# Mechanisms of Voice Control Related to Prosody in Autism Spectrum Disorder and First-Degree Relatives

Shivani P. Patel, Jason H. Kim, Charles R. Larson, and Molly Losh

Differences in prosody (e.g., intonation, rhythm) are among the most obvious language-related impairments in autism spectrum disorder (ASD), and significantly impact communication. Subtle prosodic differences have also been identified in a subset of clinically unaffected first-degree relatives of individuals with ASD, and may reflect genetic liability to ASD. This study investigated the neural basis of prosodic differences in ASD and first-degree relatives through analysis of feedforward and feedback control involved in the planning, production, self-monitoring, and self-correction of speech by using a pitch-perturbed auditory feedback paradigm during sustained vowel and speech production. Results revealed larger vocal response magnitudes to pitch-perturbed auditory feedback across tasks in ASD and ASD parent groups, with differences in sustained vowel production driven by parents who displayed subclinical personality and language features associated with ASD (i.e., broad autism phenotype). Both ASD and ASD parent groups exhibited increased response onset latencies during sustained vowel production, while the ASD parent group exhibited decreased response onset latencies during speech production. Vocal response magnitudes across tasks were associated with prosodic atypicalities in both individuals with ASD and their parents. Exploratory event-related potential (ERP) analyses in a subgroup of participants during the sustained vowel task revealed reduced P1 ERP amplitudes in the ASD group, with similar trends observed in parents. Overall, results suggest underdeveloped feedforward systems and neural attenuation in detecting audio-vocal feedback may contribute to ASD-related prosodic atypicalities. Importantly, results implicate atypical audio-vocal integration as a marker of genetic risk to ASD, evident in ASD and among clinically unaffected relatives. ***Autism Res*** *2019, 12: 1192–1210.* © 2019 The Authors. *Autism Research published by International Society for Autism Research* published by Wiley Periodicals, Inc.

**Lay Summary:** Previous research has identified atypicalities in prosody (e.g., intonation) in individuals with ASD and a subset of their first-degree relatives. In order to better understand the mechanisms underlying prosodic differences in ASD, this study examined how individuals with ASD and their parents responded to unexpected differences in what they heard themselves say to modify control of their voice (i.e., audio-vocal integration). Results suggest that disruptions to audio-vocal integration in individuals with ASD contribute to ASD-related prosodic atypicalities, and the more subtle differences observed in parents could reflect underlying genetic liability to ASD.

**Keywords:** audio-vocal integration; prosody; autism spectrum disorder; broad autism phenotype; language; pragmatics

## Introduction

Autism spectrum disorder (ASD) is a genetically based neurodevelopmental disorder characterized by impairments in social communication and restricted interests and repetitive behaviors [American Psychiatric Association, 2013]. The earliest descriptions of social communication in ASD noted impairments in prosody, or the intonation, rate, and rhythm of speech [Asperger & Frith, 1991; Kanner, 1943]. Atypical prosody is often among the most obvious differences during conversational interactions with individuals with ASD, and can pose a significant obstacle to social integration [Mesibov, 1992; Van Bourgondien & Woods, 1992]. Such atypicalities include increased or decreased intonation variability (e.g., monotone or sing-songy intonation), atypical stress patterns, inappropriate phrasing, and atypical volume modulation [Baltaxe & Simmons, 1985; Fosnot & Jun, 1999; McCann & Peppé, 2003; Nadig & Shaw, 2012; Paul, Augustyn, Klin, & Volkmar, 2005]. To date, assessments of prosody in individuals with ASD have focused primarily on listener-based perceptual ratings and acoustic measures, which, though helpful in broadly characterizing prosodic profiles, have not focused on the mechanisms that may underlie prosodic atypicalities in ASD [Diehl & Paul, 2012; Diehl, Watson, Bennetto, Mcdonough, & Gunlogson, 2009; Losh et al.,

From the Roxelyn and Richard Pepper Department of Communication Sciences and Disorders, Northwestern University, Evanston, Illinois (S.P.P., J.H.K., C.R.L., M.L.)

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Address for correspondence and reprints: Molly Losh, Roxelyn and Richard Pepper Department of Communication Sciences and Disorders, Northwestern University, Evanston, IL. E-mail: m-losh@northwestern.edu



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2012; Nadig & Shaw, 2012; Paul et al., 2005]. To do so, this study investigated audio-vocal integration as a potential source of prosodic atypicalities in individuals with ASD. We also investigated audio-vocal integration in parents to determine whether common mechanisms might underlie the prosodic differences noted in both ASD and among first-degree relatives, and potentially serve as a marker of genetic liability to ASD.

Differences in prosodic qualities of speech have been observed among first-degree relatives of individuals with ASD [Landa et al., 1992; Losh et al., 2012], together with broader pragmatic language differences that have been described as constituting a broad autism phenotype (BAP) which is thought to reflect genetic liability to ASD among clinically unaffected relatives [Bailey et al., 1995; Folstein & Rutter, 1977; Frazier et al., 2015; Landa et al., 1992; Losh, Childress, Lam, & Piven, 2008; Losh et al., 2012]. Given the clinical and etiologic heterogeneity of ASD, studies of subclinical traits in the BAP can be useful for understanding the distilled expression of core ASD features linked to genetic liability to ASD, and that are not obscured by intellectual disability, developmental delays, and comorbidities common in ASD. With this goal in mind, the present study conducted a parallel investigation of audio-vocal integration in parents of individuals with ASD and in relationship to clinical-behavioral features of the BAP.

A key element in the appropriate use of prosody involves the online integration of auditory feedback to adjust vocal output. Auditory feedback enables individuals to ensure that their actual vocal output matches their intended vocal output, such that the vocal message is appropriately conveyed. Evidence from individuals with postlingual deafness and cochlear implants provide strong evidence for the role of auditory feedback in controlling voice fundamental frequency ($f_o$) [Campisi et al., 2005; Hamzavi, Deutsch, Baumgartner, Bigenzahn, & Gstoettner, 2000; Higgins, McCleary, & Schulte, 1999; Lane et al., 1997; Leder et al., 1987; Monini, Banci, Barbara, Argiro, & Filipo, 1997; Perkell, Lane, Svirsky, & Webster, 1992; Svirsky, Lane, Perkell, & Wozniak, 1992]. For instance, individuals with postlingual deafness exhibit more rapid deterioration of prosodic components of speech, such as voice $f_o$, but slower deterioration of segmental aspects of speech, such as the pronunciation of phonemes. Similarly, prior to receiving a cochlear implant, deaf individuals typically exhibit abnormally high $f_o$ levels, which have been shown to decrease toward typical $f_o$ levels after implantation [Leder et al., 1987]. Although ASD is not associated with hearing impairment, given the known prosodic aberrations identified in cases where access to auditory feedback is disrupted, it is important to assess the contribution of auditory feedback to prosodic atypicalities characteristic of ASD.

A study examining responses to pitch-perturbed auditory feedback (PPAF) during sustained vowel production in children with ASD found that only a subgroup exhibited compensatory vocal responses similar to controls, whereas the remaining children exhibited vocal responses of larger magnitude, suggesting that mechanisms underlying the integration of auditory feedback into vocal control may be hyper-responsive in some individuals with ASD [Russo, Larson, & Kraus, 2008]. Interestingly, larger vocal responses in individuals with ASD were associated with poorer receptive and expressive language abilities [Russo, Larson, & Kraus, 2008]. Similar associations have been found in studies of auditory processing and language abilities of individuals with ASD, such that individuals with ASD, who exhibited enhanced pitch perception for simple auditory stimuli (e.g., musical tones) compared to typically developing controls, were noted to have greater language difficulties, suggesting that these abilities may influence language development and processing [Bonnel et al., 2010; Heaton, Hermelin, & Pring, 1998; Mottron, Dawson, Soulières, Hubert, & Burack, 2006; O'Connor, 2012]. Further, neurophysiological studies of auditory processing in individuals with ASD have identified poorer processing of the spectral components of speech and poorer neural tracking of the pitch of speech sounds [Russo, Nicol, Trommer, Zecker, & Kraus, 2009; Russo et al., 2008]. Despite evidence of atypical integration of auditory feedback and differences in auditory processing, as well as the relation of these domains to language abilities, there is little information about how these domains are related specifically to prosodic production in individuals with ASD.

Using a PPAF paradigm allows for the investigation of reflexive responses to altered auditory feedback and can provide insights into the coupling of auditory feedback and vocal motor control, both of which contribute to the appropriate use of prosody. This paradigm has been used to demonstrate the importance of auditory feedback on controlling voice $f_o$ during the production of sustained vowels [Bauer & Larson, 2003; Hain et al., 2000; Larson, Burnett, Bauer, Kiran, & Hain, 2001; Sivasankar, Bauer, Babu, & Larson, 2005], nonsense syllables [Donath, Natke, & Kalveram, 2002; Natke, Donath, & Kalveram, 2003; Natke & Kalveram, 2001], speech [Chen, Liu, Xu, & Larson, 2007; Liu, Chen, Larson, Huang, & Liu, 2010], and singing [Natke et al., 2003]. Based on this extensive body of literature, we know that typically developing individuals most often exhibit a compensatory reflexive response that opposes the direction of the pitch-perturbed feedback. For example, if the frequency of the auditory feedback increases by 100 cents (1 semitone), a typically developing individual would likely exhibit a vocal response that decreases fundamental frequency in an attempt to correct for the unintended alteration. A cents scale, which is a logarithmic scale of frequency, is used in this paradigm to allow for comparisons of voice $f_o$ across individuals with different voice $f_o$ levels.

A study of typically developing English speakers found that this compensatory response is larger and occurs

more rapidly during speech compared to sustained vowel production, suggesting that modulation of voice $f_o$ is task-dependent and that higher-level linguistic tasks, such as speech, may recruit greater neural resources [Chen et al., 2007]. Furthermore, this study used a question (with an utterance-final rise in $f_o$) as the speech task and found that compensatory responses to downward pitch perturbations, which would have disrupted conveying the utterance as a question, were larger than responses to upward shifted pitch alterations. This result suggests that the audio-vocal regulatory system is sensitive to planned patterns of speech prosody, which are often critical to imparting the appropriate meaning of a message. Given current understanding of response patterns in typically developing individuals and the atypical prosodic patterns identified in individuals with ASD, the PPAF paradigm offers a useful and potentially highly sensitive method of investigating mechanisms underlying prosodic impairments in individuals with ASD. Studying these mechanisms in parents of individuals with ASD as well may provide further insights into their biological significance and relation to ASD genetic liability in clinically affected and unaffected first-degree relatives.

