Title: Abnormal Speech Motor Control in Individuals with 16p11.2 Deletions

Abbreviated Title: Abnormal Speech Feedback Processing in 16p11.2 Deletion

Authors: Carly Demopoulos, Ph.D.* (1), Hardik Kothare, M.S. (1), Danielle Mizuiri, B.S. (1), Jennifer Henderson-Sabes, Ph.D. (2), Brieana Fregeau, B.A. (3), Jennifer Tjernagel, M.S. (4), John Houde, Ph.D. (2), Elliott H. Sherr, M.D., Ph.D. (3), and Srikantan S. Nagarajan, Ph.D.* (1)

(1) University of California-San Francisco, Department of Radiology & Biomedical Imaging, 513 Parnassus Avenue, S362. San Francisco, CA 94143

(2) University of California-San Francisco, Department of Otolaryngology-Head and Neck Surgery, 2233 Post Street, San Francisco, CA 94115

(3) University of California-San Francisco, Department of Neurology, 675 Nelson Rising Lane, San Francisco, CA 94143

(4) Simons Foundation Autism Research Initiative, 160 Fifth Avenue, 7th Floor New York, NY 10010

*Corresponding Authors:

Carly Demopoulos, Ph.D.
Department of Radiology & Biomedical Imaging
513 Parnassus Avenue, S362
San Francisco, CA 94143
Carly.Demopoulos@ucsf.edu

Srikantan S. Nagarajan, Ph.D.
Department of Radiology & Biomedical Imaging
513 Parnassus Avenue, S362
San Francisco, CA 94143
Srikantan.Nagarajan@ucsf.edu

Abstract

Speech and motor deficits are highly prevalent (>70%) in individuals with the 600 kb BP4-BP5 16p11.2 deletion; however, the mechanisms that drive these deficits are unclear, limiting our ability to target interventions and advance treatment. This study examined fundamental aspects of speech motor control in participants with the 16p11.2 deletion. To assess capacity for control of voice, we examined how accurately and quickly subjects changed the pitch of their voice within a trial to correct for a transient perturbation of the pitch of their auditory feedback. When compared to sibling controls, 16p11.2 deletion carriers show an over-exaggerated pitch compensation response to unpredictable mid-vocalization pitch perturbations. We also examined sensorimotor adaptation of speech by assessing how subjects learned to adapt their sustained productions of formants (speech spectral peak frequencies important for vowel identity), in response to consistent changes in their auditory feedback during vowel production. Deletion carriers show reduced sensorimotor adaptation to sustained vowel identity changes in auditory feedback. These results together suggest that 16p11.2 deletion carriers have fundamental impairments in the basic mechanisms of speech motor control and these impairments may partially explain the deficits in speech and language in these individuals.

Speech and communication deficits can have a pervasive impact on learning, development, and quality of life and are highly prevalent in individuals with Autism Spectrum Disorders (ASD; Tager-Flusberg et al., 2005; Van Agt et al., 2011). There is also increasing recognition that general motor abnormalities, present in 79% of individuals with ASD (Lai et al., 2014), predict delayed speech and language development (Gernsbacher et al., 2008; Bhat et al., 2012; Sacrey et al., 2014).

Recently, given the advances in understanding the genetic basis of ASD in some individuals, an effort has been made to categorize ASD into different genetically defined subtypes (Spiro et al., 2012) by examining the behavioral, anatomical and physiological phenotypes associated with mutations in single genes or copy number variants for contiguous genes. For example, the recurrent nearly 600 kb deletion at 16p11.2 (BP4-BP5) is one of the most common genetic etiologies of ASD and, more generally, of neurodevelopmental impairment (Kumar et al., 2008; Weiss et al., 2008; Zufferey et al., 2012). Although a variety of cognitive domains have been reported to be impacted in 16p11.2 deletion carriers, the most commonly observed diagnoses are developmental coordination disorder, phonological processing disorder, language disorders, and ASD (Hanson et al., 2015). One or more speech and language diagnoses are present in 71% of all individuals with the 16p11.2 deletion (Hanson et al., 2015), including a higher than normal prevalence of childhood apraxia of speech (Shinawi et al., 2010; Hanson et al., 2015; Fedorenko et al., 2016; Hippolyte et al., 2016). These deficits seem to be specific to 16p11.2 deletion carriers, as these clinical deficits are absent in those with duplications of the same locus (Hippolyte et al., 2016). The etiologies of these speech production deficits, both in children with ASD and 16p11.2 deletion carriers, remain unclear, and this poses a considerable barrier to advancing treatment and intervention to improve speech in these populations.

