUD [Ramig et al., 1995], which entailed 16, 1-h sessions, 4 days a week within a month. The first 30 min of each session included (*a*) a minimum of 15 maximum duration phonations (e.g. "say 'ah' for as long as you can using your loud voice"); (*b*) a minimum of 15 maximum f_0 range (e.g. "say 'ah' as high/low as you can with your loud voice"); and (*c*) a minimum of five repetitions of 10 predetermined functional phrases. The final 30 min comprised individualized speech hierarchies designed to maximize functional communication goals. Throughout, emphasis was on sensory awareness and functionality. Participants completed homework once a day on treatment days and twice a day on nontreatment days (treatment details in [Fox and Boliek 2012]; see Boliek and Fox [2014] for repetition details). Supporting Information, Table 3 describes the tasks and minimum number of repetitions (e.g., dose).

MRI Acquisition

MRI data were acquired on a 1.5 T Siemens Sonata MRI scanner. A single-channel head-coil was used with foam padding for head stabilization. Customized ear tubes enabled participants to hear task instructions, over which headphones were worn to attenuate scanner noise. Structural MPRAGE images were collected as follows: TR = 1870 ms, TE = 4.38 ms, flip angle = 15°, 144 slices (FOV 256 × 192 × 144 mm^3, voxel size 1 × 1 × 1 mm^3, scan time 4:29 min). Functional T2*-weighted gradient echo-planar images were collected as follows: TR = 2000 ms, TE = 30 ms, flip angle 90°, 36 slices (64 × 64 matrix, voxel size 4 × 4 × 4 mm^3, FOV 256 × 256, scan time 5:24 min).

EXPERIMENTAL DESIGN

fMRI Data

Using an event-related design with an interstimulus interval (ISI) of 12 s, 157 volumes of data were acquired for each of three overt speech tasks. In each speech task (i.e., phonation, speech, prosody), there were 24 total cue commands (i.e., trials) delivered. For each trial, the cue was delivered during the first volume of the ISI, the response was provided during the second volume of the ISI, followed by four volumes where the participant remained silent (i.e., each trial consisted of 6 volumes). Each run ended with a rest period where 13 volumes of data were collected. Each task was presented in a separate run. All cues were presented binaurally through MRI safe in-the-ear speaker buds using E-Prime® software (Psychology Software Tools, Inc., Pittsburgh, PA, http://www.pstnet.com). MRI sounds were attenuated using over the

ear headphones. **Phonation.** Twelve times each, the instruction "*normal*" prompted participants to produce *ah* at conversational loudness for 2 s, and "*loud*" prompted participants to produce *ah* at perceived twice-conversational loudness. **Speech.** Eight repetitions of three different words that contained corner vowels (heed, hood, had). **Prosody.** Twelve times each, participants repeated *mama* as a declarative and as a question. For speech and prosody, standardized audio tokens for each of the words served as the cue. No cues of "loudness" were given for any of the word productions. The presentation of tasks (phonation, phonation-loud, speech, and prosody) was the same for all participants. For all conditions, the time interval between cues, which were delivered binaurally using E-Prime® software (Psychology Software Tools, Inc., Pittsburgh, PA, http://www.pstnet.com), was 6 volumes (12 seconds). Participant responses were recorded using an MRI-compatible microphone and TF32, a Windows-based version of CSpeech software at a sampling frequency of 44,100 Hz [Milenkovic, 2005] to quantify the timing of voice onset and offset and determine accuracy.

Behavioral Data

Behavioral measures were collected in a speech physiology lab. For participants with CP, intelligibility scores were calculated using the Test of Children's Speech Plus [Hodge et al., 2012]. For both groups, a treatment task and two nontreatment tasks to assess spreading effects were administered. At least three trials of a maximum duration phonation ("*ah*") task produced at perceived conversational loudness was used to assess gains on one of the treatment targets. Measurements of maximum phonation durations and vocal loudness (dB SPL) were extracted. Nontreatment tasks included phrase repetitions (i.e., *Buy Bobby a puppy*; *The blue spot is on the key; The potato stew is in the pot*) and speeded sequential motion repetitions (DDK task; *pa-ta-ka*) at conversational loudness. Phrase repetition measurements of interest were vocal loudness (dB SPL), speech rate (syllables per second), and pitch variation (f_o). The DDK task provided a measurement of maximum speech rate (syllables per second). Acoustic signals were acquired via an omnidirectional condenser microphone (Audio-Technica, Model AT 803b), mounted on the forehead, mouth-to-microphone distance of 10 cm, amplified, acquired, and analyzed using TF32 software. Calibration signals were recorded at the end of each session by holding a tone generator (440 Hz) at a sound to microphone distance of 10 cm and recording the exact dB SPL. Randomly, 20% of the data in the CP and control group were selected and calculated by another expert, with high interrater reliability in both the CP ($r = 0.999$, $P < 0.000$) and control group ($r = 1.000$, $P < 0.000$).

MRI Data Analysis

Images were preprocessed and analyzed with SPM8 software (www.fil.ion.ucl.ac.uk/spm/). After discarding the first six images in each run, the remaining volumes were realigned to the first remaining image using INRIA-Lign Toolbox (A. Roche, INRIA Sophia Antipolis, EPI-DAURE Group) for motion correction. For detection and removal of outliers, ART Toolbox (http://www.nitrc.org/projects/art/) with a motion threshold of 6 mm was used. Control participant functional images were spatially normalized to a symmetric 10–14-year-old pediatric EPI template (http://www.bic.mni.mcgill.ca/~vfonov/nihpd/obj1/nihpd_sym_10.0-14.0_nifti.zip), resampled to $3 \times 3 \times 3$ mm voxel size, and smoothed using a 6 mm FWHM Gaussian kernel. To verify that movement artefacts were sufficiently removed using the ART Toolbox, we calculated movement for the remaining volumes prior to including them in the final analyses. Average movement remaining for the control group was 0.47 mm and was 1.23 mm for the CP group. Both values were significantly smaller than our resampled voxel size of $3 \times 3 \times 3$ mm and smoothing kernel of 6 mm. CP participant functional images were co-registered to their T_1 anatomical image and smoothed using an 8 mm FWHM Gaussian kernel. Cue onset times (considered as event with 0 s duration; i.e., the first volume of each trial) and participant's response onsets (i.e., the second volume of each trial) and durations were extracted and convolved with the canonical hemodynamic response function in the first level model. Specifically, for each speech production condition, a regressor with onset and duration extracted from participants' response, and for each cue, a regressor with zero duration were defined. All remaining volumes were coded as "rest" and used as the baseline condition. A HDR was convolved with these regressors to determine "task"-related activity.

