RESEARCH ARTICLE

Cerebellar contribution to auditory feedback control of speech production: Evidence from patients with spinocerebellar ataxia

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Abstract

The cerebellum has been implicated in the feedforward control of speech production. However, the role of the cerebellum in the feedback control of speech production remains unclear. To address this question, the present event-related potential study examined the behavioral and neural correlates of auditory feedback control of vocal production in patients with spinocerebellar ataxia (SCA) and healthy controls. All participants were instructed to produce sustained vowels while hearing their voice unexpectedly pitch-shifted -200 or -500 cents. The behavioral results revealed significantly larger vocal compensations for pitch perturbations in patients with SCA relative to healthy controls. At the cortical level, patients with SCA exhibited significantly smaller cortical P2 responses that were source localized in the right superior temporal gyrus, primary auditory cortex, and supramarginal gyrus than healthy controls. These findings indicate that reduced brain activity in the right temporal and parietal regions are significant neural contributors to abnormal auditory-motor processing of vocal pitch regulation as a consequence of cerebellar degeneration, which may be related to disrupted reciprocal interactions between the cerebellum and cortical regions that support the top-down modulation of auditory-vocal integration. These differences in behavior and cortical activity between healthy controls and patients with SCA demonstrate that the cerebellum is not only essential for feedforward control but also plays a crucial role in the feedback-based control of speech production.

KEYWORDS

auditory feedback, cerebellum, event-related potential, speech motor control, spinocerebellar ataxia

1 | INTRODUCTION

The cerebellum has been long believed to be exclusively involved in the control of motor actions via projections to the primary motor cortex (Brodal & Bjaalie, 1997; Glickstein, 1992). Numerous

neuroanatomical studies, however, have shown that efferents from the cerebellum also project to other cerebral regions including the premotor, prefrontal, and parietal areas (Clower, West, Lynch, & Strick, 2001; Kelly & Strick, 2003; Middleton & Strick, 2001). Also, a number of neuroimaging studies have identified the involvement of the cerebellum in a variety of cognitive and perceptual abilities, including temporal processing (Ivry & Keele, 1989; Pastor et al., 2002), language production (Desmond, Gabrieli, Wagner, Ginier, & Glover, 1997; Fiez et al., 1996), and music perception (Parsons, 2001). Therefore, it is now clear that the cerebellum is not only involved in motor control but also, in concert with the prefrontal and parietal regions, plays an important role in the cognitive processing of different forms of information (Ramnani, 2006).

The control of speech production is a highly complex process that imposes high demands on the neurocognitive mechanisms of motor control. There is abundant evidence for cerebellar contributions to motor and cognitive aspects of speech production, which include phonatory and articulatory control and verbal working memory (Ackermann, Wildgruber, Daum, & Grodd, 1998; Ben-Yehudah, Guediche, & Fiez, 2007; Chen & Desmond, 2005; Manto et al., 2012; Marien et al., 2014). Specifically, the cerebellum has been implicated in controlling the online sequencing of syllable production during overt speech (Ackermann, 2008; Bohland & Guenther, 2006; Ghosh, Tourville, & Guenther, 2008; Riecker et al., 2005). From a network perspective, the cerebellum exerts prominent functional influences on the segregation and integration of the speech production network, as reflected by its heterogeneous connectivity with other brain regions during resting but not speaking and bilateral differences in cerebellar connectivity during resting versus speaking (Simonyan & Fuertinger, 2015). Finally, clinical evidence points to the important role of the cerebellum to speech production. For example, ataxic dysarthria is a motor speech disorder caused by cerebellar lesions and is characterized by an impaired ability to produce fluent speech, slow execution of single articulatory gestures, and disrupted orofacial and laryngeal movements (Ackermann, Mathiak, & Riecker, 2007; Manto et al., 2012). Together, there is growing support for the hypothesis that the cerebellum is critical for the neurocognitive control of speech production. The underlying mechanisms, however, remain to be elucidated.