Intact speech results from a careful orchestration of several processes to control the vocal tract (Houde and Nagarajan, 2011). For example, articulation of vowel sounds requires vocalization at the larynx while simultaneously holding the tongue and jaw in just the right shape.

During articulation, we also hear the speech we are producing (auditory feedback), and if what we hear is not what we meant to say (i.e., is not consistent with our internal prediction of intended speech), we respond by correcting our speech. Thus, the control of speech requires (1) the ability to generate an expectation for the intended speech outcome (*internal speech modeling*), (2) the ability to control the muscles of the vocal apparatus to achieve that intended outcome (*vocal motor control*), and (3) the ability to accurately process and respond to auditory feedback of one's own speech in real time (*online speech error monitoring*) (Houde and Nagarajan, 2011). How these specific fundamental processes of speech motor control are impacted in children with ASD and the 16p11.2 deletion is poorly understood. Given the highly penetrant speech production deficits in children with the 16p11.2 deletion, examination of these speech motor control sub-processes in this group offers an opportunity to identify discrete points of failure in speech production. In particular, better understanding the role of auditory feedback in the control of speech in these participants could lead to insights into potential targets for speech and language intervention and directions for the development of novel therapeutics.

Thus, the present study investigates the speech motor control and auditory feedback processing during speech in participants with the 16p11.2 deletion. In particular, we assessed (1) how quickly participants reacted to changes in auditory feedback, and (2) how well they could learn from their auditory feedback. We made these assessments by examining two well-studied phenomena: (1) The *pitch perturbation reflex* is seen when the pitch of speakers' auditory feedback of their ongoing speech is suddenly and unexpectedly perturbed (Burnett et al., 1998). Speakers quickly respond to such perturbations (within 100-200ms) by compensating, changing their pitch to negate the perceived effect of the pitch perturbation. The pitch perturbation reflex thus measures how speakers immediately react to auditory feedback for online speech error monitoring and correction. (2) *Speech sensorimotor adaptation* can be seen when the formants of speakers' auditory feedback are consistently altered on repeated vowel productions (Houde and Jordan, 1998, 2002). Such formant alterations change how speakers perceive their vowel sounds:

the vowel they hear in their auditory feedback does not match the vowel they intended to produce. Speakers respond to this mismatch by adapting their vowel productions over repeated trials, with each successive production changed to more fully counter the perceived effects of the formant alterations. Speech sensorimotor adaptation thus measures how well speakers can use auditory feedback to incorporate long-term changes in their speech production. Both the pitch perturbation reflex and speech sensorimotor adaptation response have proven to be sensitive indicators of abnormal speech feedback processing in other neurological conditions (Mollaei et al., 2013; Daliri et al., 2017; van den Bunt et al., 2017), and were therefore natural choices for assessing feedback processing in our participants.