To compare activation between the groups, PSC was extracted using the MarsBar toolbox (http://marsbar.sourceforge.net) [Brett et al., 2002] in predefined ROIs. Spherical ROIs (radius of 6 mm cortical and 8 mm cerebellar) were created in the pediatric template for controls and in the anatomical image of each individual with CP using MRIcron©. Coordinates for the ROI in the right hemisphere are ACG (8, 35, 20), IFG (53, 21, 17), cerebellum (22, −51, −27), MTG (61, −7, −15), SMA (10, −10, 71), SMG (57, −43, 45), STG (61, −6, 1), PCG (23, −19, 68).

Graphical Model Analysis

Mean time series for each condition were extracted using Rex Toolbox (Whitefield-Gabrieli, 2013 http://gablab.mit.edu/index.php/research/95-gablab-site/gablab/people/swg). For each condition (normal phonation, loud phonation, speech, and prosody), a maximum of six volumes following response onset were considered, of which,

the first two were discarded to control for the rising edge of the hemodynamic response. Correlation and their associated *P* values based on the number of points in the four conditions were estimated for each participant. Connections that survived *Bonferroni* correction were deemed significant and were kept in the graph (16 ROIs resulting in 120 possible connections; $P < 0.00083$). Because this was a *Phase I* treatment study, a less stringent criteria was sufficient for inference [Robey, 2004], so connections that appeared in four or more participants were entered into the group level network.

RESULTS

Behavioral Data

In each group, repeated measures ANOVAs and pairwise comparisons were conducted to evaluate change across time points (Table I). Changes across time were investigated for both fast phase changes (T_1 vs T_2) and slow phase changes (T_1 vs T_3, and T_2 vs T_3).

Target tasks

Controls exhibited increased vocal loudness for the maximum duration phonation tasks ($T_2 < T_3$: $t(7) = -2.4$, $P = 0.046$; $T_1 < T_3$: $t(7) = -2.8$, $P = 0.027$). For the same task, the CP group exhibited slow-phase increases of maximum duration ($T_1 < T_3$: $t(7) = -2.6$, $P = 0.036$) and in vocal loudness ($T_2 < T_3$: $t(7) = -5.5$, $P = 0.001$; $T_1 < T_3$: $t(7) = -5.3$, $P = 0.001$).

Nontarget tasks

Controls exhibited increased loudness during phrases ($T_1 < T_3$: $t(7) = -2.6$, $P = 0.035$) and pitch variability ($T_1 < T_3$: $t(7) = -2.7$, $P = 0.031$), and increased DDK rate ($T_1 < T_2$: $t(7) = -2.7$, $P = 0.031$; $T_2 < T_3$: $t(7) = -4.3$, $P = 0.003$; $T_1 < T_3$: $t(7) = -6.8$, $P = 0.000$). The CP group exhibited slow phase increases in loudness during phrases ($T_2 < T_3$: $t(7) = -3.3$, $P = 0.014$; $T_1 < T_3$: $t(7) = -5.0$, $P = 0.002$) and in the pitch variability task ($T_2 < T_3$: $t(7) = -3.0$, $P = 0.020$), and fast- and slow-phase increases in intelligibility scores ($T_1 < T_2$: $t(7) = -3.5$, $P = 0.01$; $T_1 < T_3$: $t(7) = -2.6$, $P = 0.035$).

Comparing Brain Activation Between Groups

Independent sample *t*-tests for each condition were conducted to compare brain activity between groups. Data for each control participant in all three sessions were averaged to form a composite of 8 control participants (Fig. 1). This was done to increase statistical power based on the assumption that there would be minimal brain activity changes across the four-month time interval in typically developing children. Moreover, small changes observed

TABLE I. Behavioral changes in the control and CP groups

Group	Task	Mean ± STD (N)			F-test	*t* value (*P* value) direction		
		T_1	T_2	T_3	(*P* value)	T_1–T_2	T_2–T_3	T_1–T_3
Control	Max phonation duration	18.18 ± 6.45 (8)	19.17 ± 7.07 (8)	19.68 ± 5.62 (8)	0.523 (0.604)	-	-	-
	Vocal loudness phonation	73.47 ± 6.05 (8)	78.30 ± 6.48 (8)	84.19 ± 7.43 (8)	5.589 (0.016)	−1.5 (0.176)	−2.4 (0.046)↑	−2.8 (0.027)↑
	Vocal loudness phrases	70.22 ± 6.31 (8)	72.18 ± 7.54 (8)	79.19 ± 7.26 (8)	4.564 (0.030)	−0.7 (0.479)	−2.2 (0.068)	−2.6 (0.035)↑
	Rate phrases	3.89 ± 0.44 (8)	3.68 ± 0.40 (8)	3.79 ± 0.32 (8)	2.122 (0.157)	-	-	-
	Pitch variability	30.69 ± 5.84 (8)	33.40 ± 10.63 (8)	37.17 ± 9.36 (8)	2.966 (0.084)	−0.9 (0.417)	−1.6 (0.159)	−2.7 (0.031)↑
	Average syllable/sec DDK	5.14 ± 1.29 (8)	5.53 ± 1.03 (8)	6.05 ± 1.10 (8)	23.44 (0.000)	−2.7 (0.031)↑	−4.3 (0.003)↑	−6.8 (0.000)↑
CP	Max phonation duration	8.81 ± 3.76 (8)	11.45 ± 5.36 (8)	11.73 ± 3.49 (8)	4.0 (0.042)	−1.8 (0.109)	−0.4 (0.722)	−2.6 (0.036)↑
	Vocal loudness phonation	77.47 ± 4.60 (8)	80.42 ± 7.11 (8)	92.98 ± 10.82 (8)	21.4 (0.000)	−1.3 (0.236)	−5.5 (0.001)↑	−5.3 (0.001)↑
	Vocal loudness phrases	72.74 ± 3.22 (8)	75.83 ± 4.78 (8)	84.55 ± 8.19 (8)	13.8 (0.000)	−1.6 (0.150)	−3.3 (0.014)↑	−5.0 (0.002)↑
	Rate phrases	2.77 ± 0.72 (8)	2.68 ± 0.63 (8)	2.72 ± 0.57 (8)	0.2 (0.848)	-	-	-
	Pitch variability	35.46 ± 6.66 (8)	31.85 ± 7.5 (8)	36.90 ± 10.46 (8)	2.8 (0.091)	1.9 (0.104)	−3.0 (0.02)↑	−0.5 (0.62)
	Average syllable/sec DDK	3.35 ± 1.00 (5)	3.61 ± 1.19 (6)	3.26 ± 0.76 (7)	1.3 (0.312)	-	-	-
	Intelligibility	64.02 ± 34.18 (8)	73.08 ± 32.55 (8)	71.51 ± 29.87 (8)	6.6 (0.009)	−3.5 (0.01)↑	0.6 (0.552)	−2.6 (0.035)

Maximum phonation durations (s), vocal loudness (dB SPL), rate phrases (syllables/s).

across time points was assumed to be indicative of general measurement variability in pediatric fMRI protocols and served as a baseline from which to compare the CP group.