Based on evidence from limb control studies, it is widely believed that the cerebellum plays a critical role in the learning and maintenance of feedforward motor commands that are established during the acquisition of motor skills (Blakemore, Wolpert, & Frith, 1999; Flament, Ellermann, Kim, Ugurbil, & Ebner, 1996; Imamizu et al., 2000). Likewise, in the DIVA model of speech production, the cerebellum is hypothesized to receive feedback signals from auditory and somatosensory areas and through projections to the motor cortex, plays a fundamental role in feedforward control of speech production by updating the internal mappings between sensory prediction and vocal output (Tourville & Guenther, 2011). This hypothesis is supported by the observation that patients with spinocerebellar ataxia (SCA) showed reduced adaptive compensations for predictable speech F_1 perturbations and the absence of an aftereffect when auditory

feedback was returned to normal (Parrell, Agnew, Nagarajan, Houde, & Ivry, 2017). In addition to its apparent role in feedforward control, the cerebellum has also been implicated in the feedback control of speech production. For example, increased cerebellar activity has been identified when participants compensate for F_1 perturbations in auditory feedback (Tourville, Reilly, & Guenther, 2008) and jaw perturbations in somatosensory feedback (Golfopoulos et al., 2011) during speech production. Also, Parrell et al. (2017) found that patients with SCA exhibited significantly larger speech compensations for unexpected F_1 perturbations compared with healthy controls. These findings lend support to the idea that the cerebellum is involved in both feedback and feedforward control of speech production.

Nevertheless, the functional roles of the cerebellum in the feedback and feedforward control of speech production are still a matter of debate. Empirical and clinical studies of limb movement control (Grafton, Woods, & Tyszka, 1994; Kawato et al., 2003; Morton & Bastian, 2006; Smith & Shadmehr, 2005) suggest that cerebellar feedforward mechanisms allow adaptive control of motor actions without the need for feedback control (Ohshima, Nares, Murphy, & Mauk, 2003). Accordingly, reduced sensorimotor adaptations of speech F_1 perturbations in patients with SCA may reflect the essential role of the cerebellum for maintaining accurate feedforward control of speech production, while their enhanced speech compensations for unexpected F_1 perturbations may be the result of an overreliance on auditory feedback (Parrell et al., 2017). Thus, Parrell et al. (2017) argued that the cerebellum may be critically involved in feedforward control but relatively uninvolved in feedback control during speech production. In contrast with this hypothesis, the observation of increased cerebellar activity in response to perturbations in auditory (Tourville et al., 2008) and somatosensory feedback (Golfopoulos et al., 2011) during speech production suggests cerebellar contributions to feedback control of speech production. It is thus possible that enhanced speech compensations for unexpected F_1 perturbations elicited by patients with SCA (Parrell et al., 2017) may not reflect intact feedback control mechanisms, but instead may be a symptom of cerebellar degeneration. If this is true, the cerebellum would also play a crucial role in auditory feedback control of speech production.

In order to address this question, the present study used a combination of the altered auditory feedback paradigm and event-related potential (ERP) technique to examine the neurobehavioral correlates of feedback-based vocal pitch regulation in patients with SCA and healthy controls. All participants were exposed to unexpected pitch perturbations in their auditory feedback during vowel phonations, and their vocal and ERP (N1 and P2) responses were collected and compared across the conditions. An attempt was made to localize the sources of the current density occurring in the time-range of the N1 and P2 component in three-dimensional space within the brain using standardized low-resolution brain electromagnetic tomography (sLORETA). Our aim was to determine the neural substrates involved in the distinct cortical responses to vocal pitch errors across the two groups. Similar to Parrell et al. (2017), we predicted that patients with SCA would exhibit enhanced vocal compensations for pitch

perturbations. And due to the reciprocal cortico-cerebellar connections (Kelly & Strick, 2003), we further predicted that these enhanced vocal compensations would be accompanied by aberrant cortical brain activity.