Beyond studying behavioral response to PPAF, characterizing the neural processes associated with the PPAF can help to highlight key mechanisms underlying detection and correction of $f_o$ errors in vocal production and potentially inform our understanding of neural processing of prosody in ASD. In particular, auditory event-related potentials (ERPs) during PPAF provide a window into the temporal unfolding of the sensory-neural components driving the vocal motor response. In typically developing adults, exposure to PPAF has been shown to produce P1, N1, and P2 ERP amplitudes, which are indicative of a greater mismatch between the intended and perceived vocal output [Behroozmand, Karvelis, Liu, & Larson, 2009; Scheerer, Behich, Liu, & Jones, 2013]. Studies of PPAF in typically developing children identified age-related neural changes in the P1–N1–P2 complex such that P1, which is thought to index detection of the stimulus, decreased in amplitude and latency with age [Liu et al., 2013; Scheerer, Liu, & Jones, 2013]. The N1 component, which is believed to index differences in the magnitude of altered feedback, decreased in latency with age [Liu et al., 2013; Scheerer, Liu, & Jones, 2013]. As of yet, ERP studies using the PPAF paradigm have not been conducted in children with ASD. Generally, work investigating auditory ERPs in children and adults with ASD has identified reduced P1 amplitudes in response to nonspeech and speech stimuli compared to controls [Buchwald et al., 1992; Ceponiene et al., 2003; Lepistö et al., 2005]. Studies of the N1 component in individuals with ASD have been less consistent, likely due to extensive developmental changes related to the N1; however, many studies have found reduced N1 amplitudes in children with ASD [Bruneau, Roux, Adrien, & Barthélémy, 1999; Courchesne, Lincoln, Kilman, & Galambos, 1985; Seri, Cerquiglini, Pisani, & Curatolo, 1999]. These results suggest atypicalities in the detection and encoding of auditory stimuli in individuals with ASD may influence the integration of auditory feedback and, in turn, modulation of vocal output associated with prosody. Auditory ERPs P1, N1, and P2 have not been studied in first-degree relatives, although prior work investigating ERPs in first-degree relatives suggests evidence of atypical neural representation related to key areas of impairment in ASD, namely face processing.

This study investigated potential differences in compensatory responses to PPAF during sustained vowel production and more complex speech production in individuals with ASD and their parents in order to understand potential mechanistic disruptions underlying prosodic atypicalities in ASD and noted prosodic differences in first-degree relatives. We examined overall differences in compensatory vocal responses to PPAF, as well as potential differences in how vocal responses unfolded over time using growth curve modeling. Further, we assessed auditory ERPs to PPAF in a subset of participants using electroencephalography (EEG) and predicted that atypicalities in audio-vocal integration in individuals with ASD and their parents would be reflected by reduced P1, N1, or P2 ERP amplitudes. Associations between vocal and neural responses to PPAF, clinical-behavioral assessments of ASD, and assessments of prosodic ability were also examined. We predicted that individuals with ASD would exhibit irregularities in audio-vocal integration in nonspeech and speech tasks, and that these irregularities would be related to prosodic impairments and ASD symptom severity. We predicted that similar but more subtly expressed differences would be evident among parents. Given prior evidence that differences in language and related domains may be evident in only a subgroup of parents who display features of the BAP [Adolphs, Spezio, Parlier, & Piven, 2008; Losh et al., 2008, 2012], we predicted that differences between ASD parents and parent controls would be driven by the subgroup of parents who exhibited the BAP.

## Methods

### *Participants*

Participants were recruited through the Northwestern University Communication Research Registry (P30DC012035), the Northwestern Child Studies Group, existing studies, and by study advertisement. Twenty (7 females) individuals with ASD (ASD group), 20 (8 females) typically developing controls (ASD Control group), 24 (20 females) parents of individuals with autism (ASD parent group), and 23 (18 females) parents of typically developing controls (parent control group) participated in this study. EEG

signals during the sustained vowel task were recorded for only a subset of participants (ASD group $n = 9$; ASD control group $n = 10$; ASD parent group $n = 9$; and parent control group $n = 13$) given some participants' sensory aversions, as well as time constraints for participation in the full study. All participants were native English speakers with no history of hearing loss, brain injury, presence of a known genetic condition other than ASD, or major psychiatric disorder. Individuals in either control group were excluded if they had first- or second-degree relatives with ASD, history of language-related impairments, or were nonnative English speakers. All individuals with ASD had a formal diagnosis of autism or ASD. Diagnoses were confirmed using the Autism Diagnostic Observation Schedule-2nd Edition [ADOS-2; Lord et al., 2012] for all participants, as well as the Autism Diagnostic Interview-Revised [Lord, Rutter, & Le Couteur, 1994] when time permitted ($n = 14$). All parents in the ASD parent group had at least one child with ASD.

Intellectual functioning was assessed using the Wechsler Abbreviated Scale of Intelligence [Wechsler, 1999] for individuals 16 years of age or older and the Wechsler Intelligence Scale for Children-Fourth Edition [Wechsler, 2003] for individuals younger than 16 years of age. The ASD ($t = 0.99$, $P = 0.33$) and ASD parent ($t = 1.09$, $P = 0.28$) groups did not significantly differ in chronological age from their respective control groups (mean age in years (range): ASD group = 17.22 (9.20–32.36); ASD control group = 14.99 (6.85–35.64); ASD parent group = 48.72 (34.24–62.06); parent control group = 45.84 (30.92–66.84). The ASD group had a significantly lower full-scale IQ than the ASD control group ($t = -3.22$, $P < 0.01$). Full-scale IQ was not significantly different between the ASD parent group and parent control group ($t = -1.65$, $P = 0.11$). Consistent with current conceptualization of compensatory vocal responses to PPAF as reflexive responses and analysis procedures used in existing studies utilizing PPAF paradigms [Burnett, Freedland, Larson, & Hain, 1998; Natke & Kalveram, 2001; Russo, Larson, & Kraus, 2008; Xu, Larson, Bauer, & Hain, 2004], IQ was not included as a covariate in analyses. Table 1 summarizes the full-scale IQ and chronological age of all groups.

### *PPAF Paradigm*

***Audio instrumentation.*** A PPAF paradigm similar to that used in previous studies was implemented [Burnett et al., 1998; Larson, Sun, & Hain, 2007; Russo, Larson, & Kraus, 2008]. Participants wore Etymotic insert earphones (model ER2-14A) and an AKG headset microphone (model C420), with the microphone placed approximately 1 in. from the corner of the mouth. In order to minimize the influence of air and bone-conducted voice feedback, audio output was amplified (Aphex Headpod 4) to provide a cumulative 10 dB gain from the voice input. A prepolarized free-field microphone (Type 4189), a Brüel and Kjær sound level meter (Type 2250), and a Zwislocki coupler were used to calibrate the gain between voice and audio channels using a 1 kHz sinusoidal pure tone. The participant was seated approximately 10–12 in. away from a computer monitor on which visual cues for each task were provided.

***Sustained vowel task.*** The experimenter verbally instructed the participant to vocalize /a/ for as long as the light on the screen was green, stop and take a breath when the light turned red, and then repeat. The vocalization period was approximately 5 sec long. Participants completed up to 10 practice vocalizations during which the experimenter provided feedback regarding vocalization length, steadiness, and volume, prior to initiating the experiment. A total of 75 vocalizations were collected from each participant. The onset of the vocalization was detected using a voice onset detector module in MaxMSP (v5.0, Cycling '74). The output from the voice onset detector was used to trigger an Eventide Eclipse Harmonizer to produce four pitch perturbations of pseudo-randomized magnitude (+100 cents, −100 cents, 0 cents) at random intervals during the vocalization period. The pitch-perturbed stimuli were delivered with 700–900 msec variable interstimulus intervals within each 5-sec vocalization period and had durations of 200 msec in order to elicit only reflexive responses rather than volitional responses triggered by longer duration stimuli [Burnett et al., 1998; Hain et al., 2000]. Stimulus magnitudes of +100 and −100 cents were chosen due to their perceptibility and wide use in studies using a PPAF paradigm [Bauer & Larson, 2003; Burnett et al., 1998; Hain et al., 2000].

***Speech task.*** During the speech task, participants vocalized the question "You know Nina?" [Chen et al., 2007]. A prerecorded auditory model of the question was presented prior to each vocalization. A visual aid

**Table 1. Group Characteristics**

| | ASD group *M* (*SD*) | ASD control group *M* (*SD*) | ASD parent group *M* (*SD*) | Parent control group *M* (*SD*) |
|---|---|---|---|---|
| Males:females | 12:7 | 12:8 | 4:20 | 5:18 |
| Chronological age | 17.22 (6.30) | 14.99 (7.60) | 48.72 (7.98) | 45.84 (10.06) |
| Full-scale IQ | 98.11 (22.55)** | 116.92 (13.44) | 113.17 (13.06) | 119.09 (11.43) |

**denotes a difference of $P < 0.01$.

consisting of an arrow for each syllable in the phrase was used to represent the target intonation contour for the question. Voice onset triggered the arrows in the visual aid to light up in order to provide cues about the timing of the question and promote consistency of syllable duration across participants. The phrase "You know Nina?" was selected due to the continuous voicing and the inherent upward pitch inflection on the final syllable of "Nina" [Chen et al., 2007]. Two sets of 75 vocalizations each were collected for the speech task using the same procedures described above for the sustained vowel task. Unlike prior studies, in the present study one 200 msec pitch perturbation occurred 640 msec post-voice onset during each vocalization. A delay of 640 msec was selected based on measurements of the target phrase so that the stimulus would occur prior to the rise in $f_o$ on the final syllable ("na"). The stimulus was presented at this location in order to assess the effect of the perturbation on compensatory vocal responses when the planned intonation contour includes a large $f_o$ rise, which influences whether or not the phrase is conveyed as a question. The task included +100 cent, −100 cent, and 0 cent perturbations to allow for randomization. Review of our data revealed nearly indistinguishable compensatory vocal responses to the +100 cent perturbation, which may be attributable to the location of the perturbation leading into an expected $f_o$ rise. Furthermore, previous research has documented smaller vocal responses to upward perturbations during question production, which may have further contributed to difficulty detecting compensatory vocal responses in this condition [Chen et al., 2007]. Therefore, only compensatory vocal responses to the −100 cent and 0 cent perturbations were analyzed.