Compared to controls, the CP group exhibited decreased brain activity for normal phonation condition in: right PCG ($t(14) = -2.6$, $P = 0.023$) at T_1; and in left PCG ($t(14) = -2.6$, $P = 0.020$), right PCG ($t(14) = -3.1$, $P = 0.008$), left SMA ($t(14) = -3.1$, $P = 0.008$), and right cerebellum ($t(13) = -3.3$, $P = 0.006$) at T_2. In the speech condition, the CP group exhibited decreased brain activity compared to controls in: left SMA ($t(14) = -2.4$, $P = 0.034$) at T_2 and left SMG ($t(13) = -2.7$, $P = 0.017$) at T_3; similarly for the prosody condition: left PCG ($t(8.5) = -2.3$, $P = 0.045$) and left SMA ($t(14) = -2.6$, $P = 0.023$) at T_1; left PCG ($t(12) = -4.0$, $P = 0.002$), right SMA ($t(13) = -2.2$, $P = 0.043$), left cerebellum ($t(12) = -3.0$, $P = 0.012$), and right SMG ($t(7.7) = -2.4$, $P = 0.045$) at T_2; and in left cerebellum ($t(13) = -2.2$, $P = 0.045$) at T_3.

In contrast, the CP group exhibited increased brain activity compared to controls for normal phonation condition in left ACG ($t(13) = 2.3$, $P = 0.042$) at T_2; for the loud phonation condition in left ACG ($t(14) = 2.4$, $P = 0.028$) at T_2; for the speech condition, in left STG ($t(13) = 2.6$, $P = 0.022$) at T_2, and in left ACG ($t(14) = 2.9$, $P = 0.012$) and right ACG ($t(14) = 3.1$, $P = 0.008$) at T_3; and for the prosody condition, in right STG ($t(14) = 2.9$, $P = 0.011$) and left MTG ($t(14) = 2.3$, $P = 0.040$) at T_1.

Within-Group Changes in Brain Activation

PSC in ROIs was used to evaluate neural changes immediately following LSVT LOUD and after 12 weeks of maintenance. Points that were at least three times the inter-quantile range (IQR) below the first and above the third quantile were removed (<2% of data). For the control group, the grand standard deviation for all three days was calculated and used in paired sample t tests (i.e., the group mean difference across time points was divided by standard error of mean, which is the grand standard deviation of the control group divided by the squared root of number of subjects in that test). Figure 2 illustrates the significant PSC changes across days for each group. A change was considered significant if two differences were in the same direction (i.e., both increased or both decreased).

In controls, for the normal phonation condition, decreases in PSC were observed in right cerebellum ($T_1 > T_2$: $t(7) = 2.6$, $P = 0.035$, $T_1 > T_3$: $t(7) = 2.8$, $P = 0.026$); and for the loud phonation condition, in right ACG ($T_2 > T_3$: $t(7) = 2.5$, $P = 0.042$, $T_1 > T_3$: $t(7) = 3.5$, $P = 0.011$). In the CP group, for the normal phonation condition, increases in PSC were observed in left SMG ($T_2 < T_3$: $t(7) = -3.9$, $P = 0.006$, $T_1 < T_3$: $t(7) = -3.0$, $P = 0.020$); and for the speech condition, in right MTG ($T_2 < T_3$: $t(7) = -5.3$, $P = 0.001$, $T_1 < T_3$: $t(7) = -5.1$, $P = 0.001$). Decreases in the PSC for the speech condition were observed in: left PCG ($T_1 > T_2$: $t(7) = 3.9$, $P = 0.006$, $T_1 > T_3$: $t(6) = 2.7$, $P = 0.032$), left SMG ($T_2 > T_3$: $t(6) = 3.2$, $P = 0.020$, $T_1 > T_3$: $t(6) = 4.5$, $P = 0.004$), left STG ($T_2 > T_3$: $t(6) = 3.2$, $P = 0.019$, $T_1 > T_3$: $t(6) = 4.4$, $P = 0.005$), and right SMG ($T_1 > T_2$: $t(7) = 4.5$, $P = 0.003$, $T_1 > T_3$: $t(7) = 3.2$, $P = 0.016$).

Correlations With Behavioral Data

For each ROI, relationships between PSC and the behavioral measures were assessed using Pearson's correlation. Behavioral measures for the normal phonation and loud phonation conditions were loudness and maximum phonation duration from the target task. For the speech and prosody conditions, behavioral measures were loudness, rate, pitch variability, average DDK rate, and intelligibility scores from the nontarget tasks. To minimize the impact of outliers (with fewer data points in this case), any score more than 1.5 times the IQR away below the first and above the third quantile was substituted with the group average (<5% of data). Correlations that survived multiple comparisons ($P < 0.025$ target; 0.01 nontarget tasks) are reported. Furthermore, correlations were calculated for all conditions and ROIs, where significant changes in both behavior and PSC were observed.

Significant correlations between PSC and targeted behavioral tasks across time points (i.e., T_1, T_2, T_3) are presented in Table II for the control group, and children with CP for target and nontarget tasks. Figure 3 shows the significant correlations between changes of PSC and changes of the measure of dB SPL in the control and CP groups on phonation and phrases across time points.

Graphical Model Analysis

Control group

Connections that existed in at least four participants per session, over at least two sessions, were included in the group level network. The probability that any two regions would be connected was 13% (i.e., the average number of connections across all tasks, sessions, and groups, divided by the total number of possible connections). The cumulative probability that at least four individuals would show the same connection was $P < 0.013$ (two-tailed). Connections are shown for normal phonation (Fig. 4A), loud phonation (Fig. 4B), speech, (Fig. 4C), and prosody (Fig. 4D) conditions.