2 | METHODS

2.1 | Subjects

Twelve patients with cerebellar degeneration (seven males and five females; age [mean $\pm$ SD]: 37.3 ± 11.6 years; range: 21–62 years) recruited from The First Affiliated Hospital of Sun Yat-sen University participated in the experiment. They were diagnosed as having a genetically defined SCA that was either Type 3 ($n = 11$) or Type 1 ($n = 1$). Neurological examination revealed atrophy confined to the cerebellum and no disorders involving extracerebellar areas. Twelve healthy controls (seven males and five females; age: 36.4 ± 11.6 years; range: 22–61 years), who reported no history of speech, language, and neurological disorders, were also included in this study. Patients with SCA and healthy controls were matched in age ($t = 1.332$, $df = 11$, $p = .210$) and sex, and passed a binaural hearing screen with thresholds of 25 dB sound pressure level (SPL) or less at 250–4000 Hz. Written informed consent was obtained from all participants. The research protocol was approved by the institutional review board of The First Affiliated Hospital of Sun Yat-sen University.

2.2 | Procedure

Both patients with SCA and healthy controls were instructed to vocalize the vowel sound /u/ for approximately 5–6 s at their comfortable pitch and loudness level. While vocalizing, they heard their voice pitch unexpectedly shifted downward five times. During each vocalization, the duration of each pitch perturbation was fixed at 200 ms and the magnitude was either -200 or -500 cents (100 cents equals one semitone). Choosing pitch perturbations of -200 and -500 cents was to examine the effects of perturbation magnitudes (Liu, Meshman, Behroozmand, & Larson, 2011; Scheerer, Behich, Liu, & Jones, 2013) and reduce the adaptive effects of repetitive stimulus presentations. In our preliminary test, we found several aging adults in both patients and control groups had difficulty to perceive smaller perturbations (e.g., -50 cents) or discriminate differences between -100 and -200 cents despite their normal hearing. Thus, all participants were exposed to pitch perturbations of -200 and -500 cents in the present study. The initial pitch perturbation was presented with a delay that was randomized between 500 and 1,000 ms after the participant's vocal onset, and the interstimulus interval of the succeeding pitch shifts varied between 700 and 900 ms. A break of 2–3 s occurred between successive vocalizations to avoid vocal fatigue. Each participant was required to produce 40 consecutive vocalizations, leading to a total of 200 trials that included 100 trials for the -200 cents condition and 100 trials for the -500 cents condition.

2.3 | Voice and EEG data acquisition

The acoustic and electroencephalogram (EEG) data were collected from participants in a sound-treated booth. In order to reduce the participant's perception of unaltered air-born and bone-conducted voice feedback, the voice feedback was amplified such that it was 10 dB SPL higher than that of participant's vocal output throughout the experiment. The participant's voice signals were picked up using a dynamic microphone (DM2200; Takstar Inc. Huizhou, China) and then amplified with a MOTU Ultralite Mk3 FireWire audio interface (Cambridge, MA). The amplified voice signals were then pitch-shifted by an Eventide Eclipse Harmonizer (Little Ferry, NJ). A custom-developed MIDI software program (Max/MSP v.5.0 by Cycling 74, San Francisco, CA) was used to control the Harmonizer, where the parameters (e.g., direction, magnitude, and timing) of the pitch perturbation were manipulated. To analyze the vocal responses, the onset of each perturbation was marked using transistor–transistor logic (TTL) pulses generated by the Max/MSP software program. Finally, the pitch-shifted voice signals were further amplified by an ICON NeoAmp (Middleton, WI) headphone amplifier and played back to participants through insert earphones (ER-1; Etymotic Research Inc., Elk Grove Village, IL). The voice signals and the TTL pulses were digitally sampled at 10 kHz by a PowerLab A/D converter (model ML880; AD Instruments, Castle Hill, Australia) and recorded using the LabChart software (v.7.0 by AD Instruments).

Simultaneously, scalp-recorded EEG data were collected using a 64-electrode Geodesic Sensor Net that was connected to a Net Amps 300 amplifier (Electrical Geodesics Inc., Eugene, OR). The EEG signals were referenced to the vertex (Cz) and digitized at a sampling frequency of 1 kHz and recorded using the NetStation software (v.4.5; Electrical Geodesics Inc.). The impedance levels of individual sensors were less than 50 k Ω throughout the online recording (Ferree, Luu, Russell, & Tucker, 2001). An experimental synch Deutsches Institut für Normung (DIN) cable delivered the TTL pulses to the EEG recording system for the synchronization of the ERPs to pitch perturbations.