***Voice $f_o$ processing and analysis.*** In both the sustained vowel and speech tasks, the MaxMSP software generated a transistor–transistor logic (TTL) pulse at the onset of each pitch-perturbed stimulus in order to allow for averaging of vocal responses across vocalizations. Voice, feedback, and TTL pulses were sampled at 10 kHz using PowerLab A/D Converter (model ML880, AD Instruments) and recorded on a laboratory computer utilizing LabChart software (v7.0, AD Instruments). Once collected, vocalizations were segmented from −200 to 500 msec for the sustained vowel task and −200 to 200 msec for the speech task with respect to stimulus onset. Praat [Boersma & Weenink, 2017] was used to extract the $f_o$ contour and remove vocalizations in which there were disruptions to pitch tracking (e.g., participant coughed, stopped vocalizing, was too soft or loud). IGOR Pro [2015] (v6.0, WaveMetrics, Inc.) was then used to automatically categorize compensatory (e.g., +100 cent perturbation with a downward response; −100 cent shift with an upward response) and following responses (e.g., +100 cent perturbation with an upward response; −100 cent perturbation with a downward response) [Behroozmand & Larson, 2011]. The $f_o$ contour for each compensatory response was subsequently visually screened using IGOR Pro to remove outstanding aberrant vocalizations prior to analysis. In particular, data for the speech task were compared against the $f_o$ contour of the auditory model to determine use of the correct intonation contour as this was necessary to assess the effect of the perturbation on compensatory vocal responses to the standard intonation contour of a question. As a result, three participants from the ASD group were excluded from subsequent analysis of the speech task data. Tables 2 and 3 outline the average number of compensatory and following responses obtained from each group for the sustained vowel and speech tasks, respectively. Only compensatory responses were analyzed in the present study given the goal of understanding how individuals correct for perturbed auditory feedback.

***ERP recording and signal processing.*** During the sustained vowel task, EEG signals were recorded from 32 scalp Ag-AgCl electrodes (EasyCap) in accordance with the international 10–20 system. The signals were amplified

**Table 2. Average Number of Following (i.e., vocal response follows the direction of the stimulus) and Compensatory (i.e., vocal response opposes the direction of the stimulus) Vocal Responses During the Sustained Vowel Task[a]**

| | Compensatory responses | | Following responses | |
|---|---|---|---|---|
| | +100 cent *M* (*SD*) | −100 cent *M* (*SD*) | +100 cent *M* (*SD*) | −100 cent *M* (*SD*) |
| ASD group | 46.37 (17.60) | 41.21 (18.34) | 32.47 (11.72) | 39.68 (16.01) |
| ASD control group | 52.20 (27.77) | 50.60 (23.49) | 34.05 (16.22) | 35.00 (15.97) |
| ASD parent group | 65.78 (16.60) | 64.04 (17.13) | 25.52 (11.85) | 27.87 (12.25) |
| BAP(+) | 73.25 (14.62) | 68.13 (17.08) | 18.50 (9.46) | 25.25 (14.26) |
| BAP(−) | 61.80 (16.66) | 61.87 (17.33) | 29.27 (11.52) | 29.27 (11.31) |
| Parent control group | 64.33 (15.60) | 64.40 (16.23) | 25.45 (9.82) | 26.00 (12.78) |

[a]The average number of usable compensatory vocal responses for each perturbation condition were not statistically different between the ASD and ASD control (+100 cent perturbation: $P = 0.44$; −100 cent shift: $P = 0.17$; Table 2) or the ASD parent and parent control groups (+100 cent perturbation: $P = 1.00$; −100 cent shift: $P = 0.89$).

**Table 3. Average Number of Following (i.e., vocal response follows the direction of the stimulus) and Compensatory (i.e., vocal response opposes the direction of the stimulus) Vocal Responses During the Speech Task[a]**

| | Compensatory responses −100 cent *M* (*SD*) | Following responses −100 cent *M* (*SD*) |
|---|---|---|
| ASD group | 24.26 (11.86) | 10.82 (7.76) |
| ASD control group | 28.16 (13.98) | 17.00 (13.11) |
| ASD parent group | 24.59 (8.81) | 10.82 (7.76) |
| BAP(+) | 27.00 (7.89) | 7.56 (6.15) |
| BAP(−) | 22.92 (9.34) | 13.08 (8.17) |
| Parent control group | 24.91 (9.11) | 12.09 (9.27) |

[a]The average number of usable compensatory vocal responses for the −100 cent perturbation condition was not statistically different between the ASD and ASD control ($P = 0.36$) or ASD parent and parent control groups ($P = 0.74$).

(BrainAmp, Brain Products GmbH) and digitized with the BrainVision Recorder (v. 1.2) software onto a recording computer with a sampling frequency of 5 kHz using FCz as the reference. Electrode impedances of <5 kΩ were maintained throughout the experiment. Following data acquisition, EEG recordings were re-referenced to the average voltage across all recorded sites. BrainVision Analyzer (v. 2.1) applied offline filtering across all recorded EEG channels with a band-pass filter (1–30 Hz) and notch filter (60 Hz). Epochs of −100 to 500 msec, with respect to the stimulus onset, were used for segmentation of individual vocalizations and baseline corrected. The Artifact Detection package in BrainVision Analyzer with a threshold of ±50 μV was used to identify and reject segmented vocalizations with artifact contamination due to excessive muscular activity, eye blinks, or eye movements. The average number of vocalizations across perturbation conditions retained for analysis was as follows for each group: ASD group = 99, ASD control group = 99, ASD parent group = 96; and parent control group = 98.

Six EEG channels were chosen for ERP analysis of the P1–N1–P2 complex: F3, F4, Fz, C3, C4, and Cz. These locations are in agreement with previous reports, which have demonstrated that the P1–N1–P2 complex in response to PPAF is particularly robust in fronto-central and centro-medial areas of the scalp [Behroozmand et al., 2009; Chen et al., 2012; Hawco, Jones, Ferretti, & Keough, 2009]. Amplitudes and latencies of the P1–N1–P2 complex were extracted from 20 msec-long windows centered around the negative (N1) or positive (P1, P2) peaks in the time windows of 50–100 msec (P1), 100–200 msec (N1), and 200–300 msec (P2) after the onset of the stimulus.

### *Clinical–Behavioral Correlates*

***ASD symptom severity.*** ASD symptom severity was measured using algorithm scores from the *Social Affect* domain and *Restricted and Repetitive Behavior* domain for ADOS-2 Module 3 and the *Communication and Social Interaction* domain and *Stereotyped Behaviors and Restricted Interests* domain scores for ADOS-2 Module 4, as well as calibrated overall severity comparison scores for both Modules 3 and 4 [Gotham, Pickles, & Lord, 2009; Lord et al., 2012]. Higher scores on each of these components reflect greater symptom severity.

***Assessment of the BAP.*** The Modified Personality Assessment Schedule-Revised [MPAS-R; Piven et al., 1994; Tyrer, 1988] was used to assess the presence of personality traits of the BAP in the ASD parent group. Participants were asked a series of questions regarding personality traits associated with ASD, particularly social reticence, rigidity, and untactfulness. All interviews were independently rated from video by two trained coders on a scale ranging from 0 to 2, which was incremented by 0.5. A score of 0 indicated the trait was absent, a score 1 indicated the trait was mildly or questionably present, and a score of 2 indicated the trait was definitely present. The coders discussed discrepancies in ratings and reached a consensus for each file. Participants were characterized as BAP(+) if they received a consensus score of 2 on the *Aloof*, *Rigid*, or *Untactful* components of the MPAS-R. Participants who did not receive a score of 2 on any of these components were characterized as BAP(−).

***Prosodic ability.*** Prosodic ability was assessed in all participants using the Profiling Elements of Prosody in Speech-Communication [PEPS-C; Peppé & McCann, 2003]. The PEPS-C measures receptive and expressive prosody across six domains of prosodic function and two domains of prosodic form. The function domains assess participants' ability to understand and use prosody in a way that communicates a specific function, such as contrastive stress or affect. The form domains assess the participants' ability to discriminate and imitate intonation patterns. Each domain of the PEPS-C contained 16 items and participants received one point per correct response.

***Pragmatic language skills.*** Pragmatic language was assessed using the Pragmatic Rating Scale-School Age [PRS-SA; Landa, 2011] for individuals in the ASD and ASD control groups and the Pragmatic Rating Scale [PRS; Landa et al., 1992] for individuals in the ASD parent and parent control groups. The PRS-SA is rated from semi-structured play and conversation from the ADOS-2 [Lord et al., 2012]. The PRS is coded based on a semi-structured conversational interview in which an examiner asks the parent a series of questions about their early family life, academic interests and achievements, social relationships, and occupation. For both scales, two coders blind to group independently rated the interactions for pragmatic language features, including subjective measures of prosody, on a three-point scale, with 0 indicating absent,

1 indicating mild, and 2 indicating present. Discrepancies between the independent coders' ratings were resolved through discussion.

*Statistical Analysis Plan*

***IGOR analyses.*** Difference waves for each group were calculated for the sustained vowel task by subtracting the average $f_o$ trace of vocalizations with 0 cent perturbations (control vocalizations) from the average $f_o$ trace with +100 and −100 cent perturbations (Fig. 1). Similarly, a difference wave for each group was calculated for the speech task by subtracting the average $f_o$ trace of vocalizations with 0 cent perturbations from the average $f_o$ trace with −100 cent perturbations. Compensatory vocal responses to PPAF were examined using *t* tests (equal variance; two-tailed) to compare response magnitude and onset latency between the difference waves generated for the ASD and ASD control groups, as well as the ASD parent (collapsed and separated by BAP status) and parent control groups, on a point-by-point basis [Xu et al., 2004]. To protect against type I error, a Bonferroni corrected *P* value of 0.0004 was applied. Response magnitude was defined as the greatest deviation in the $f_o$ contour after the onset of the perturbation. Response onset latency was defined as the point after stimulus onset at which the vocal response magnitude exceeded 2 SD of the prestimulus average.