Methods

Participants

Twelve 16p11.2 deletion carriers (three females and nine males, mean age=12.4, SD=3.2, range=8.3-18.3) and six unaffected siblings (one female and 5 males, mean age=12.8, SD=1.5, range=11.3-15.4) were enrolled from the 2015 Simon's Variation in Individuals Project Family Meeting in Falls Church, VA. The study was offered to attendees as a speech and hearing study. In addition, five neurotypical control participants (two females and three males, mean age=12.4, SD=1.8, range=10.3-14.2) were recruited through community advertisement. Subjects were matched for age across the groups - deletion carriers, unaffected sibling controls and neurotypical controls ($F(2,20)=.037$, $p=.96$). Inclusion criteria were (1) presence of a BP4-BP5 16p11.2 deletion, sibling of a participant with a BP4-BP5 16p11.2 deletion who did not have the 16p11.2 deletion or any other known genetic or neuropsychiatric disorder, (2) age range of 8-18 years, and (3) ability to produce a sustained phonation (e.g., say "ah" for 2-3 seconds). Written consent and assent were obtained in accordance with the requirements of the Committee on Human Research at University of California-San Francisco.

Measures

Participants were assessed on two measures of sensitivity to auditory feedback during speech: a Pitch Perturbation Task and a Formant Adaptation Task. For both of these tasks the auditory feedback the participant hears while speaking is altered in real time. To screen for hearing abilities, auditory brainstem responses (ABRs) were also assessed for participants with the 16p11.2 deletion and their siblings. In the 16p11.2 deletion group, time constraints prevented two participants from completing the ABR task and three from completing the speech production tasks. Additionally, one participant discontinued participation in the study due to extreme sound sensitivity to the ABR task stimuli. In the neurotypical control group, one participant was excluded from the speech adaptation task due to technical issues.

Pitch Perturbation Task. This task measured subjects' immediate corrective responses to unexpected perturbations of the pitch of the auditory feedback of their ongoing speech. In each trial, participants produced and sustained the vowel sound, "ah", for at least 2.5 seconds into a microphone. Speech from the microphone was sent through a digital signal processing (DSP) system before being returned to the subjects' headphones as auditory feedback of their speech. The DSP was capable of altering speech feedback (in either pitch or formant frequencies) in real time (12 ms feedback delay) (Katseff et al., 2012; Kort et al., 2014; Ranasinghe et al., 2017). During each trial the participant's auditory feedback was randomly raised or lowered in pitch by $1/12^{th}$ of an octave (+/- 100 cents) at a variable lag from speech onset for 400 ms duration. This process was repeated for 74 trials with an inter-trial interval of 2.5 seconds. This task measures how quickly participants adjust their speech within each trial in order to compensate for the perceived speech error created by the mid-vocalization pitch perturbation. The compensation is subtle, and the participants may not be aware of it. Peak magnitude of compensation is determined by peak response change from pre- to post-perturbation baseline by: cents change = $100 \times [12 \times \log2(\text{pitch response peak (Hz)} / \text{mean pitch frequency of pre-perturbation baseline (Hz)})]$ (Kort et al., 2014). Baseline begins at voice onset and ends at onset of perturbation. For statistical comparison between groups, the mean of the peak compensation for each subject was

calculated by extracting the peak deviation from baseline pitch in each trial and computing the average of the peak compensation response across trials.

Formant Adaptation Task. This task measured how much subjects learned to adjust their speech production to consistently minimize perceived speech errors (altered formants) in their auditory feedback. The microphone/DSP/headphone setup was the same as for the pitch perturbation task. In each trial, participants said the word "bed" upon cue into a microphone, and heard auditory feedback of their production in the headphones, with an inter-trial interval of 2.5 seconds. For the first 20 trials, the DSP provided subjects with unaltered feedback of their productions. In the following 30 trials, however, the DSP altered the formants (F1 and F2) of the auditory feedback so that subjects heard the vowel /ae/ when they produced the vowel /eh/. F1 was raised by 200 Hz and F2 was reduced by -250 Hz during the altered block of 30 trials. Thus, on these trials, when subjects produced the word "bed" they heard the word "bad." To compute adaptation we first represented the applied formant shift and produced formants as vectors from baseline formant values in an F1-F2 (first and second formants) Euclidean space. Produced formant frequencies were extracted from spectrograms of entire vowel utterances. Formant dropouts and instances of incorrect tracking were excluded from the analysis. We then determined the scalar projection of the produced formants vector on the formant shift vector. Percentage adaptation was calculated as -100 x (scalar projection) / (magnitude of applied shift).