CP group

To evaluate the effect of treatment, connectivity graphs were calculated for T_1, T_2, and T_3 and for each condition. The connections that appeared in at least four participants

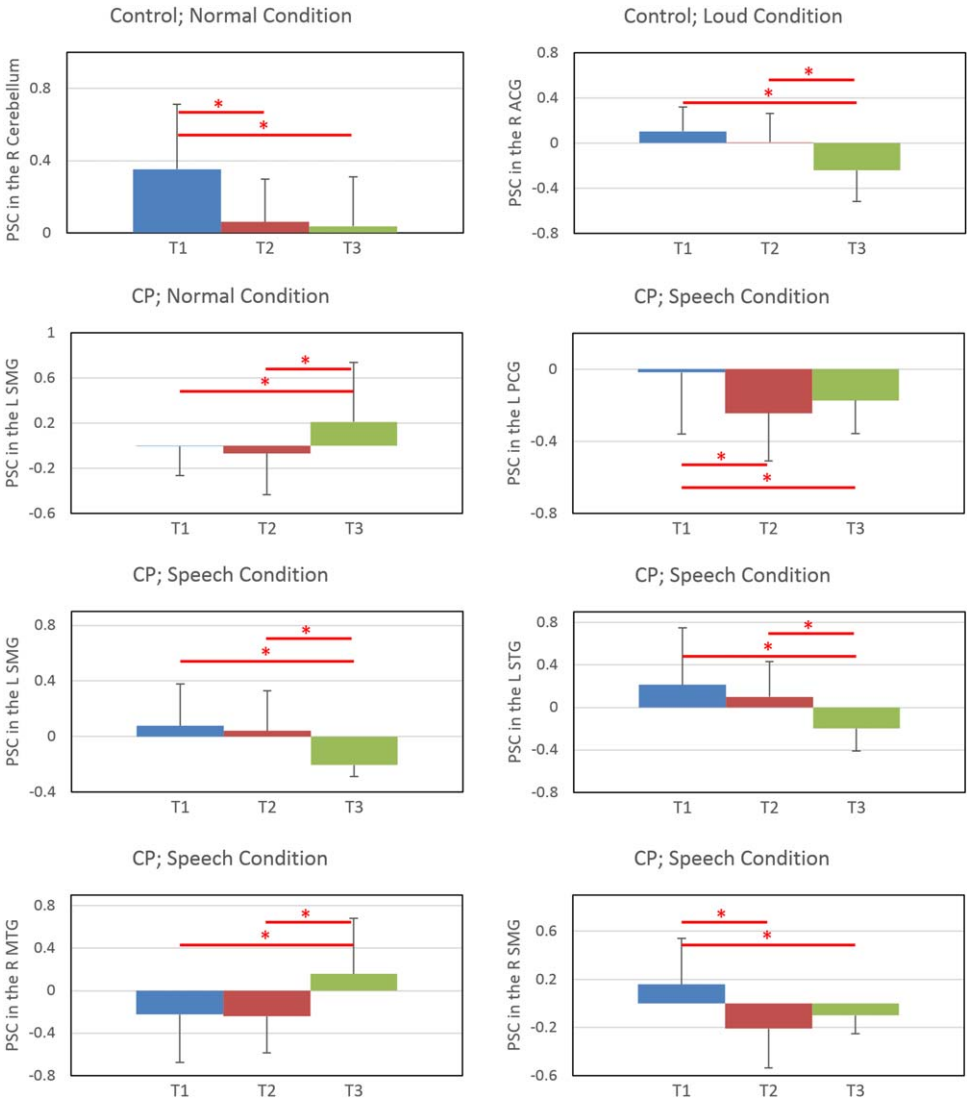

Figure 2.
Significant change of PSC in the control and CP groups across time. [Color figure can be viewed at wileyonlinelibrary.com]

are mentioned. Connections are shown across time points for normal phonation (Fig. 5A–C), loud phonation (Fig. 5D–F), speech (Fig. 5G–I), and prosody (Fig. 5J–L) conditions.

Changes in Networks

We constrained our analysis to look at only those ROIs that showed consistent and significant changes across days (Table III). Z-tests were performed to test the significance of connections that appeared and/or disappeared.

Control group

Table III shows the only change found in the control group. During loud phonation condition, a connection appeared between right ACG and left IFG at T_3 ($T_1 < T_3$: $z(8) = -2.7$, $P = 0.007$, $T_2 < T_3$: $z(8) = -2.7$, $P = 0.007$).

CP group

In the CP group (Table III), during normal phonation condition, the connection between left SMG and left PCG disappeared at T_2 and T_3 ($T_1 > T_2$: $z(8) = 2.3$, $P = 0.021$, $T_1 > T_3$: $z(8) = 2.3$, $P = 0.021$), and the connection between

TABLE II. Significant Correlations Between PSC and Behavioral Measures for Target and Nontarget Tasks, in the Control and CP Groups

Group/task type	Time	Condition	Behavioral measure	ROI	Pearson's r (P value)
Control/target	T_1	Normal phonation	Maximum phonation duration	L PCG	−0.797 (0.018)
	T_1	Loud phonation	Maximum phonation duration	R ACG	0.937 (0.001)
	T_2	Normal phonation	Vocal loudness in phonation	R PCG	0.776 (0.023)
CP/target	T_1	Loud phonation	Maximum phonation duration	R SMA	0.813 (0.014)
	T_1	Loud phonation	Vocal loudness in phonation	R SMA	0.871 (0.005)
	T_2	Loud phonation	Maximum phonation duration	L IFG	−0.868 (0.005)
	T_3	Normal phonation	Vocal loudness in phonation	R STG	0.790 (0.020)
Control/nontarget	T_2	Speech	Pitch variability in phrase	R SMA	−0.887 (0.003)
	T_2	Prosody	Rate phrases	R PCG	0.875 (0.004)
CP/nontarget	T_2	Speech	Intelligibility	R IFG	−0.865 (0.006)
	T_3	Speech	Rate phrases	L IFG	−0.850 (0.005)
	T_3	Prosody	Pitch variability in phrases	R MTG	0.855 (0.007)

left SMG and right SMG appeared at T_2 and T_3 ($T_1 < T_2$: $z(8) = -2.3$, $P = 0.021$, $T_1 < T_3$: $z(8) = -2.3$, $P = 0.021$). For the speech condition, the following connections disappeared at T_2 and T_3: right MTG to right ACG ($T_1 > T_2$: $z(8) = 2.3$, $P = 0.021$, $T_1 > T_3$: $z(8) = 2.3$, $P = 0.021$); right MTG to left MTG ($T_1 > T_2$: $z(8) = 2.7$, $P = 0.007$, $T_1 > T_3$: $z(8) = 2.7$, $P = 0.007$); left SMG to right SMA ($T_1 > T_2$: $z(8) = 2.3$, $P = 0.021$, $T_1 > T_3$: $z(8) = 2.3$, $P = 0.021$); left PCG to right SMG ($T_1 > T_2$: $z(8) = 3.1$, $P = 0.001$, $T_1 > T_3$: $z(8) = 3.1$, $P = 0.001$); and left STG to left MTG ($T_1 > T_2$: $z(8) = 2.7$, $P = 0.007$, $T_1 > T_3$: $z(8) = 2.7$, $P = 0.007$).