***Growth curve analyses.*** Given the dynamic nature of vocal responses, growth curve modeling was applied to provide further insight into how vocal responses unfold over time. In addition to assessing response magnitude (greatest deviation in the $f_o$ contour) and response onset latency (msec after stimulus) as in the *t*-test analyses described above, growth curve modeling allowed for analysis of transience of response (i.e., the steepness of the onset and offset of the response). A series of three third order (cubic) orthogonal polynomial models with fixed effects of group and perturbation direction (+100 and −100 cent) were applied using adapted code [Mirman, 2014] in *R* statistical software to compare compensatory vocal responses for the sustained vowel task between the ASD and ASD control groups; the ASD parent and parent control groups; and the BAP(+), BAP(−), and parent control groups. Each model also included participant random effects and participant-by-condition random effects on all compensatory vocal response terms. Similarly, compensatory vocal

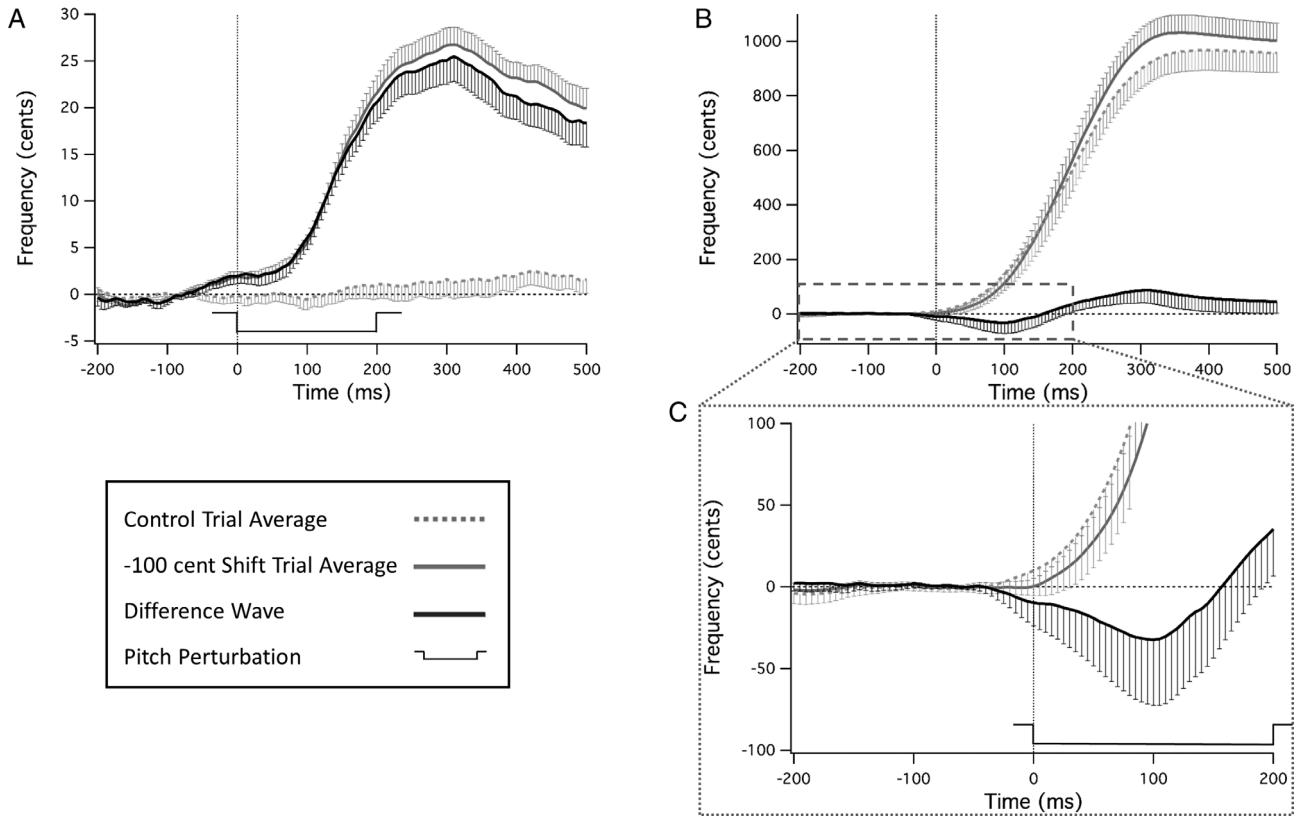


**Figure 1.** Grand average vocal responses and difference waves. Difference waves (black) were produced from the grand average wave of the control trials (gray, dashed) and the grand average wave of trials with −100 cent perturbations. The vertical dashed line indicates the onset of the pitch perturbation. The horizontal line indicates the mean baseline vocalization prior to the perturbation. (**A**) Displays the grand averages and difference wave for the sustained vowel task. (**B**) Displays the grand averages and difference wave for the speech task. (**C**) Displays a magnified view of Figure 1B and the first 200 msec after the pitch perturbation onset.

responses for the speech task were modeled using three third order (cubic) orthogonal polynomial models and fixed effects of group with participant random effects on all compensatory vocal response terms. Finally, a series of three growth curve models comparing compensatory vocal responses between the sustained vowel and speech task were conducted using a third order (cubic) orthogonal polynomial with fixed effects of group and task (sustained vowel vs. speech), as well as participant and participant-by-condition random effects on all compensatory vocal response terms, to assess task-dependent modulation of $f_o$, which is consistent with prior literature [Chen et al., 2007].

***ERP analyses.*** ERP analysis included six electrode sites (F3, Fz, F4, C3, Cz, and C4). A series of $2 \times 2 \times 3$ mixed RM-ANOVAS using the least significant difference procedure for pairwise comparisons were used to compare group differences in P1, N1, and P2 ERP response amplitude and latency based on perturbation direction (+100; −100 cents), frontality (frontal [F3, Fz, F4]; central [C3, Cz, C4]), and laterality (left [F3, C3]; midline [Fz, Cz]; right [Cz, C4]).

***Correlations with clinical–behavioral measures.*** To examine how compensatory vocal responses might relate to broader ASD symptomatology, prosodic abilities, and pragmatic language, Pearson correlations between response magnitude, response latency, and aforementioned clinical-behavioral correlates were conducted in the ASD and ASD control groups collapsed, as well as in the ASD parent and parent control groups collapsed.

## Results

*Sustained Vowel Task*

***Vocal responses in ASD and ASD control groups.*** The ASD group exhibited a significantly larger response magnitude to the −100 cent perturbation ($t(140) = 16.07$, $P < 0.0004$) and +100 cent perturbation ($t(140) = 9.13$, $P < 0.0004$) compared to the ASD control group (Fig. 2). The ASD and ASD control groups did not differ in response onset latency in the −100 ($t(37) = -0.92$, $P = 0.36$) or +100 ($t(37) = 0.79$, $P = 0.43$) cent conditions.

Analysis of overall response patterns using growth curve modeling revealed additional information not captured by analyses of individual points using $t$ tests. Growth curve analyses of the ASD and ASD control group revealed significant effects of group on the linear and cubic polynomial terms, indicating increased vocal response magnitudes (estimate = −49.11, $SE = 16.50$, $P < 0.01$) and latency (estimate = 22.39, $SE = 7.60$, $P < 0.01$) in the ASD group. A marginal effect of group on the quadratic term was revealed, indicating a shallower or more gradual response in the ASD group (estimate = 16.76, $SE = 9.10$, $P = 0.07$). Additionally, there was an interaction between group and perturbation direction on the linear, quadratic, and cubic polynomial terms, indicating a greater increase in response magnitude (estimate = 34.54, $SE = 3.10$, $P < 0.001$), steeper response (estimate = −19.86, $SE = 3.10$, $P < 0.001$), and earlier shifted response onset (estimate = −7.61, $SE = 3.11$, $P = 0.01$) to the −100 cent perturbation in the ASD group.

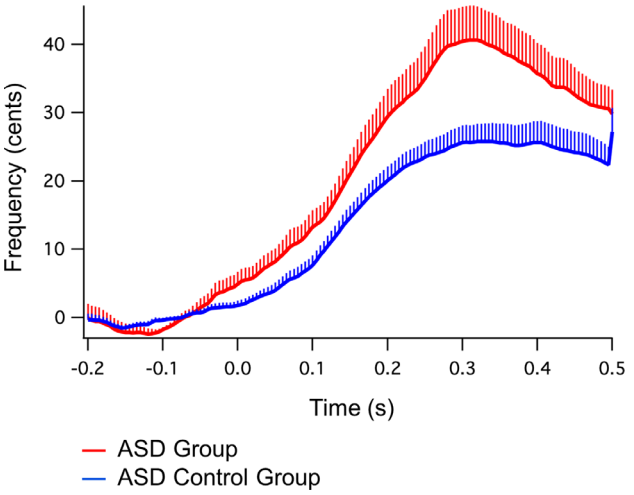


**Figure 2.** ASD and ASD control groups' average compensatory vocal responses (difference waves) during the sustained vowel task. The ASD group exhibited a significantly larger response magnitude to the −100 (pictured above) and +100 cent perturbation ($P$s < 0.0004) compared to the ASD control group.