Auditory Brainstem Response (ABR) Task. Because the goal of the study was to examine the role of auditory feedback in speech for a group of participants who may have abnormalities in auditory processing, we also administered an auditory brainstem response task to assess basic auditory processing in the absence of speech. This task required the participants to passively listen to clicking sounds through headphones while auditory brainstem responses were collected through electrodes placed on both earlobes with a reference electrode on the forehead. The ABR is a neurophysiological response reflecting activity in peripheral aspects of the auditory system (e.g., cochlear nucleus, medial lemniscus, and brainstem nuclei). Because this is measured

passively, ABRs allow for estimation of pronounced hearing loss without the cooperation and cognitive task demands required by behavioral methods for estimating hearing thresholds; however, the ABR is not a sensitive measure of mild hearing loss, and it generally does not provide information on potential hearing loss at low frequencies. Data were collected in response to 75 dB clicks presented at a rate of 11.1 Hz, with a total of 1000 stimuli presented to each ear. Data were analyzed by a licensed clinical audiologist (JHS) with respect to the latencies of ABR waves I, III, and V, wave I–III and III–V interpeak latencies, the wave V amplitude and interaural amplitude differences, and overall morphology.

Hypotheses and Data Analytic Plan

Based on prior literature documenting speech abnormalities in children and adolescents with 16p11.2 deletions (Fedorenko et al., 2016), we hypothesized that deletion carriers would show abnormalities on the pitch perturbation and formant adaptation tasks. To test this hypothesis we performed two independent samples t-tests to examine group differences in (1) peak magnitude of compensation (assessed via the pitch perturbation task) and (2) adaptation of the internal speech model (assessed via the formant adaptation task).

Results

ABR data were evaluated for evidence of severe hearing impairment and Wave V abnormalities. No evidence of hearing impairment was identified by our licensed clinical audiologist (JHS) for any of the participants, and no group differences were detected for independent samples t-tests examining differences in Wave V latency or amplitude variables (Table 1).

Table 1

ABR Results for 16p11.2 Deletion Carriers and Unaffected Siblings (M ± SD [*range*])

	16p11.2 Deletion Group (N=12)		Sibling Control Group (N=6)		Statistics
R Latency (ms)	5.70 ± .36	[5.24-6.36]	5.63 ± .28	[5.32-6.03]	t(12) = .45
L Latency (ms)	5.72 ± .20	[5.45-6.36]	5.65 ± .19	[5.40-5.90]	t(13) = .74
R Amplitude	.59 ± .29	[.23-1.16]	.60 ± .15	[.45-.88]	t(13) = -.07
L Amplitude	.50 ± .19	[.28-.95]	.48 ± .09	[.31-.54]	t(13) = .25
R-L Amplitude	.09 ± .30	[-.30-.71]	.12 ± .13	[.01-.35]	t(13) = -.23

The average compensatory response to the applied pitch perturbation, over the pre-perturbation through post-perturbation vocalization interval, is shown across subjects for the deletion carriers and their siblings in Figure 1. Vocalizations were similar between groups at baseline and until 200ms following the onset of the feedback perturbation of pitch. However, the groups' pitch compensation responses subsequently diverged in their vocal response to the auditory feedback perturbation, wherein the deletion carriers show an enhanced compensatory response when compared with controls starting at around 200ms post-perturbation onset and persisting through the response interval. The mean compensation response to pitch feedback perturbations was significantly enhanced in 16p11.2 deletion carriers (40+/- 6.3 (sem) cents) when compared to unaffected siblings (9.6+/- 9.8 cents), t(8)=2.610, p=.031. The observed enhancement is seen even when the unaffected sibling and control participant groups were pooled, wherein the compensation response in the 16p11.2 deletion group was once again significantly enhanced compared to the pooled control group (Figure 2). The mean compensation

response to pitch feedback perturbations in the pooled controls was (12.3+/- 5.7 cents), and significantly lower than the response in 16p11.2 carrier participants (t(15)= 3.276, p= 0.005.