DISCUSSION

Using fMRI and graphical modeling, we investigated the underlying neural changes following LSVT LOUD in children with CP. We provide evidence of activity-dependent neuroplasticity for treatment targets (maximum

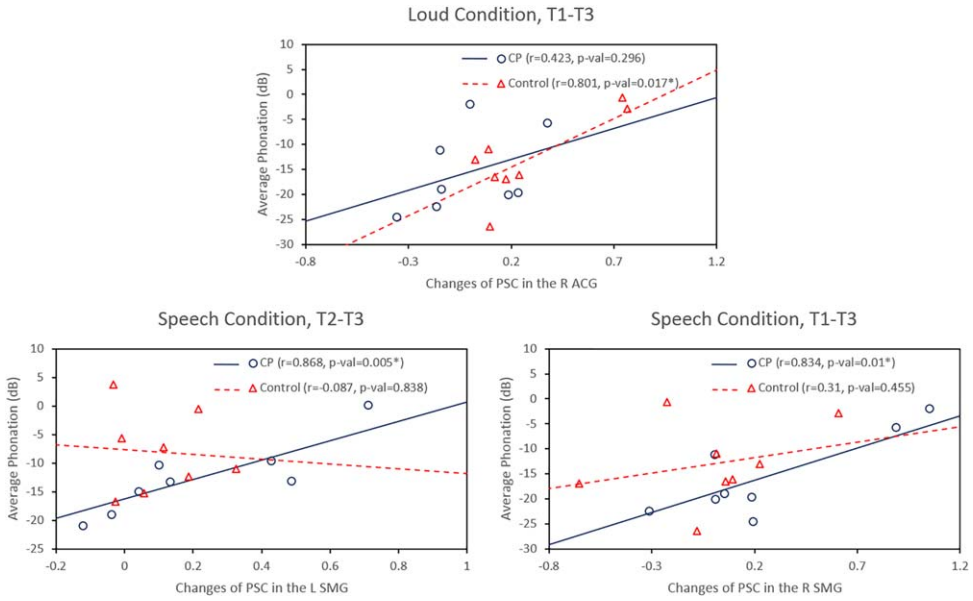

Figure 3.
Significant correlations between changes of PSC and changes of behavioral measures across time, for target tasks in the control group and nontarget tasks in the CP group. [Color figure can be viewed at wileyonlinelibrary.com]

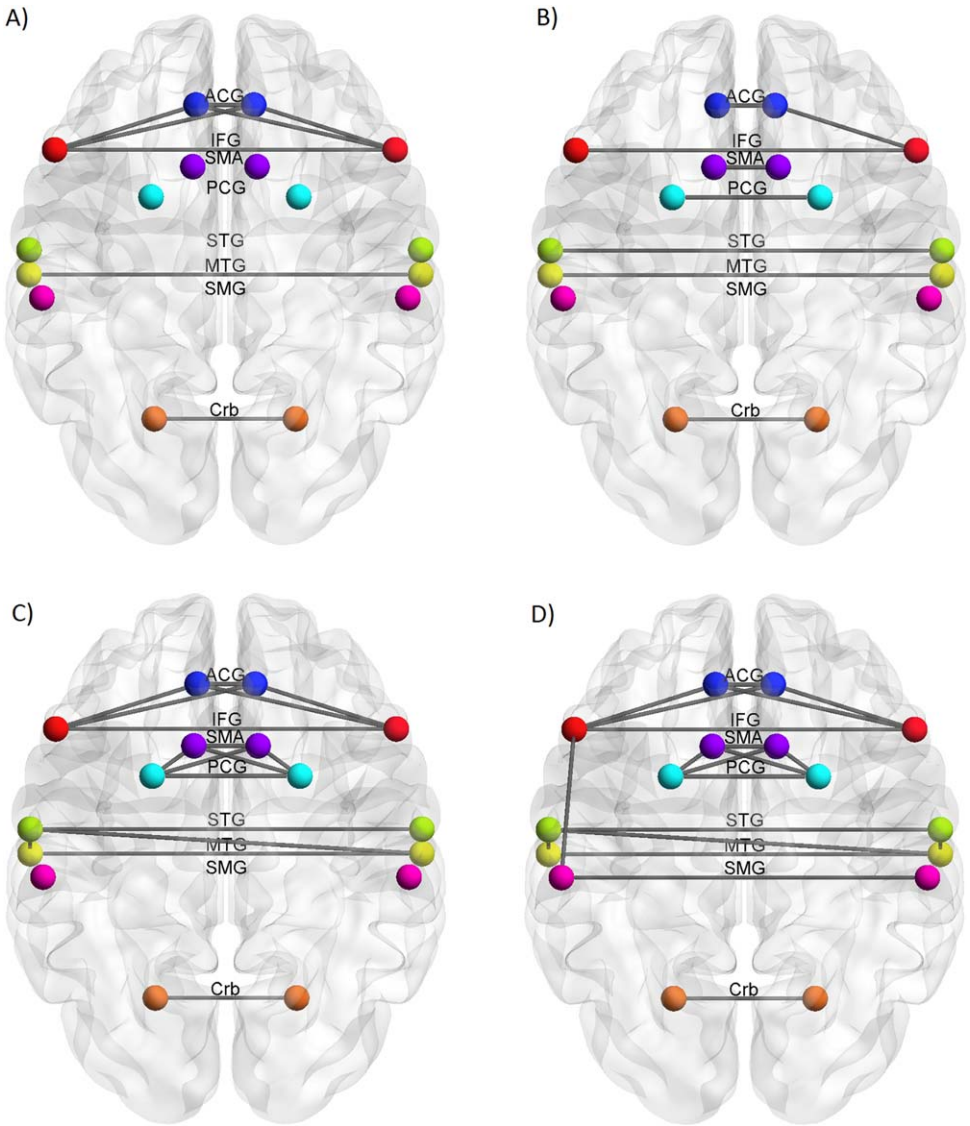

Figure 4.
Networks in the control group: (A) normal phonation, (B) loud phonation, (C) speech, and (D) prosody conditions. [Color figure can be viewed at wileyonlinelibrary.com]