***Vocal responses in ASD parent and parent control groups.*** The ASD parent group demonstrated a significantly larger response magnitude to the −100 ($t(140) = 15.70$, $P < 0.0004$) and +100 ($t(140) = 4.40$, $P < 0.0004$) cent perturbations compared to the parent control group. The ASD parent and parent control groups did not differ in response onset latency in the −100 ($t(45) = -1.70$, $P = 0.10$) or +100 ($t(45) = -0.67$, $P = 0.50$) cent conditions. However, the BAP(+) subgroup group demonstrated a significantly larger response magnitude to the −100 and +100 cent perturbation compared to the BAP(−) ($t(140) = 14.52$, $P < 0.0004$; $t(140) = 8.85$, $P < 0.0004$, respectively) and parent control ($t(140) = 21.25$, $P < 0.0004$; $t(140) = 10.04$, $P < 0.0004$, respectively) groups. The BAP(−) group exhibited a significantly larger response magnitude to the −100 cent ($t(140) = 6.13$, $P < 0.0004$) but not the +100 cent ($t(140) = 1.64$, $P = 0.09$) perturbation compared to the parent control group (Fig. 3). The BAP(+) and BAP(−) parent groups did not differ in response onset latency from each other (−100 cent: $t(22) = -0.86$, $P = 0.40$; +100 cent: $t(22) = 0.63$, $P = 0.54$) or from the parent control group (−100 cent: $t(30) = 1.95$, $P = 0.06$, +100 cent: $t(30) = 0.12$, $P = 0.91$; −100 cent: $t(36) = 1.08$, $P = 0.29$, +100 cent: $t(36) = 0.84$, $P = 0.41$, respectively). See Table 4 for the means and standard

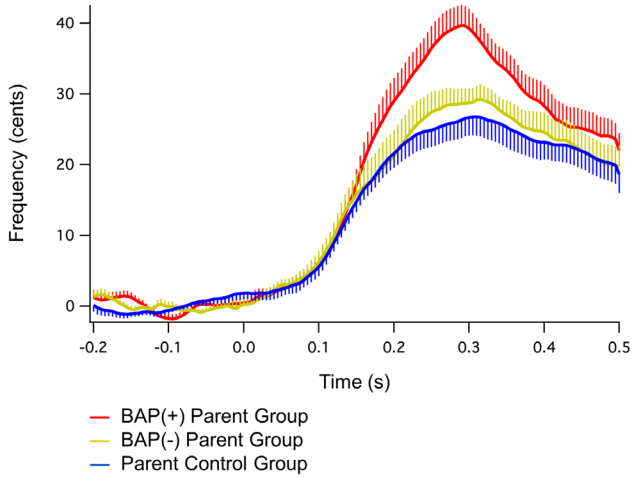


**Figure 3.** Parent groups' average compensatory vocal responses (difference waves) during the sustained vowel task. The BAP(+) parent group demonstrated a significantly larger response magnitude to the −100 (pictured above) and +100 cent perturbation compared to the BAP(−) parent and parent control (*P*s < 0.0004) groups.

deviations of vocal response magnitudes and onset response latencies for each group.

Growth curve analyses in the ASD parent and parent control groups revealed significant effects of the linear and cubic polynomial terms, indicating increased vocal response magnitude (estimate = −27.72, *SE* = 10.43, *P* = 0.01) and increased latency (estimate = 22.44, *SE* = 6.06, *P* < 0.01) in the ASD parent group. The effect of group on the quadratic term was not significant (estimate = 2.07, *SE* = 5.67, *P* = 0.71). There was an interaction between group and perturbation direction on the linear and cubic polynomial terms, indicating a greater increase in response magnitude (estimate = 18.06, *SE* = 2.43, *P* < 0.001) and earlier shifted response onset (estimate = −23.12, *SE* = 2.44, *P* < 0.001) to the −100 cent perturbation in the ASD parent group. The interaction of group and perturbation direction on the quadratic term was not significant (estimate = 2.13, *SE* = 2.44, *P* = 0.38).

Analysis of BAP status revealed significant effects of the linear and cubic polynomial terms, indicating that the BAP (+) group demonstrated increased vocal response magnitude (estimate = −47.52, *SE* = 14.28, *P* < 0.01) and onset latency (estimate = 38.87, *SE* = 7.33, *P* < 0.001) compared to the parent control group. The BAP(+) group also demonstrated increased response onset latency (estimate = 30.93, *SE* = 7.75, *P* < 0.001) and a trending increase in vocal response magnitude (estimate = −26.52, *SE* = 15.11, *P* = 0.08) compared to the BAP(−) group. Trending effects of BAP status on the quadratic term were identified such that the BAP(+) group demonstrated patterns of a shallower or more gradual vocal response (estimate = 12.71, *SE* = 7.36, *P* = 0.08; estimate = 12.77, *SE* = 7.79, *P* = 0.10) compared to the parent control and BAP(−) groups, respectively. An effect of perturbation direction was identified on the linear, quadratic, and cubic terms, indicating increased response magnitudes (estimate = −27.17, *SE* = 2.70, *P* < 0.001), steeper responses (estimate = −5.46, *SE* = 2.71, *P* < 0.05), and increased response onset latency (estimate = 17.30, *SE* = 2.72, *P* < 0.001) to the −100 cent perturbation. There was a significant interaction between group and perturbation direction on the linear term indicating a greater increase in response magnitude to the −100 cent perturbation in the BAP(+) group compared to the parent control (estimate = 53.24, *SE* = 3.22, *P* < 0.001) and BAP(−) (estimate = 46.00, *SE* = 3.41, *P* < 0.001) groups. The effect of the interaction on the quadratic term revealed that the BAP(+) group had a significantly shallower or more gradual vocal response to the −100 cent perturbation compared to the BAP(−) group (estimate = 14.95, *SE* = 3.42, *P* < 0.001). A similar marginal interaction effect was identified when comparing the BAP(+) group to the parent control group (estimate = 5.85, *SE* = 3.23, *P* = 0.07). The effect of the interaction on the cubic term indicated increased response onset latency to the +100 cent perturbation in the BAP(+) group while the parent control group exhibited an earlier response onset latency to the +100 cent perturbation (estimate = −20.68, *SE* = 3.24, *P* < 0.001). The effect of the group and perturbation direction interaction in the BAP(−) group was nonsignificant (estimate = −2.55, *SE* = 3.43, *P* = 0.46).

**Table 4. Mean and *SD* of Vocal Responses During the Sustained Vowel Task**

| | Sustained vowel | | | |
|---|---|---|---|---|
| | +100 cent | | −100 cent | |
| | Magnitude *M* (*SD*) | Onset latency *M* (*SD*) | Magnitude *M* (*SD*) | Onset latency *M* (*SD*) |
| ASD group | −29.70 (2.78) | 0.06 (0.04) | 40.62 (5.07) | 0.08 (0.07) |
| ASD control group | −25.76 (1.71) | 0.07 (0.05) | 25.67 (2.52) | 0.06 (0.04) |
| ASD parent group | −31.06 (2.35) | 0.08 (0.03) | 33.38 (2.01) | 0.09 (0.05) |
| BAP(+) | −32.56 (2.61) | 0.08 (0.03) | 39.67 (2.87) | 0.10 (0.05) |
| BAP(−) | −29.89 (3.74) | 0.09 (0.03) | 28.62 (2.12) | 0.08 (0.05) |
| Parent control group | −28.30 (2.38) | 0.08 (0.04) | 25.33 (2.61) | 0.07 (0.04) |

***ERP responses.*** ERP results should be interpreted with caution given that only a subset of a participants completed this component of the study. A mixed RM-ANOVA of the ASD and ASD control groups revealed significantly reduced P1 ERP amplitudes in the ASD group ($F(1, 17) = 5.53$, $P = 0.03$; Figure 4). There were no significant main effects of group on N1 or P2 ERP amplitude and latency or on P1 ERP latency (*P*s > 0.26). However, a three-way interaction between group, laterality, and anteriority revealed a difference in P2 ERP latency between the left-lateralized frontal and central electrodes in the ASD group (*P* = 0.03).

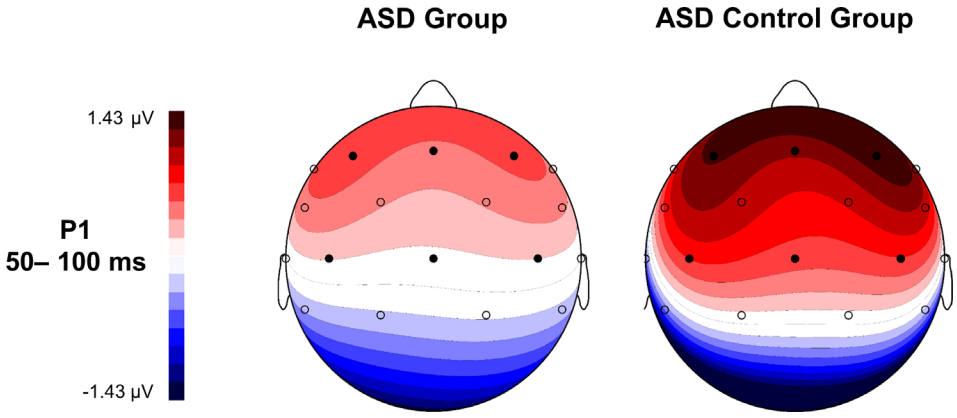


**Figure 4.** P1 ERP to PPAF during the sustained vowel task.

In analyses of the ASD parent and parent control groups, there were no main effects of group on P1, N1, and P2 ERP amplitude and latency (*P*s > 0.23). A significant four-way interaction between group, perturbation direction, laterality, and anteriority revealed a difference in P2 ERP latency between frontal and central electrodes in the ASD parent group ($P$ = 0.02). Specifically, latency differences were identified in the left central electrode in response to the +100 cent perturbation, compared to the right central electrode in response to the −100 cent perturbation. Figures 5 and 6 depict grand average ERP responses to +100 and −100 cent perturbations for each group.