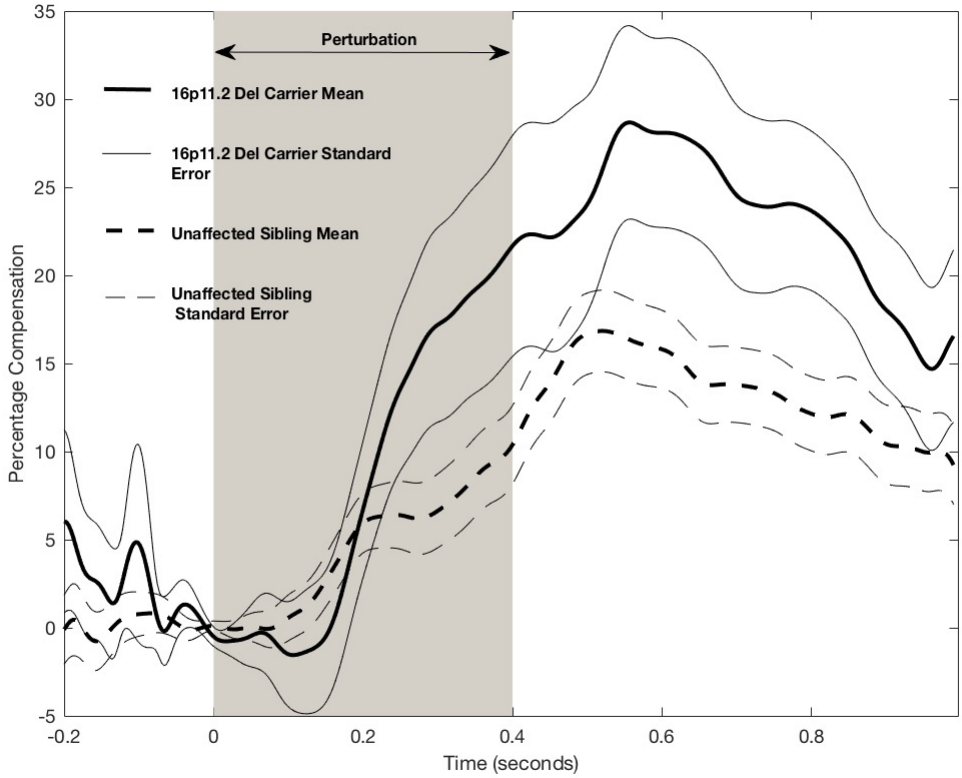

Figure 1. Average changes in compensation over the course of the vocalization in the Pitch Perturbation Task for participants with 16p11.2 deletions and unaffected siblings. The shaded area indicates the onset of auditory feedback perturbation. 16p11.2 deletion carriers demonstrate an exaggerated compensation response relative to the sibling control participants.