duration phonation) and nontargeted tasks representing the spreading of treatment effects (e.g., speech). Consistent with Adkins et al.'s [2006] model of neural plasticity, fast-phase changes were evidenced by differences between T_1 and T_2 for the speech condition in left PCG and right SMG, and slow-phase changes were evidenced by differences in left SMG for the normal phonation condition, and left SMG, left STG, and right MTG for the speech condition. The graphical models provide the first description of functional connectivity in children with and without CP during phonation and speech, where we provided evidence that graphical models are sensitive to fast- and slow-phase changes following intensive treatment. For controls, connectivity between regions such as bilateral SMA and PCG revealed the underlying mechanism of speech production in children.

Phonation and Speech in the CP and Control Group

Reduced brain activation (PSC) in children with CP compared to controls was observed in the SMA, PCG,

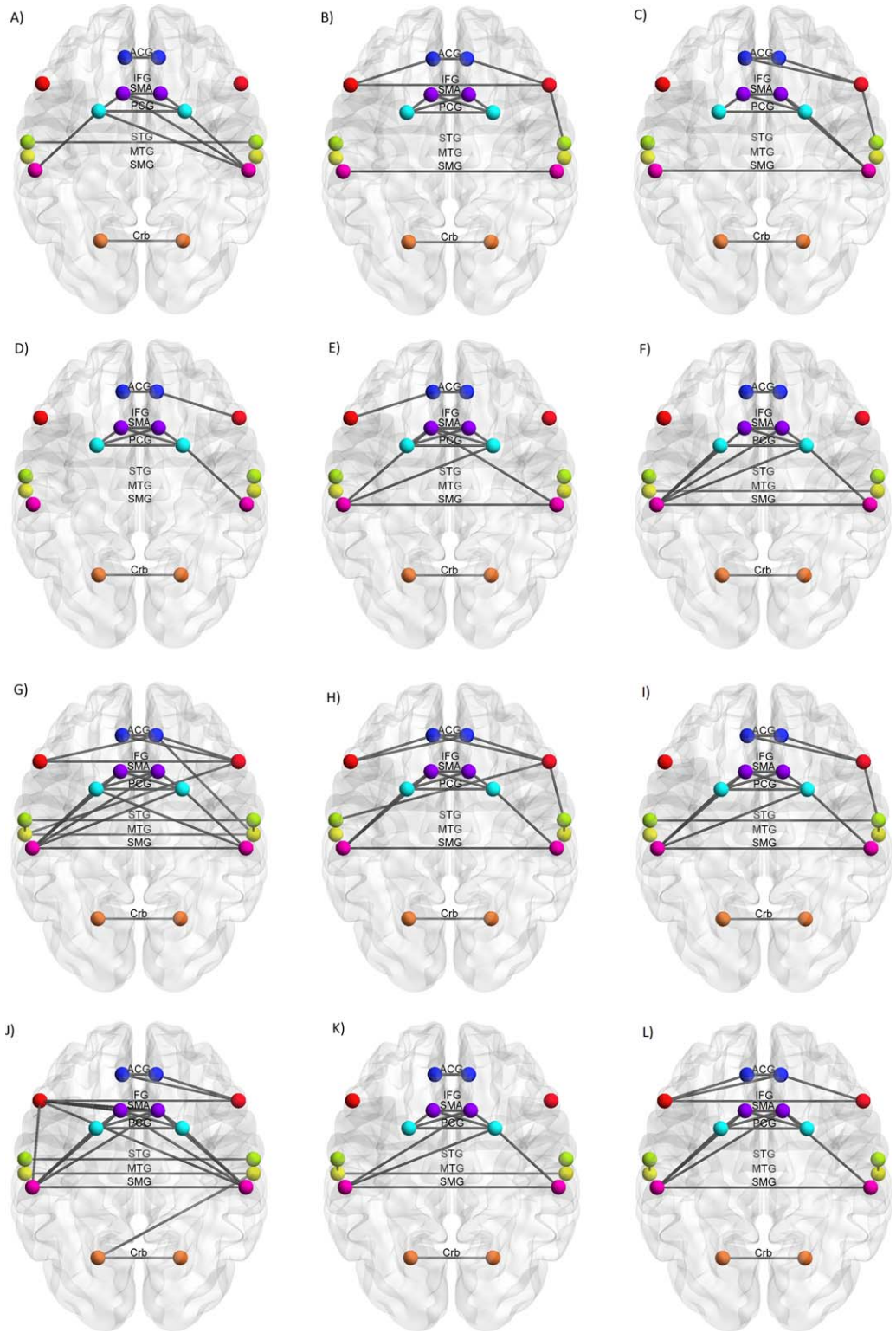

Figure 5.

Networks in the CP group: (A–C) normal phonation, (D–F) loud phonation, (G–I) speech, and (J–L) prosody conditions. (A,D,G,J) T_1 session, (B,E,H,K) T_2 session, and (C,F,I,L) T_3 session. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE III. Significant Changes of Graphical Model Links in the Control and CP Groups Across Time

			Number of participants with links			*z*-score (*P* value) direction		
Group	Link	Condition	T_1	T_2	T_3	T_1–T_2	T_2–T_3	T_1–T_3
Control	R ACG ↔ L IFG	Loud phonation	0	0	5	0 (N/A)	−2.7 (0.007)↑	−2.7 (0.007)
	R ACG ↔ L ACG	Loud phonation	4	0	6	2.3 (0.021)↓	−3.1 (0.001)↑	−1.0 (0.3)
	R ACG ↔ R IFG	Loud phonation	5	0	5	2.7 (0.007)↓	0 (N/A)	−2.7 (0.007)↑
CP	L SMG ↔ L PCG	Normal phonation	4	0	0	2.3 (0.021)↓	0 (N/A)	2.3 (0.021)↓
	L SMG ↔ R SMG	Normal phonation	0	4	4	−2.3 (0.021)↑	0 (N/A)	−2.3 (0.021) ↑
	R MTG ↔ R ACG	Speech	4	0	0	2.3 (0.021)↓	0 (N/A)	2.3 (0.021)↓
	R MTG ↔ L MTG	Speech	5	0	0	2.7 (0.007)↓	0 (N/A)	2.7 (0.007)↓
	L SMG ↔ R SMA	Speech	4	0	0	2.3 (0.021)↓	0 (N/A)	2.3 (0.021)↓
	L PCG ↔ R SMG	Speech	6	0	0	3.1 (0.001)↓	0 (N/A)	3.1 (0.001)↓
	L STG ↔ L MTG	Speech	5	0	0	2.7 (0.007)↓	0 (N/A)	2.7 (0.007)↓
	L STG ↔ R IFG	Speech	0	4	0	2.3 (0.021)↑	2.3 (0.021)↓	0 (N/A)
	L SMG ↔ R PCG	Speech	5	0	4	2.7 (0.007)↓	2.3 (0.021)↑	0.5 (0.0617)
	L STG ↔ R STG	Speech	4	0	4	2.3 (0.021)↓	2.3 (0.021)↑	0 (N/A)