2.4 | Vocal data analysis

The measurement of vocal responses to pitch perturbations was performed using the IGOR Pro software (v.6.0 by Wavemetrics Inc., Lake Oswego, OR). The voice f_0 contours in Hertz were extracted using the Praat software (Boersma, 2001) and converted to the cent scale with the following formula: cents = $100 \times (12 \times \log_2[f_0/\text{reference}])$ (reference = 195.997 Hz [G3 note]). The voice contours were then epoched into segments from 200 ms before the perturbation onset (the baseline period) to 700 ms after the perturbation onset. After excluding individual segmented trials that contained vocal interruptions or signal processing errors, artifact-free trials were averaged and baseline corrected to generate an overall vocal response for each condition. The magnitude and latency of each vocal response was calculated as the f_0 value in cents and time in ms, when the voice f_0 contours reached its maximum values.

2.5 | EEG data analysis

The EEG data were analyzed offline using the NetStation software. Data were first band-passed filtered (1–20 Hz) and segmented into epochs that ranged from 200 ms before to 500 ms after the perturbation onset. Following an artifact detection procedure, segmented trials were then excluded from analyses if their voltage values exceeded $\pm 55 \mu\text{V}$ of the moving average over an 80-ms window. An additional visual inspection was performed to ensure appropriate rejection of the artifacts. Finally, artifact-free trials were rereferenced to the average of electrodes on each mastoid, averaged across the condition, and baseline corrected by removing the mean amplitude of the pre-stimulus window (–200 to 0 ms). ERP responses from 15 electrodes (F1, F2, Fz, F3, F4, FC1, FC2, FCz, FC3, FC4, C1, C2, Cz, C3, and C4) were grand averaged to generate an overall ERP response for each condition, from which the amplitudes and latencies of the N1 and P2 components were separately measured as the negative and positive peaks in the time windows of 80–160 and 160–280 ms after the perturbation onset. These electrodes were chosen because previous studies have shown the robust cortical responses to voice pitch perturbations in the frontal and central electrodes (Chen et al., 2012; Scheerer et al., 2013).

2.6 | Source localization analysis

sLORETA (Fuchs, Kastner, Wagner, Hawes, & Ebersole, 2002; Jurcak, Tsuzuki, & Dan, 2007) embedded in the EEGLAB software (<http://www.sccn.ucsd.edu/eeeglab>) was used to localize the neural sources of the group differences in the cortical responses to vocal pitch perturbations in the N1 and P2 time windows. Independent validation of localizing possible sources using sLORETA has been identified from studies combining sLORETA with functional magnetic resonance imaging (Mulert et al., 2004) and intracerebral recordings (Zumsteg, Lozano, & Wennberg, 2006). This method has also been successfully applied in recent studies on speech motor control (Behroozmand & Sangtian, 2018; Guo et al., 2017; Huang et al., 2016). sLORETA calculates the standardized current density in 6239 cortical gray matter voxels of a reference brain map normalized to the Montreal Neurological Institute (MNI) space at 5 mm spatial resolution. sLORETA images were computed based on the averaged ERPs for each participant at the 5 ms time windows of maximal global field power peaks in the N1 and P2 time windows in a realistic standardized head model (Fuchs et al., 2002) within the MNI152 template (Mazziotta et al., 2001). Voxel-by-voxel between-group comparisons of the current density distributions were performed using an independent samples Student *t* test through sLORETA voxelwise randomization tests with 10,000 permutations. Statistical nonparametric mapping was used to correct for multiple whole-brain comparisons. The voxels with significant differences (for corrected $p < .05$) were specified in MNI coordinates and labeled as Brodmann areas (BAs) within the EEGLAB software (Delorme & Makeig, 2004).

2.7 | Statistical analysis

The magnitudes and latencies of vocal and ERP responses to pitch perturbations were submitted to SPSS (v.20.0) and analyzed using two-way repeated-measures analysis of variances (RM-ANOVAs), including a between-subject factor of group (patients with SCA vs. healthy controls) and a within-subject factor of stimulus magnitude (–200 vs. –500 cents). Significant interactions between these two factors led to subsidiary RM-ANOVAs. The Greenhouse–Geisser was used to correct probability values for multiple degrees of freedom when the sphericity assumption was violated, but the original values were reported for easy interpretation. Partial η^2 was calculated as an index of effect size to describe the size of differences between the conditions. The difference was considered significant only in cases where p -values $< .05$ and partial $\eta^2 > 0.14$ (Richardson, 2011).