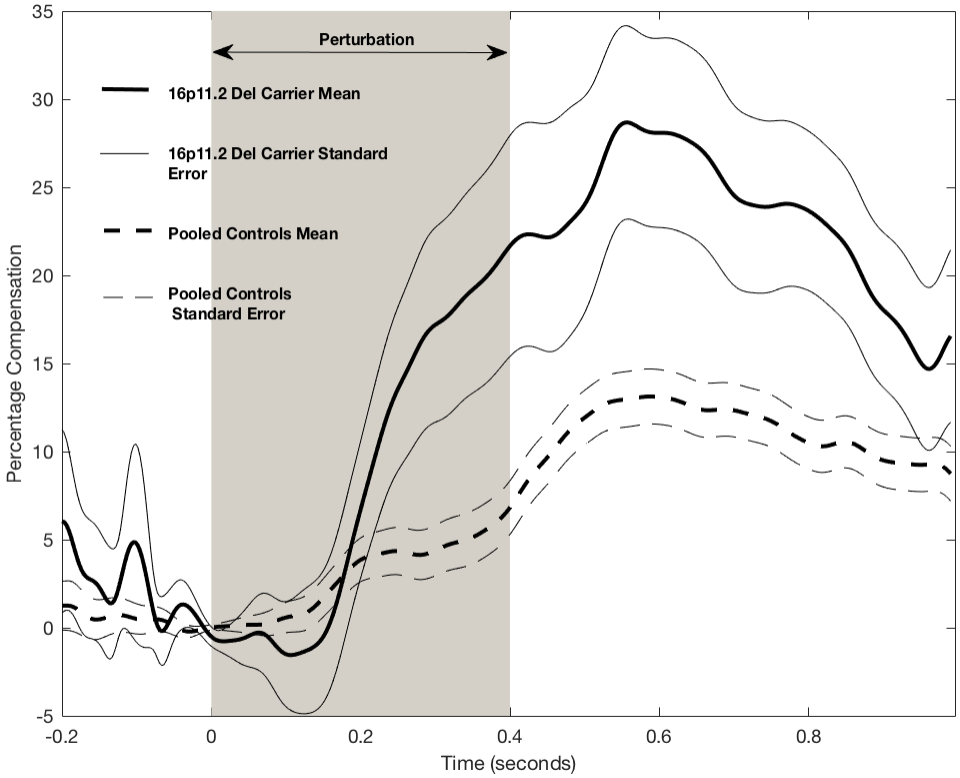

Figure 2. Average changes in compensation over the course of the vocalization in the Pitch Perturbation Task for participants with 16p11.2 deletions and the pooled control group. The shaded area indicates the onset of auditory feedback perturbation. 16p11.2 deletion carriers demonstrate an exaggerated compensation response relative to the control participants.

We then examined the magnitude of formant adaptation in response to repeated perturbations of formants in auditory feedback. While unaffected siblings and control participants learned to adjust their speech in anticipation of the altered auditory feedback, the 16p11.2 deletion carriers did not adjust their speech in response to predictable auditory feedback alterations. Figure 3 illustrates the mean group differences in formant adaptation response across 16p11.2 deletion carriers, sibling controls and pooled controls. In contrast to within trial pitch compensation responses, reduction in the magnitude of formant adaptation in response to repeated perturbation of formants in auditory feedback across trials was highly significant in

16p11.2 deletion carriers (4.2 +/- 1.8(sem)%) when compared to both unaffected siblings (11.7+/-1.4%), t(11)=3.212, p=.008, and to the pooled control group (13.1+/-1.5%), t(14) = 3.708, p=0.002.

Finally, we examined whether the overcompensation response was associated with poor adaptation, a correlation was performed for the deletion carrier group. However, no significant association was identified, r=.28, p=.532.