and cerebellum; mostly during T_1 and T_2; indicating lower brain activity in brain regions associated with speech motor control. This contrasts with previous work in adults with Parkinson's disease, where, before LSVT LOUD, there was excessive activity in the SMA compared to controls [Liotti et al., 2003], which they attributed to effort. The discrepancy between our study and previous work might arise from the different pathologies; Parkinson's disease is a late onset disorder that disrupts a once healthy speech system, whereas CP is an early onset disorder that impacts a developing system. Hence, individuals with Parkinson's disease have prior expectations and experience with healthy speech and endeavor to regain previous performance, whereas children with CP have no prior expectations or experience and thus have no previous target performance to strive for. Consistent with this hypothesis, we observed increased brain activity in the ACG after LSVT LOUD in the children with CP, which, given the role of this region in cognitive control and decision making, may reflect increased effort associated with maintaining a recently learned target.

Evaluating Cortical Networks

Functional connectivity between ROIs indicates temporally correlated activity during task performance in the ROIs. Although it does not necessarily correspond to structural connectivity, functional connectivity sheds light onto underlying mechanisms of undirected synchronization and information integration in the brain. Therefore, graphical modeling is valuable when studying brain functionality as it permits the interpretation of network changes following treatment as possible cortical reorganization, which occurs in the late stages of training (i.e., after learning curve stabilization [Adkins et al., 2006; Kleim et al., 2004]).

Phonation and Speech Networks in the Control Group

This is the first study to investigate connectivity networks associated with phonation and speech in children. Our findings are consistent with the DIVA model framework for motor speech control [Guenther, 2006] and further our understanding of this model in a typically developing population. In general, the graph for normal phonation condition in controls is the simplest amongst all conditions. As task complexity increases, from normal phonation, to loud phonation, to speech and prosody conditions, the number of connections in the graph increases, which indicates greater coordination needed among different regions and is similar to previous findings in healthy adults [Fuertinger et al., 2015]. In the following sections, we interpret our findings within the framework of DIVA feedforward and feedback subsystems[1].

[1]Graphical modeling provides information on interactions among different regions. In cases where both regions were in either the feedforward or feedback subsystems (e.g., between left SMA and left PCG in the speech condition), attributing the link to either feedforward or feedback subsystem is straightforward. However, in some cases, we observed a link between a region in the feedforward subsystem and a region in the feedback subsystem (e.g., between the left SMG and the left IFG in the prosody condition). In these cases, we consider the link a part of the feedback subsystem.

Feedforward Control Network

The trend of increasing network complexity according to task difficulty was evident among connections in bilateral SMA and PCG, which indicated more coordination and involvement between initiation maps and articulatory velocity and position maps for loud phonation, speech, and prosody conditions compared to the normal phonation condition. Primary motor and surrounding cortex (i.e., premotor, somatosensory, and parietal) has been identified as a hub for syllable and speech production, wherein connectivity correlation values increased by task demand [Fuertinger et al., 2015]. Furthermore, we found connections between left and right cerebellum and left and right MTG for all conditions, suggesting bilateral feedforward control in children.

Feedback Control Network

In all conditions, there were significant positive correlations between activation in bilateral IFG and ACG. This finding supports the role of IFG as the speech sound map in the DIVA model; more specifically, left IFG as the input region for the entire speech–motor–control system, and thus the location for stored speech sound maps [Ghosh et al., 2008; Tourville and Guenther, 2011; Tourville et al., 2008]. Activation in right IFG has been shown to increase during perturbed auditory [Tourville et al., 2008] and somatosensory [Golfinopoulos et al., 2011] feedback. While ACG is not currently included in the DIVA model, it has an established role in speech and language [Price, 2012], and dorsal ACG is important for integrating information necessary for initiation and decision making [Delorme et al., 2007; Williams et al., 2004]. Hence, our finding of IFG–ACG connections across all tasks suggests that these regions work together during development and maintenance of speech–motor–control in children. Furthermore, left and right STG were connected in the loud phonation, speech, and prosody conditions. The STG plays a role in acoustic analysis of speech and nonspeech sounds [Price, 2012]. The absence of this connection during normal phonation condition was not surprising given the reduced auditory processing load required compared to the other conditions. However, correlations existed between left STG and left and right MTG for both speech and prosody conditions, suggesting the need for coordination among auditory and semantic processing regions when children are presented with and produce words with prosodic characteristics, which is important for conveying the meaning of the sentences [Dahan, 2015]. Our observations are consistent with studies showing that during semantic processing of speech, simultaneous activation of STG and MTG are related to language tasks requiring semantic processing [Price, 2012]. Only in the prosody condition were right MTG and STG connected, which aligns with previous findings of right STG involvement in prosodic processing and sensitivity to variations in frequency and rhythm [Obleser et al., 2008; Zhang et al., 2010]. Finally, we provide evidence for bilateral somatosensory feedback by way of a left/right SMG connection during the prosody condition.

Phonation and Speech Network in the CP Group

Behavioral results suggested that following LSVT LOUD, intelligibility improved in fast phase, while vocal loudness, maximum phonation duration, and pitch variability changes occurred in slow phase. The changes in the treated target observe in this group of children with CP did appear after continued practice beyond the treatment protocol. For example, initially some children with CP had difficulty modulating healthy vocal loudness (Table I) at baseline, meaning they were too loud or exhibited variable loudness. The changes observed with continued practice may be indicative of a need for a more intensive or a longer treatment dosage than that used with adults having Parkinson disease (i.e., Narayana et al. [2010]). Moreover, these are group data and as such we are not able to report on individual children, some of whom may have been very responsive to change within the 4 week dosage structure [Boliek and Fox, 2014]. The fact that several changes were not observed until T3 indicates the critical need for continued practice of the treatment target well beyond the prescribed 4 week dose in an effort to solidify slow-phase neuroplasticity. Based on this reasoning and the behavioral outcomes, we expected to observe both fast and slow phase changes in brain networks.