*Speech Task*

***Vocal responses in ASD and ASD control groups.*** The ASD group exhibited a significantly larger response

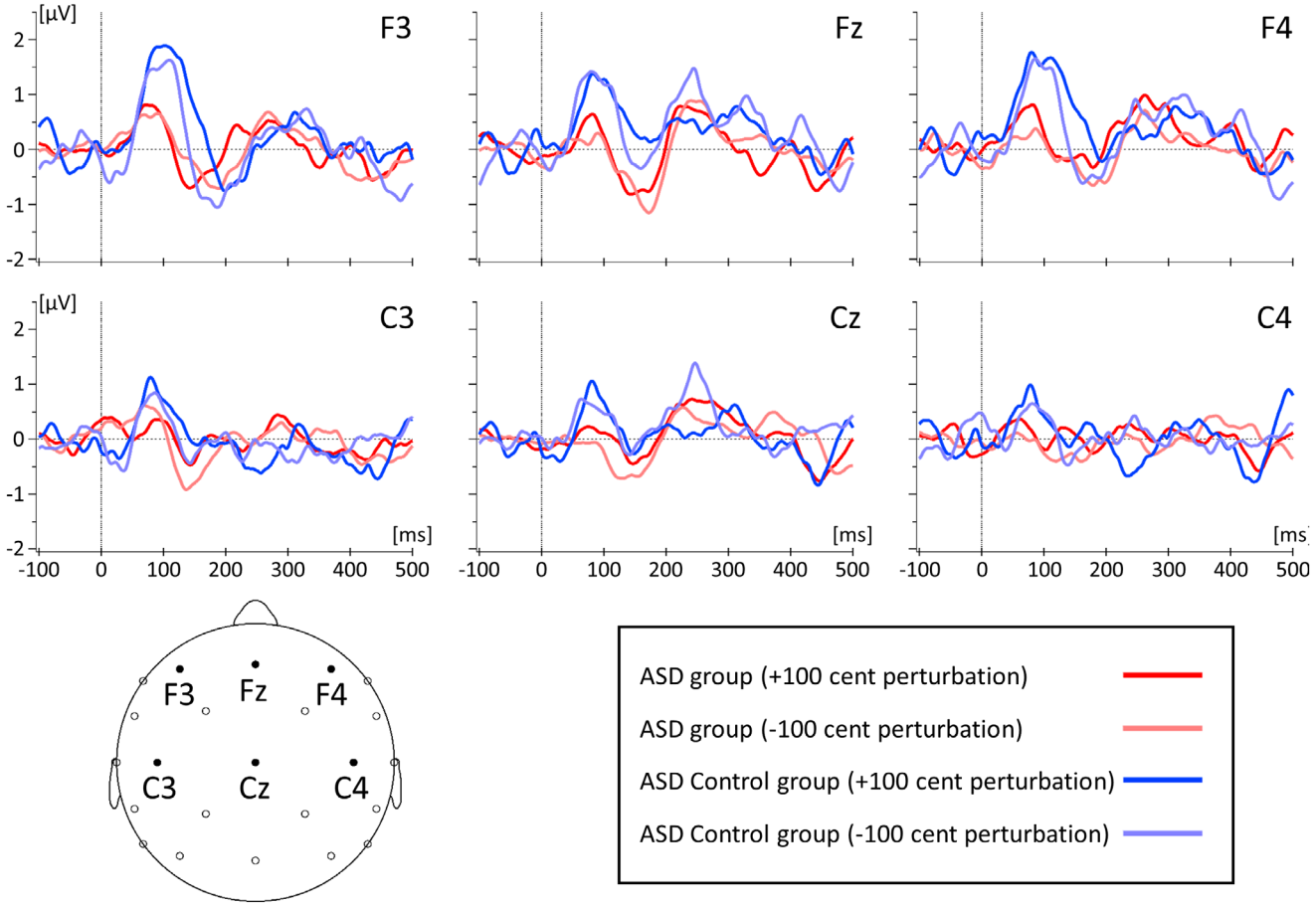


**Figure 5.** Grand average EEG traces of individual channels for the ASD and ASD control groups. Traces are overlaid across group and perturbation direction. EEG traces were obtained from six electrode locations: F3, Fz, F4, C3, Cz, and C4.

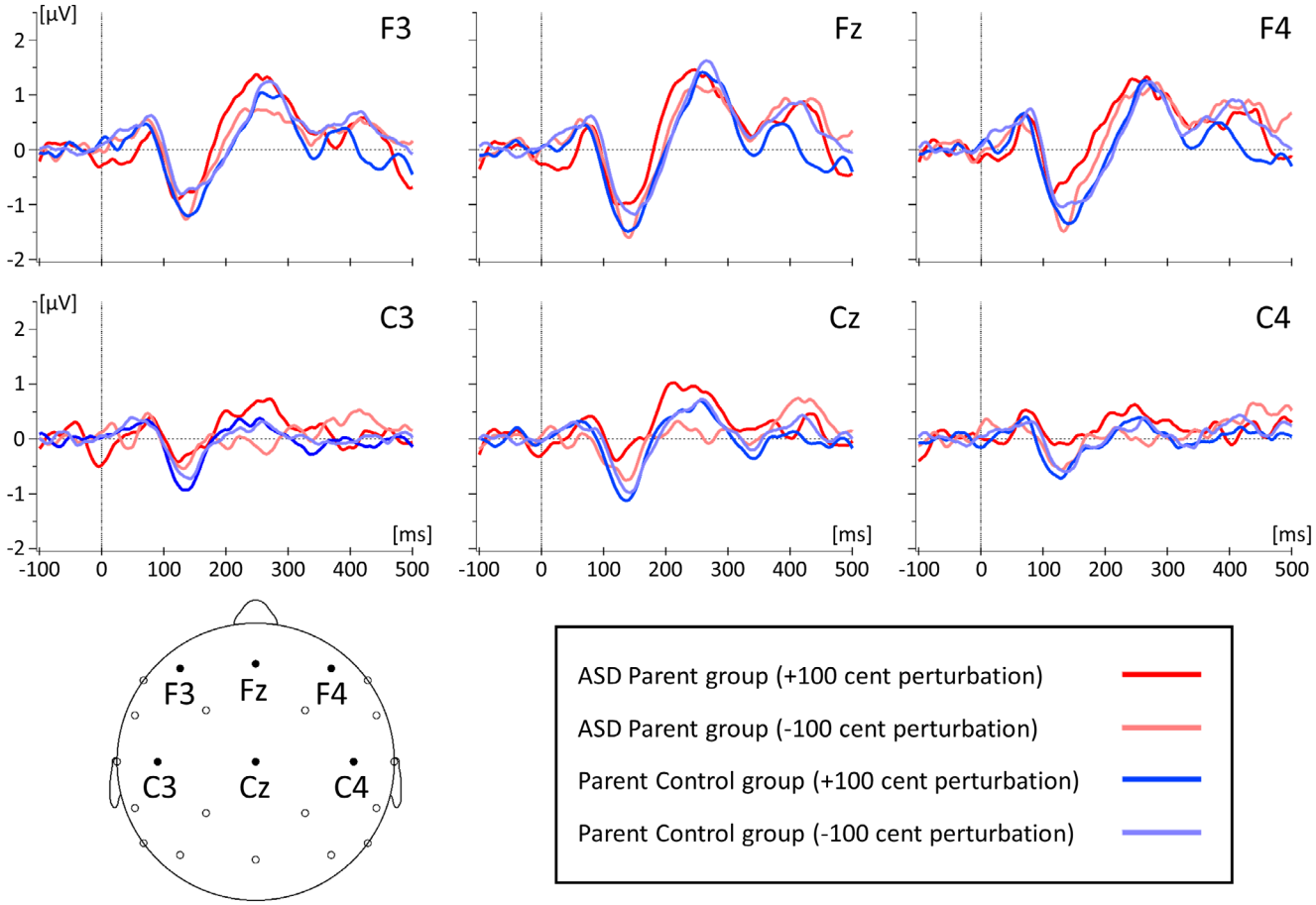


**Figure 6.** Grand average EEG traces of individual channels for the ASD parent and parent control groups. Traces are overlaid across group and perturbation direction. EEG traces were obtained from six electrode locations: F3, Fz, F4, C3, Cz, and C4.

magnitude to the −100 cent perturbation compared to the ASD control group ($t(140) = 8.53$, $P < 0.0004$; Figure 7). The ASD and ASD control groups did not differ in response onset latency ($t(34) = -0.97$, $P = 0.34$).

Growth curve analyses of the ASD and ASD Control group revealed a significant effect of group on the quadratic polynomial term, indicating a shallower or more gradual vocal response in the ASD group (estimate = 100.35, $SE = 48.25$, $P = 0.04$), and a marginal effect of group on the cubic polynomial term indicating a marginally decreased response onset latency in the ASD group (estimate = 40.62, $SE = 22.44$, $P = 0.07$). The effect of group on the linear polynomial term was not significant (estimate = −63.30, $SE = 112.12$, $P = 0.57$).

***Vocal responses in ASD parent and parent control groups.*** The ASD parent group demonstrated a significantly larger response magnitude to the −100 cent perturbation compared to the parent control group ($t(140) = 7.39$, $P < 0.0004$) but did not differ in response onset latency ($t(45) = -0.53$, $P = 0.60$). The BAP(+) group

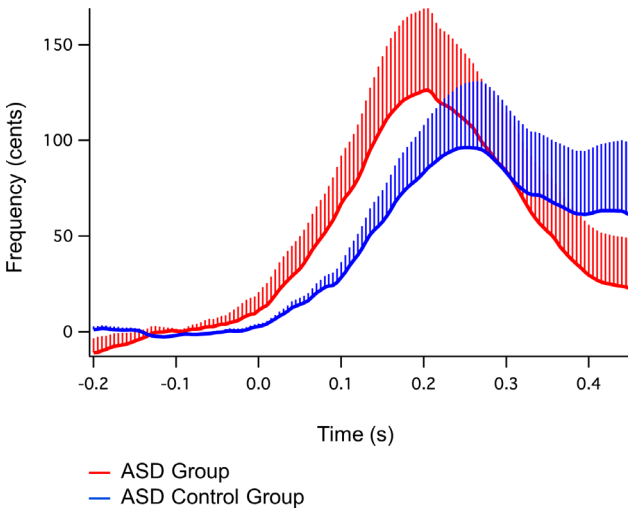


**Figure 7.** ASD and ASD control groups' average compensatory vocal responses (difference waves) during the speech task. The ASD group exhibited a significantly larger response magnitude to the −100 cent perturbation compared to the ASD control group ($P < 0.0004$).

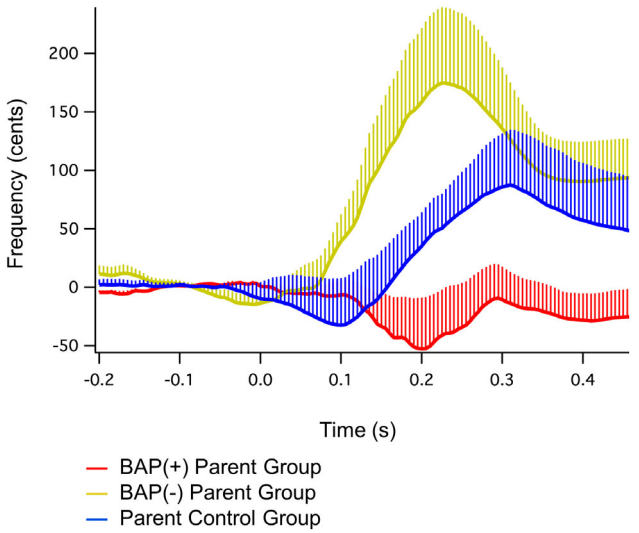


**Figure 8.** Parent groups' average compensatory vocal responses (difference waves) during the speech task. The BAP(+) group demonstrated a significantly reduced response magnitude to the −100 cent perturbation compared to the BAP(−) and parent control groups ($P$s < 0.0004), while the BAP(−) group exhibited a significantly larger response magnitude to the −100 cent perturbation compared to the parent control group ($P$ < 0.0004).

demonstrated a significantly reduced response magnitude to the −100 cent perturbation compared to the BAP(−) ($t(140) = 13.36$, $P < 0.0004$) and parent control ($t(140) = 10.68$, $P < 0.0004$) groups. Additionally, the BAP (−) group exhibited a significantly larger response magnitude to the −100 cent perturbation compared to the parent control group ($t(140) = 10.45$, $P < 0.0004$; Fig. 8). The BAP(+) and BAP(−) groups did not differ in response onset latency from each other ($t(22) = 1.01$, $P = 0.33$) or from the parent control group ($t(30) = -0.43$, $P = 0.67$; $t(36) = -0.37$, $P = 0.72$, respectively). The means and standard deviations of vocal response magnitudes and onset latencies for the speech task are outlined by group in Table 5.