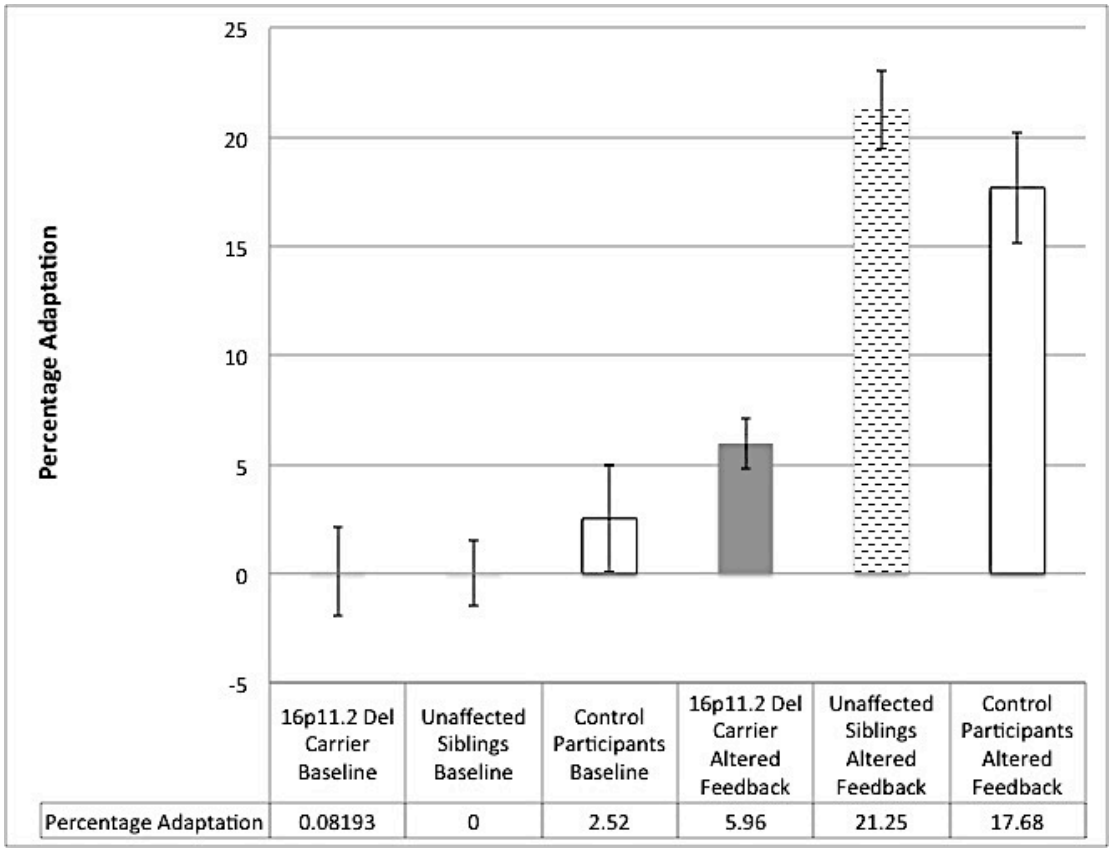

Figure 3. Mean group adaptation across trials for the baseline and altered feedback conditions in the Formant Adaptation Task. While groups did not differ at baseline, significant group differences were identified in the altered feedback condition, with the deletion carriers showing significantly reduced mean compensation (indicating less adaptation of the internal speech model).

Discussion

This study examined fundamental processes of speech motor control in participants with a 16p11.2 deletion. Specifically, we examined sensitivity to auditory feedback processing during speech production using measures of (1) online error monitoring and resultant compensatory speech in response to mid-utterance auditory feedback alterations, and (2) across-trial adaptation of vowel production in response to computer generated consistent auditory feedback errors. First, our results support the hypothesis that 16p11.2 deletion carriers show abnormalities in compensation, as carriers demonstrated an overcompensation response to pitch perturbations. Our findings extend and confirm hints of overcompensation reported in some ASD individuals, where a subset of participants with idiopathic autism with weaker language ability showed increased pitch compensation (Russo et al., 2008). One possible explanation for this overcompensation response is that auditory processing dysfunction results in distorted perception of the mismatch between expected and actual auditory feedback, thereby driving overcompensation by way of inaccurate perception of the target during speech correction. However, similar timing of the onset of the compensatory responses suggests that duration of auditory error processing is not impaired in 16p11.2 deletion carriers. A second possibility is the heightening of the motoric responses to auditory feedback errors in 16p11.2 deletion carriers.

Our data also showed reduced speech model adaptation following consecutive trials in which auditory feedback of vowel sounds was consistently altered in a predictable way. A reduced adaptation response has been reported in typically developing younger children and to an even greater extent in toddlers (MacDonald et al., 2012), which may suggest a maturational dysfunction in one or more speech production mechanisms in 16p11.2 deletion carriers. This reduced speech model adaptation when taken together with the strong compensation response during the pitch perturbation task suggests that while deletion carriers were able to detect and make some effort to correct perceived speech errors in real time, they were impaired in learning

to anticipate the effects of the highly predictable alterations in auditory feedback in their vowel productions.