Changes Following Speech Therapy

In the normal phonation condition, neural activity in left SMG increased following treatment. Left SMG, which is involved in auditory attention and categorization functions [Price, 2012], is included in somatosensory error and state maps within the DIVA model. Therefore, our finding of increased SMG activation may indicate greater attentional effort. This aligns with previous research indicating top–down treatment effects of LSVT LOUD in adults with Parkinson's disease via increased activation in right dorsolateral prefrontal cortex following treatment [Narayana et al., 2010].

Change in left SMG activity was accompanied by two changes in the graphical model: disappearance of the left SMG to left PCG connection at T_2 and T_3, and the appearance of a left to right SMG connection at T_2 and T_3 during normal phonation. The existence of the left SMG to left PCG connection only at T_1, indicates that individuals with CP relied on an ineffectual combination of feedback and feedforward motor programs to regulate phonation prior to treatment [Tourville and Guenther, 2011], which may, in turn be related to observed weak or variable performance (i.e., short phonation durations, poor loudness

modulation, poor intelligibility). In turn, increased functional connectivity between left and right SMG following therapy may indicate that clinician incitement and feedback during LSVT LOUD modulated attention and enhanced features of the feedback control system. Post-treatment establishment of connectivity between left and right SMG at T_2 and T_3, and right SMG and right PCG at T_3 indicates the importance of the right hemisphere in somatosensory calibration and sensory motor integration to provide feedback. This is consistent previous Parkinson's disease research, which showed shifting of neural activity from left- to right-hemisphere following LSVT LOUD [Narayana et al., 2010]. At T_1, during the loud phonation condition, PSC in right SMA and maximum phonation duration and loudness were correlated. Because right SMA represents the initiation map in DIVA's feedforward control system, the correlation reinforces that the feedforward rather than feedback network was involved in phonation at T_1. After training, we observed correlations between maximum phonation duration and PSC in left IFG (speech sound map) for the loud phonation condition, and between vocal loudness in phonation and PSC in right STG (auditory error and state maps; part of feedback network) for the normal phonation condition which is commensurate with the sensory recalibration associated with treatment.

For the speech condition, PSC fast- and slow-phase decreases were observed in left PCG and right SMG, slow-phase decreases were observed in left SMG and left STG, and a slow-phase increase was observed in right MTG. According to the DIVA model, left STG and SMG are involved in the feedback network via auditory error and state maps, and somatosensory error and state maps, respectively. Left PCG contributes to motor control. Reduced neural activity in left PCG in the speech condition after LSVT LOUD, despite increased vocal loudness, suggests less effortful and more efficient modulation of speech–motor actions. Connections between right SMG and left PCG, and between left SMG and right SMA, may indicate the importance of somatosensory feedback for speech motor control. Several connections present at T_1 disappeared at T_2 and T_3, and such pruning is another indicator of increased efficiency of the network following treatment.

The discussion above focused on the ROIs with consistent and stable neural activity changes and the connections whose appearance or disappearance were stable and consistent across time. However, there were instances where a single or inconsistent change was noted (e.g., PSC in the right PCG increased at T_2 but decreased at T_3; left STG–right IFG appeared at T_2 only for the speech condition). Interpretation of these fast-phase, unstable changes was not possible with the current data, yet warrant further investigation, as their transience may illustrate the dynamic characteristics of cortical reorganization during training [Adkins et al., 2006]. We speculate that these changes facilitate the establishment and/or pruning of network connections, which may have been necessary during early or fast-phase stages to achieve slow-phase behavioral gains observed after continued practice of trained targets.

LIMITATIONS

Even with a small sample size of 16 children, we were able to achieve statistical power. Early phase treatment studies (Phase I and II, [Robey, 2004]) typically involve small sample sizes in an effort to detect therapeutic effects. The results from this study revealed positive therapeutic outcomes and evidence of treatment-based neuroplasticity. However, larger samples of children with dysarthria and CP are needed to advance our ability to generalize treatment outcomes. Even though participant instructions were standardized across groups and all three laboratory visits, we observed several changes on behavioral measures between T_2 and T_3 in the control group. Some of these changes were thought to be indicative of normal variability in performance. More specifically, some children wanted to "compete" with themselves by doing a better job with each consecutive visit. In contrast, children with CP were performing maximally (i.e., at their ceiling level) on all tasks during each visit to the laboratory. Because of the small sample size, performance variability (e.g., practice, effort, comfort with the testing protocol over time) on behavioral tasks in the typical group might have negatively influenced our ability to detect stable correlations between behavioral and brain activity measures. We considered the observed changes in functional connectivity for the control group to represent typical variability across scanning events. Thus, the control group served as a baseline for typical variability from which we could then compare variability in the CP group. We were cautious in our interpretation of fast- and slow-phase changes in the CP group by eliminating any observation that was within the range of typical variability as expressed in the control data. Therefore, alternative between-group comparisons needed to be employed in an effort to interpret true changes due to treatment in the group of children with CP.

CONCLUSION

Consistent with previous literature, we demonstrated improved speech performance in individuals with CP following LSVT LOUD [Boliek and Fox, 2014; Fox and Boliek, 2012; Levy et al., 2012]. Behavioral changes were accompanied by underlying neural changes associated with the auditory and somatosensory feedback systems. To enhance rehabilitation via optimized functional outcomes and altered patterns of neural connectivity, key

principles of activity-dependent neural plasticity should be employed [Kleim and Jones, 2008; Schertz and Gordon, 2009]. Treatment should involve learning or skill acquisition (e.g., as evidenced by improved intelligibility), mode of delivery should be intensive and should include significant repetitions and opportunities for practice, and task complexity should increase over time. Traditional CP treatments that do not implement these key elements have been ineffective in treating children with CP and dysarthria [Pennington et al., 2009]. Our results strengthen the evidence for neuroplasticity following LSVT LOUD [Liotti et al., 2003; Narayana et al., 2010].

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CONFLICT OF INTEREST

Drs Boliek and Fox receive lecture honorarium and travel reimbursement from LSVT Global, Inc. Dr Fox is an employee of and has ownership interest in LSVT Global, Inc.

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