3 | RESULTS

3.1 | Behavioral findings

As shown in Figure 1a,b, patients with SCA retained their ability to compensate for pitch perturbations in voice auditory feedback, as reflected by their vocal responses that opposed the direction of the pitch perturbation. Regardless of the size of pitch perturbations, patients with SCA exhibited a larger degree of vocal compensations than healthy controls. A two-way RM-ANOVA conducted on the magnitudes of vocal compensations demonstrated this group difference to be statistically significant ($F(1, 22) = 14.447$, $p = .001$, partial $\eta^2 = 0.396$) (mean $\pm$ SE of the mean; hereafter, patients with SCA: 36.4 ± 5.1 cents vs. healthy controls: 14.5 ± 1.1 cents) (see Figure 1c). However, the magnitudes of vocal responses did not vary as a function of stimulus magnitude ($F(1, 22) = 0.119$, $p = .733$) (–200 cents perturbations: 25.6 ± 4.5 cents vs. –500 cents perturbations: 25.3 ± 4.1 cents). The interaction between group and stimulus magnitude ($F(1, 22) = 2.930$, $p = .101$) was not significant either.

For the latencies of vocal responses, there were no significant main effects of group ($F(1, 22) = 1.249$, $p = .276$) (patients with SCA: 305 ± 17 ms vs. healthy controls: 280 ± 20 ms) and stimulus magnitude ($F(1, 22) = 2.334$, $p = .141$) (–200 cents perturbations: 274 ± 16 ms vs. –500 cents perturbations: 311 ± 20 ms) (see Figure 1d). Also, the interaction between group and stimulus magnitude was not significant ($F(1, 22) = 0.009$, $p = .925$).

3.2 | ERP findings

Figure 2 shows the grand-averaged waveforms and topographical maps of two ERP components (N1 and P2) in response to pitch perturbations of –200 and –500 cents for patients with SCA and healthy controls. As can be seen, the differences in the N1 responses were subtle across the group and stimulus magnitude. A two-way RM-ANOVA conducted on the N1 amplitudes showed no significant main effects of group ($F(1, 22) = 0.096$, $p = .759$) (patients with SCA: $-1.74 \pm 0.32 \mu\text{V}$ vs. healthy controls: $-1.87 \pm 0.26 \mu\text{V}$) and stimulus

FIGURE 1 Top: grand-averaged voice f_0 contours in response to pitch perturbations of -200 (a) and -500 cents (b) produced by patients with SCA (red solid lines) and CTR (blue solid lines). Highlighted areas indicate the SE of the mean vocal responses. Bottom: T-bar plots of the magnitudes (c) and latencies (d) of vocal responses (mean and SE) across stimulus magnitude and group. The asterisks indicate significantly larger vocal compensations for pitch perturbations produced by patients with SCA than CTR. CTR, healthy controls; SCA, spinocerebellar ataxia [Color figure can be viewed at wileyonlinelibrary.com]

magnitude ($F(1, 22) = 0.304, p = .587$) (-200 cents perturbations: $-1.75 \pm 0.34 \mu V$ vs. -500 cents perturbations: $-1.86 \pm 0.23 \mu V$) as well as their interaction ($F(1, 22) = 3.843, p = .063$) (see Figure 3a).

Likewise, the N1 latencies did not vary as a function of group ($F(1, 22) = 0.320, p = .578$) (patients with SCA: 130 ± 7 ms vs. healthy controls: 129 ± 6 ms) and stimulus magnitude ($F(1, 22) = 0.029, p = .866$) (-200 cents perturbations: 129 ± 7 ms vs. -500 cents perturbations: 130 ± 6 ms) (see Figure 3b). There was also no significant interaction between group and stimulus magnitude ($F(1, 22) = 0.616, p = .441$).