There are several possible interpretations for these results. Normal speakers are assumed to have internal pre-stored representations of the motor programs they need for producing the repertoire of speech sounds corresponding to the languages in which they converse. These internal representations allow speakers to correctly produce speech even in the absence of sensory feedback; they need not rely on immediate sensory feedback for the moment-to-moment control of their speech. Nevertheless, sensory feedback—and especially auditory feedback—plays a critical role in maintaining the accuracy of these internal representations, which are constantly being adjusted to eliminate any consistent sensory feedback prediction errors (Houde and Nagarajan, 2011). In comparison, participants with 16p11.2 deletions may have impairments in sensorimotor predicting/learning, resulting in an inability to anticipate the consistent auditory feedback prediction errors created by the formant feedback alterations. Alternatively, they may not have any reliable pre-stored representations to govern their speech production, and may instead be forced to rely on immediate sensory feedback for the moment-to-moment control of their speech. In the context of intact ability to generate internal speech motor programs, they may only be able to adapt them in a rigid way, perhaps due to a limited repertoire of speech motor programs, or rote approach to speech learning, resulting in difficulty in flexibly adapting the internal representations of their speech motor programs. Difficulty with generating or adapting these internal speech motor representations could result in a compensatory over-reliance on feedback for error correction during speech and subsequently, the reduced adaptation and overcompensation response observed in our sample. Finally, a lack of association between compensation and adaptation may suggest that these are independent sub-processes of speech motor control. Future studies that combine speech psychophysics with neuroimaging are necessary tease apart the above-mentioned possibilities, and to examine if observed speech motor control abnormalities are directly associated with speech and language deficits.

Limitations And Future Directions

Several limitations of the present study must be acknowledged. Most notably, the small sample size resulted in limited power to detect modest effects and greater potential for spurious findings. Therefore, these findings should be replicated with a larger sample. In addition, future studies should include a more comprehensive assessment of auditory processing, speech, and language function, along with assessment of vocal motor control to fully understand the impact of sensory and motor function on abnormal speech perturbation responses.

Conclusions

Intact speech results from a careful orchestration of several fundamental processes of speech motor control, and dysfunction in any part of speech motor control could impact speech production in numerous ways. If we are to understand the causal factors in the emergence of speech deficits in 16p11.2 deletion carriers, we must first understand these fundamental processes associated with the earliest presenting symptoms, such as sensory and motor dysfunction, and their subsequent impact on more complex processes, such as speech and language. This study suggests some initial directions for this line of inquiry.

Acknowledgments

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Author Contributions

CD was responsible for data collection, processing, analysis, interpretation and writing of the manuscript. HK was responsible for data collection, processing, and analysis. DM was responsible for data collection. JHS was responsible for data processing. BF was involved in study coordination, consenting and data management. JT was involved in study execution and coordination of the data collection meeting. JH was responsible for task development and was involved in manuscript review. EHS and SSN were involved in conceptualization and design of the project and writing of the manuscript.

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Figure Captions

Figure 1. Average changes in compensation over the course of the vocalization in the Pitch Perturbation Task for participants with 16p11.2 deletions and unaffected siblings. The shaded area indicates the onset of auditory feedback perturbation. 16p11.2 deletion carriers demonstrate an exaggerated compensation response relative to the sibling control participants.

Figure 2. Average changes in compensation over the course of the vocalization in the Pitch Perturbation Task for participants with 16p11.2 deletions and the pooled control group. The shaded area indicates the onset of auditory feedback perturbation. 16p11.2 deletion carriers demonstrate an exaggerated compensation response relative to the control participants.

Figure 3. Mean group adaptation across trials for the baseline and altered feedback conditions in the Formant Adaptation Task. While groups did not differ at baseline, significant group differences were identified in the altered feedback condition, with the deletion carriers showing significantly reduced mean compensation (indicating less adaptation of the internal speech model).