Growth curve analyses of the ASD parent and parent control groups revealed no significant effects of group on the linear (estimate = 4.50, $SE = 150.44$, $P = 0.98$), quadratic (estimate = 92.17, $SE = 83.64$, $P = 0.27$), or cubic (estimate = −8.01, $SE = 47.96$, $P = 0.87$) polynomial terms. There was an effect of BAP status on the linear polynomial term indicating that the BAP(+) group had a significantly decreased response compared to the BAP(−) group (estimate = 511.14, $SE = 203.99$, $P = 0.01$) but only marginal differences from the parent control group (estimate = 289.84, $SE = 192.76$, $P = 0.13$). There were no significant effects of BAP status on the quadratic polynomial term in comparison to the BAP(−) (estimate = −34.29, $SE = 117.50$, $P = 0.77$) or the parent control (Estimate = 49.54, $SE = 111.03$, $P = 0.66$) groups. A significant effect of BAP status on the cubic polynomial term revealed that the BAP(+) group had a decreased response onset latency compared to the BAP(−) (Estimate = −160.31, $SE = 63.13$, $P = 0.01$) and parent control (estimate = −123.38, $SE = 59.65$, $P = 0.04$) groups.

**Table 5. Mean and *SD* of Vocal Responses to −100 Cent Pitch Perturbations During the Speech Task**

| | Speech task | |
|---|---|---|
| | Magnitude *M* (*SD*) | Onset latency *M* (*SD*) |
| ASD group | 126.06 (42.73) | 0.05 (0.03) |
| ASD control group | 96.12 (34.70) | 0.06 (0.04) |
| ASD parent group | 75.77 (44.66) | 0.07 (0.02) |
| BAP(+) | 174.69 (39.05) | 0.07 (0.03) |
| BAP(−) | −50.60 (64.84) | 0.07 (0.01) |
| Parent control group | 50.42 (29.42) | 0.07 (0.04) |

*Task-Dependency of Vocal Responses*

The growth curve model of compensatory vocal responses in the ASD and ASD control groups revealed a significant effect of task on the linear polynomial term (estimate = −49.67, $SE = 18.04$, $P = 0.01$) such that response magnitudes were larger in the speech task than the sustained vowel task (Fig. 9). There was no significant effect of group on the linear polynomial term (estimate = 77.96, $SE = 104.64$, $P = 0.46$). Similarly, the model for parent groups revealed a significant effect of task on the linear polynomial term, indicating larger response magnitudes in the speech task compared to the sustained vowel task (estimate = −102.01, $SE = 21.65$, $P < 0.001$; Fig. 10). There was no significant effect of group on the linear polynomial term (estimate = 112.48, $SE = 124.05$, $P = 0.36$).

*Clinical–Behavioral Correlates of Vocal Responses*

***Sustained vowel task.*** In the ASD and ASD control groups, increased vocal response magnitude was positively correlated with overall ASD symptom severity ($r = 0.39$, $P = 0.01$) and average restricted and repetitive behavior severity ($r = 0.35$, $P = 0.03$). Increased vocal response magnitude was negatively associated with prosodic ability related to imitation ($r = -0.42$, $P = 0.03$) and lexical stress expression ($r = -0.53$, $P < 0.01$). Additionally, increased vocal response magnitude, particularly in response to the −100 perturbation, was associated with increased pragmatic language violations ($r = 0.38$, $P = 0.02$). In the parent groups, increased vocal response magnitude was negatively associated with receptive prosodic ability related to contrastive stress understanding ($r = -0.51$, $P < 0.01$) and marginally negatively associated with prosodic ability related to imitation ($r = -0.29$, $P = 0.09$).

***Speech task.*** In the ASD and ASD control groups, decreased vocal response magnitude was marginally

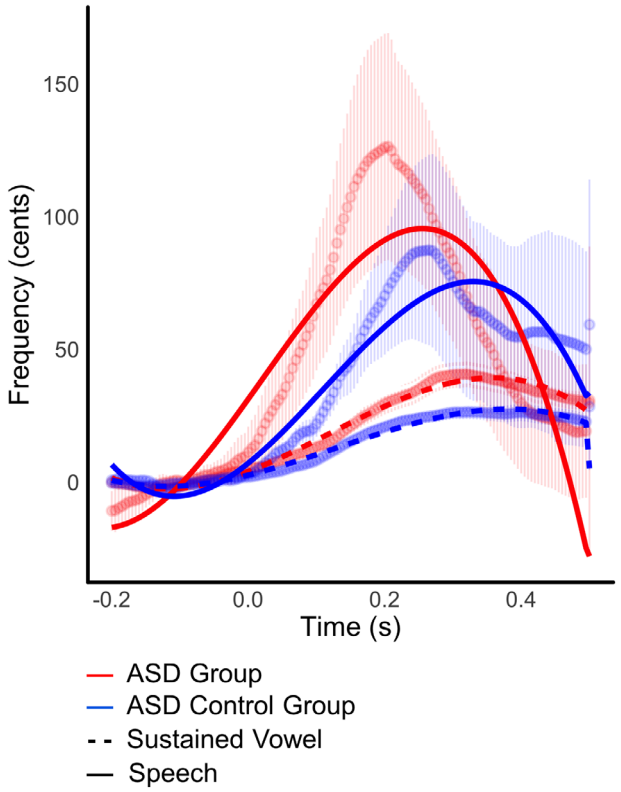


**Figure 9.** Growth curve model demonstrating task-dependency of ASD and ASD control groups' compensatory vocal responses. Average vocal response magnitudes for the speech task were larger than those for the sustained vowel task in the ASD and ASD control groups ($P = 0.01$).

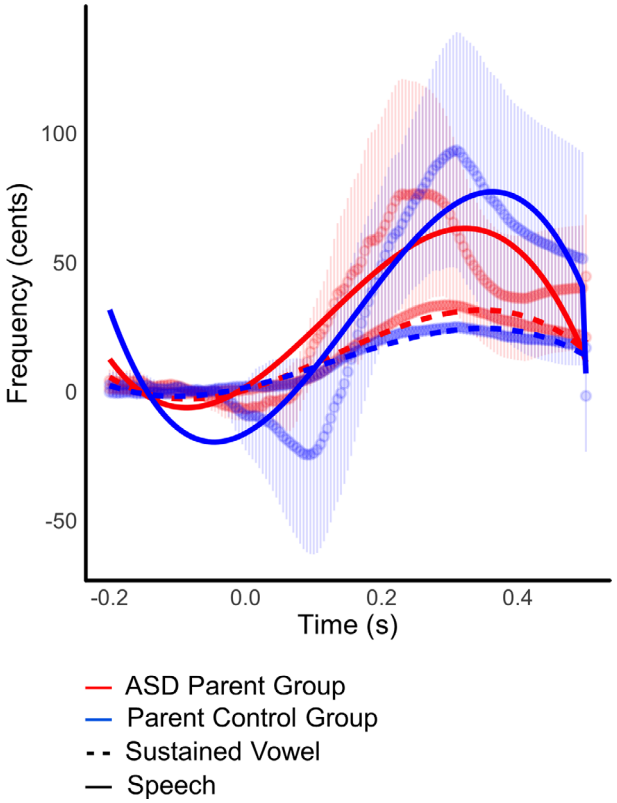


**Figure 10.** Growth curve model demonstrating task-dependency of parent groups' compensatory vocal responses. Average vocal response magnitudes in the ASD parent and parent control groups were larger in the speech task compared to the sustained vowel task ($P < 0.001$).

associated with increased average social affect severity ($r = -0.29$, $P = 0.08$). Decreased vocal response magnitude was associated with increased receptive prosodic atypicalities, including discrimination ($r = 0.57$, $P = 0.03$) and affect understanding ($r = 0.43$, $P = 0.02$), as well as expressive prosodic atypicalities specifically related to using appropriate utterance-final intonation to convey statements and questions ($r = 0.42$, $P = 0.03$). Furthermore, decreased vocal response magnitude was associated with increased pragmatic language violations ($r = -0.39$, $P = 0.02$). In the parent groups, decreased vocal response magnitude was marginally associated with poorer receptive prosody related to understanding contrastive stress ($r = 0.29$, $P = 0.10$).

## Discussion

This study examined vocal and neural responses to PPAF to investigate how audio-vocal integration in ASD and parents (with and without the BAP) may relate to prosodic atypicalities in ASD and the BAP, and potentially reflect genetic liability in parents. A PPAF paradigm was applied during two tasks—a sustained vowel task in which the participant vocalized /a/ for 5 sec and a more complex speech task with a designated intonation pattern of a question. Examining vocal response patterns in both of these tasks allowed for examination of how auditory feedback was used to modify basic vocal motor output, as well as how the system may respond differently to more complex task demands involved in sentence production. Consistent with our hypothesis, results revealed atypical audio-vocal integration in the ASD and ASD parent groups, with several key differences in parents driven by those who displayed the BAP. Many patterns of response differences were also linked with ASD-related symptomatology, and measures of expressive and receptive prosody. Findings from a subgroup of participants also indicated attenuated neural detection of auditory feedback perturbations in ASD, which taken together with vocal response patterns suggest underdeveloped feedforward models, potentially resulting from impairments in integrating feedback-based error signals with feedforward control, in both individuals with ASD and their parents, particularly those with the BAP. These findings underscore atypicalities in the mechanisms related to speech prosody in ASD and point toward the response to PPAF as a candidate language-related endophenotype reflecting genetic liability to ASD in affected and unaffected individuals.