In contrast, there was a group difference that was prominent in the P2 responses. A two-way RM-ANOVA conducted on the P2 amplitudes revealed a significant main effect of group ($F(1, 22) = 7.436, p = .012$, partial $\eta^2 = 0.253$), with smaller P2 responses produced by patients with SCA ($2.31 \pm 0.32 \mu V$) compared to healthy controls ($4.04 \pm 0.42 \mu V$) (see Figure 3c). However, the main effect of stimulus magnitude ($F(1, 22) = 0.763, p = .392$) (-200 cents perturbations: $3.17 \pm 0.46 \mu V$ vs. -500 cents perturbations: $3.18 \pm 0.37 \mu V$) and the interaction

between group and stimulus magnitude ($F(1, 22) = 1.462, p = .239$) did not reach significance.

For the P2 latencies, there was a significant main effect of stimulus magnitude ($F(1, 22) = 18.975, p < .001$, partial $\eta^2 = 0.463$), indicating that the -500 cents perturbations (239 ± 9 ms) elicited faster P2 responses than the -200 cents perturbations (255 ± 8 ms) (see Figure 3d). Although there was a trend toward slower P2 responses in patients with SCA (255 ± 11 ms) as compared to healthy controls (239 ± 6 ms), the group difference was not significant ($F(1, 22) = 0.150, p = .703$). There was no significant interaction between group and stimulus magnitude ($F(1, 22) = 3.819, p = .063$).

3.3 | Source estimation findings

Source localization analyses using sLORETA were performed to examine the neural sources underlying the distinct group differences in the cortical P2 responses to voice pitch perturbations. Given that the

FIGURE 2 Grand-averaged event-related potential (ERPs) across 15 electrodes and topographical distribution maps of the P2 and N1 responses to pitch perturbations of -200 cents (left panel) and -500 cents (right panel) produced by patients with SCA (red solid lines) and CTR (blue solid lines). Highlighted areas indicate the SE of the mean ERP responses. CTR, healthy controls; SCA, spinocerebellar ataxia [Color figure can be viewed at wileyonlinelibrary.com]

group difference in the P2 amplitudes was independent of the size of pitch perturbation, the cortical responses to pitch perturbations of -200 and -500 cents were combined into a single dataset in the source estimation analyses. Figure 4 shows current density source maps that display cortical regions where healthy controls produced significantly larger P2 responses than patients with SCA. Table 1 lists the anatomical description and the MNI coordinates corresponding to these brain regions. As compared to patients with SCA, healthy controls exhibited stronger cortical activations in the right superior temporal gyrus (STG; BA 22; $p = .0080$), primary auditory cortex (A1; BA 41/42; $p = .0194$), and supramarginal gyrus (SMG; BA 40; $p = .0397$). These results indicate the contributions of reduced activation in the right STG, A1, and SMG to abnormally enhanced vocal compensations for pitch perturbations in patients with SCA.

4 | DISCUSSION

The present study investigated the cerebellar contributions to auditory feedback control of speech production by assessing the neuro-behavioral correlates of vocal pitch regulation in patients with cerebellar degeneration. As compared to healthy controls, patients

with SCA exhibited significantly larger vocal responses but smaller cortical P2 responses that were source localized in the right STG, A1, and SMG. These findings provide evidence for the neural correlates of abnormal auditory-vocal integration caused by cerebellar degeneration. Thus, in addition to its role in feedforward control of speech production, the cerebellum also plays an important role in auditory feedback control of speech production.

Our behavioral results showed significantly larger vocal compensations for pitch perturbations in patients with SCA relative to healthy controls. Similarly, Parrell et al. (2017) found that patients with SCA compensated for F_1 perturbations that occurred to the vowel / ϵ / in the embedded word “head” to a larger degree than healthy controls. Together with the observation of increased activation of the cerebellum in response to speech F_1 perturbations (Tourville et al., 2008), these findings demonstrate that the cerebellum is engaged in auditory feedback control of speech production.

More importantly, while producing increased vocal compensations for pitch perturbations, patients with SCA exhibited reduced cortical P2 responses that were source localized in the right STG, A1, and SMG. These findings are consistent with previous neuroimaging studies showing the activation of the posterior STG, Heschl's gyrus, and

FIGURE 3 T-bar plots of the amplitudes and latencies (mean and SE) of the N1 (a,b) and P2 (c,d) responses to pitch perturbations of -200 and -500 cents across 15 electrodes for patients with SCA (red) and CTR (blue). The asterisks indicate significantly smaller P2 amplitudes produced by patients with SCA than CTR (c) and shorter P2 latencies elicited by -500 cents perturbations than -200 cents perturbations (d). CTR, healthy controls; SCA, spinocerebellar ataxia [Color figure can be viewed at wileyonlinelibrary.com]

SMG in the production of compensatory vocal responses to pitch perturbations (Behroozmand et al., 2015; Behroozmand et al., 2016; Chang, Niziolek, Knight, Nagarajan, & Houde, 2013; Kort, Cuesta,

Houde, & Nagarajan, 2016; Kort, Nagarajan, & Houde, 2014; Parkinson et al., 2012). Our source findings indicate that reduced activation of the right temporal and parietal regions may be significant mediators of abnormal auditory-motor integration for vocal pitch regulation in patients with SCA.

FIGURE 4 Grand-averaged sLORETA-based statistical nonparametric maps comparing the standardized current densities between CTR and patients with SCA in the P2 time window. Results are projected onto lateral and top three-dimensional views of a standard anatomical template. Positive t values indicate increased brain activity in CTR compared to patients with SCA (corrected $p < .05$). CTR, healthy controls; SCA, spinocerebellar ataxia; sLORETA, standardized low-resolution brain electromagnetic tomography [Color figure can be viewed at wileyonlinelibrary.com]

4.1 | Cerebellar mechanisms of speech motor control

A variety of empirical (Bohland & Guenther, 2006; Ghosh et al., 2008; Tourville et al., 2008) and clinical studies (Ackermann, 2008; Ackermann et al., 2007) have demonstrated cerebellar contributions to speech production, but the precise role of the cerebellum in speech motor control remains poorly understood. In the DIVA model (Tourville & Guenther, 2011), the cerebellum is hypothesized to use feedback signals from auditory and somatosensory areas for feedforward control of speech production. Consistently, patients with SCA exhibited reduced adaptive compensations for predictable speech F_1 perturbations (Parrell et al., 2017). On the other hand, computational simulations of stuttering and apraxia of speech with the DIVA model have revealed a compensatory overreliance on auditory

TABLE 1 sLORETA *t* statistics for maximum activations obtained from comparison between patients with SCA and CTR in the P2 time window (MNI coordinates). Displayed are *t*-values for current density maxima; threshold for significance at corrected $p < .05$

Condition	BA	Brain region	<i>t</i> -Value	X	Y	Z	<i>p</i>
CTR versus SCA	22	Right STG	4.693	65	−20	0	.0080
	42/41	Right A1	4.399	65	−20	10	.0194
	40	Right SMG	4.079	65	−20	15	.0397

Abbreviations: A1, primary auditory cortex; CTR, healthy controls; SCA, spinocerebellar ataxia; sLORETA, standardized low-resolution brain electromagnetic tomography; SMG, supramarginal gyrus; STG, superior temporal gyrus.

feedback as a consequence of impaired feedforward control (Civier, Tasko, & Guenther, 2010; Terband, Maassen, Guenther, & Brumberg, 2009). Therefore, it is possible that patients with SCA rely upon auditory feedback more heavily for the detection and correction of vocal output errors due to their feedforward dysfunctions, which resulted in enhanced vocal pitch compensations observed in the present study and enhanced speech F_1 compensations observed by Parrell et al. (2017). This compensatory strategy may reflect increased efforts from patients with SCA to integrate auditory feedback with the vocal motor systems to overcome their deficits in feedforward control.

The observation of reduced cortical responses in the right STG, A1, and SMG in patients with SCA, however, does not support the above hypothesis, which would predict increased activity in the auditory regions. Note that abnormally enhanced vocal compensations for pitch perturbations in patients with Parkinson's disease (PD) have also been hypothesized to result from their compensatory overreliance on auditory feedback to overcome somatosensory and feedforward deficits (Chen et al., 2013; Mollaei, Shiller, Baum, & Gracco, 2016; Sapir, 2014). However, enhanced vocal compensations in patients with PD were accompanied by increased cortical responses in the left fronto-tempo-parietal regions (Huang et al., 2016). Stutters, who are also hypothesized to rely on auditory feedback more heavily for feedforward impairments (Civier et al., 2010), showed increased activation of the right STG, and bilateral HG, and left PMC during speech production (Chang, Kenney, Loucks, & Ludlow, 2009). Therefore, it seems less likely that the underactivation of the temporal and parietal regions observed in patients with SCA can be attributable to their increased reliance on auditory feedback.

Alternatively, this brain activity pattern may be related to deficits in both feedback and feedforward systems caused by cerebellar degeneration. Auditory feedback provides critical information for the learning and maintenance of feedforward motor commands during speech production (Houde & Jordan, 1998; Jones & Munhall, 2005), and plasticity in the auditory system drives changes in speech motor learning (Jones & Keough, 2008; Ostry & Gribble, 2016). The STG and A1 are fundamental to the detection and correction of feedback errors in vocal output (Chang et al., 2013; Parkinson et al., 2012). Also, activation of the SMG has been linked to both online and adaptive sensorimotor control of speech production (Behroozmand & Sangtian, 2018; Kort et al., 2014; Kort et al., 2016; Shum, Shiller, Baum, & Gracco, 2011). Impaired learning of motor skills has been found to be associated with deactivation in the cerebellar-parietal network (Zwicker, Missiuna, Harris, & Boyd, 2011). Collectively, reduced

activation of the right temporal and parietal regions observed in patients with SCA may be manifestations of their dysfunctions in both feedback and feedforward control of speech production. If so, the feedback control system may not remain intact in patients with SCA (Parrell et al., 2017); rather, it may also be compromised by cerebellar degeneration.

Nevertheless, the above hypotheses cannot account for why cerebellar degeneration led to increased vocal compensations but reduced cortical activity in response to pitch perturbations. As another possibility, we postulate that this neurobehavioral activity pattern may be related to the impaired top-down inhibitory control of speech production caused by disrupted cortico-cerebellar circuits. This speculation is motivated by two lines of converging evidence. First, increased cortical P2 responses that were source localized in the frontal and parietal regions were associated with reduced vocal pitch compensations (Guo et al., 2017), while abnormally increased vocal pitch compensations were predicted by decreased activity in the left dorsolateral prefrontal cortex in patients with Alzheimer's disease (Ranasinghe et al., 2019). It is thus hypothesized that the prefrontal cortex may exert inhibitory influences on auditory-vocal integration (Guo et al., 2017; Ranasinghe et al., 2017). On the other hand, the cerebellum receives input from the temporal and parietal regions and returns projections to the prefrontal cortex via the thalamus (Desmond et al., 1997; Schmahmann, 1996), which forms the basis of a fronto-thalamo-cerebellar network that supports the preparation and inhibition of motor actions (Hwang, Velanova, & Luna, 2010; Liddle, Kiehl, & Smith, 2001), including speech motor control (Schulz, Varga, Jeffries, Ludlow, & Braun, 2005; Tourville et al., 2008). Together, it is likely that the abnormally reduced activation of right temporal and parietal regions observed in patients with SCA may be attributed to their dysfunctions of the fronto-thalamo-cerebellar network, which in turn may lead to the failure of generating inhibitory control over compensatory vocal motor behaviors that is responsible for increased vocal compensations. Given the lack of causal evidence for the top-down inhibitory control of speech production mediated by the fronto-thalamo-cerebellar networks; however, this interpretation is very speculative and more studies are needed to verify its validity.

5 | CONCLUSIONS

The present study investigated the cerebellar contributions to auditory feedback control of speech production. Patients with SCA

exhibited increased vocal compensations for pitch perturbations and reduced cortical activity in the right tempo-parietal regions. These findings provide neurobehavioral evidence to support the idea that the cerebellum is not only essential for feedforward control of speech production but also crucial for the feedback-based online monitoring of speech production.

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CONFLICT OF INTEREST

The authors declared no conflict of interest.

DATA AVAILABILITY

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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