One potential implication of these findings concerns the role of atypical audio-vocal integration in the prosodic difficulties (and potentially related to broader pragmatic impairments) observed in ASD. Successful speech production involves the coordination of the auditory and motor systems, and critically, relies on feedforward and feedback control [Guenther, 2006; Hickok, 2012]. As children acquire speech, auditory feedback plays a crucial role in establishing and refining a mapping between motor commands for speech and the associated sensory consequences. As the speech system becomes more developed and refined, however, we rely more heavily on feedforward control (i.e., predefined motor commands), which allows for the fluid execution of motor behaviors based on established patterns, leading to more efficient control of the speech motor system [Guenther, 2006; Houde, Nagarajan, Sekihara, & Merzenich, 2002]. Execution of a speech motor command is believed to be tightly bound to the sensory consequences of that command, as auditory feedback is compared to the internal model ("efference copy") [Guenther, 1994; Guenther, Hampson, & Johnson, 1998; Tourville & Guenther, 2011]. Any mismatch between the auditory feedback and internal models lead to revision of the motor plan to correct for the error [Guenther, 1994; Guenther et al., 1998; Tourville & Guenther, 2011]. A disconnect at any level in this process may result in cascading effects on the self-monitoring and correction of speech, with impacts on prosodic production.

In this study, results revealed increased vocal response magnitudes and onset latencies in the sustained vowel task in the ASD group. Preliminary ERP results also revealed associated reduced P1 ERP amplitudes in the ASD group, reflecting attenuated detection of pitch perturbations. Increased vocal response magnitudes despite decreased sensitivity to auditory feedback perturbations based on the ERP results may suggest potential atypicalities in the ability to integrate feedback-based error signals with feedforward control in individuals with ASD. Developmentally, decreased sensitivity to auditory feedback could impact the ability to refine the mappings between motor commands and sensory consequences, preventing the development of a stable internal model of motor speech commands. This process may be a potential mechanism by which neuromotor control of speech is disrupted in individuals with ASD. Additionally, response latencies to PPAF typically decrease with development [Liu et al., 2013; Scheerer, Liu, & Jones, 2013], and as such, increased response latencies detected in the ASD group (potentially reflecting increased time for error detection and correction) further suggest an underdeveloped audio-vocal system in ASD. Alternatively, it is possible that the atypicalities evident from the ERP results are not directly related to those atypicalities identified in vocal responses. For instance, a prior study [Larson, Altman, Liu, & Hain, 2008] demonstrated that reduced somatosensory feedback, achieved by way of administration of local anesthetic to the vocal folds, resulted in an increased influence of auditory feedback such that individuals produced larger vocal responses to PPAF. This finding may therefore suggest that the vocal response patterns identified in individuals with ASD result from an overreliance on auditory feedback or a reduced ability to integrate multiple forms of sensory feedback when producing a compensatory response.

Prior investigation of vocal responses to PPAF during sustained vowel production in individuals with ASD found that only a subgroup of individuals with ASD demonstrated increased vocal response magnitudes, whereas the others produced reduced vocal response magnitudes compared to controls [Russo, Larson, & Kraus, 2008]. However, in the present study, which included a larger sample size and more homogenous group of participants with confirmed diagnoses of ASD, the ASD group as a whole demonstrated increased vocal response magnitudes compared to controls. Nonetheless, our study confirms prior implications of an underdeveloped speech motor control system in ASD [Russo, Larson, & Kraus, 2008] and further suggests that this may lead to a larger impact of auditory feedback, and downstream prosodic impairment. A greater impact of feedback mechanisms in the audio-vocal domain in ASD as noted here is also supported by prior research investigating audio-vocal integration in ASD, as well as in other domains, such as the visuo-motor domain. For instance, in line with our findings, Lin et al. [2015] found that individuals with ASD relied more heavily on auditory feedback as evidenced by greater disruptions to their speech production when given delayed auditory feedback compared to external noise, which was introduced to invoke a greater feedforward response. In examining visuo-motor integration, Mosconi et al. [2015] found that during a grip strength task in which participants were asked to maintain varying levels of force, as the demands on the motor system increased, individuals with ASD began to rely more heavily on visual feedback. Taken together, the present study and existing work investigating feedforward and feedback control across domains involving sensory-motor integration suggest a greater reliance on feedback in individuals with ASD due to immature feedforward representations.

Importantly, we found similar, though more subtly expressed, differences in vocal response patterns in the ASD parent group, who exhibited increased vocal response magnitudes and response onset latencies in the sustained vowel task relative to controls. In line with our predictions, vocal response patterns in the ASD parent group were driven by parents with the BAP. In particular, a step-wise pattern was observed, with the BAP(+) parents demonstrating the greatest increase in vocal response magnitudes and latencies, followed by the BAP(−) parents and finally the parent control group. It is important to

note that these differences emerged even with limited sample sizes in the BAP groups, suggesting relatively robust response patterns linked to genetic liability to ASD that may indeed be central to audio-vocal atypicalities in ASD. While ERP results for the parent groups did not reveal any differences in the detection of perturbations (potentially due to the small sample size who completed EEG), the increased vocal response magnitudes and latencies observed particularly in the BAP(+) group suggest atypical integration of expected and perceived sensory consequences. These results suggest a similar breakdown in neuromotor control of speech in parents of individuals with ASD, particularly those with subclinical ASD-related features, and highlight atypicalities in audio-vocal integration as a potential key mechanism underlying ASD-related prosodic atypicalities. Notably, these results provide the first evidence of mechanistic disparities explaining perceptually noted prosodic atypicalities in parents of individuals with ASD [Landa et al., 1992; Losh et al., 2012] and more importantly, implicate atypical audio-vocal integration as a marker of genetic liability to ASD.

Prior studies investigating vocal responses to PPAF during speech tasks have identified increased vocal response magnitudes and decreased response onset latencies in response to PPAF during speech compared to sustained vowel production [Chen et al., 2007; Xu et al., 2004]. These studies demonstrated that neural control of voice $f_o$ incorporates auditory feedback in a way that allows for modification of $f_o$ based on task demands. Interestingly, the ASD and ASD parent groups both exhibited increased vocal response magnitudes compared to respective control groups. In parents, this finding was driven by the BAP(−) group, whereas the BAP(+) group demonstrated significantly *reduced* vocal response magnitudes compared to the BAP(−) and parent control groups. Increased vocal response magnitudes in the ASD and BAP(−) groups suggest deficits in comparing expected and perceived sensory consequences in order to produce appropriate compensatory responses, which may be the result of an underdeveloped feedforward system or alternatively, an increased reliance on auditory feedback. The opposite pattern of reduced response magnitude observed in the BAP(+) group indicates variability in the mechanisms of audio-vocal integration during speech compared to nonspeech in parents of individuals with ASD. In particular, this response pattern may reflect a decreased influence of feedback during speech production in parents with the BAP(+) or impaired integration of feedback-based error signals with vocal motor control, though further investigation is needed to clarify the relationship between feedforward and feedback mechanisms during speech production in this subgroup. Interestingly, both the BAP(+) and BAP(−) parent groups exhibited decreased response onset latencies compared to parent controls, and the ASD group showed a similar trend, though this failed to reach significance. This response pattern may be reflective of impulsivity in neural control of speech (e.g., as previously identified in children and adults with attention-deficit/hyperactivity disorder [ADHD; Korzyukov et al., 2015]. Indeed, behavioral manifestations of impulsivity have also been noted in parents of individuals with ASD, particularly those with the BAP, in the form of increased social disinhibition [Landa et al., 1992; Murphy et al., 2000; Wolff, Narayan, & Moyes, 1988]. Additionally, several studies have identified significant overlap between ADHD and ASD such that approximately half of individuals with ASD exhibit difficulties with ADHD-related behaviors, including impulsivity [Goldstein & Schwebach, 2004; Yoshida & Uchiyama, 2004]. As Korzyukov et al. [2015] suggested for individuals with ADHD, atypicalities in inhibitory mechanisms may be related to differences in involuntary motor control of the voice in individuals with ASD and their parents. Given that the pattern of impulsivity was not specific to the BAP but rather observed in the ASD parent group overall, decreased response latencies to PPAF during speech (unlike increased response magnitudes to PPAF during the sustained vowel production) may reflect more general liability to neurodevelopmental disorders, including ADHD and language-related disorders, rather than ASD specifically. Importantly, impulsivity may be specific to speech in individuals with ASD and their parents as results from the sustained vowel task demonstrated increased response latencies inconsistent with a pattern of impulsivity.

In both ASD and ASD parent groups, vocal response magnitudes across the sustained vowel and speech tasks were associated with prosodic abilities, supporting our hypothesis that atypicalities in audio-vocal integration are related to prosodic atypicalities in ASD and subtle prosodic differences in the BAP. Evidence of similar patterns in parents of individuals with ASD highlights the potential specificity of vocal responses to PPAF as a key marker of genetic risk to ASD-related prosodic atypicalities in clinically unaffected relatives of individuals with ASD. Increased vocal response magnitudes were also associated with increased ASD symptom severity, particularly for restricted/repetitive behaviors, suggesting feedforward and feedback mechanisms involved in vocal motor control may be linked to mechanisms common to those involved in repetitive behaviors in ASD. Critically, this association suggests that neuromotor control related to speech could be intimately tied to other core features of ASD, such as repetitive behaviors, which often include a sensory component. Finally, decreased vocal response magnitudes in the speech task were associated with increased pragmatic language atypicalities in the ASD and ASD control groups, supporting our current understanding that prosodic impairments in ASD impact more global social language abilities. In particular, the inability

to appropriately correct for vocal errors critical to imparting meaning, such as the use of an upward intonation pattern to ask a question, was associated with a broader set of pragmatic language difficulties, pointing to basic mechanistic differences that can contribute to downstream, clinically significant phenotypes in ASD.

In summary, findings indicate atypical audio-vocal integration evidenced by attenuated neural detection of deviant auditory feedback and increased vocal response magnitudes to PPAF. Importantly, a step-wise pattern indicating similarly increased vocal response magnitudes to PPAF in parents with the BAP, followed by parents without the BAP, and parent controls in the sustained vowel task suggests underdeveloped feedforward models or an increased reliance on auditory feedback in parents of individuals with ASD. That such differences were most severely expressed among parents with the BAP suggests that responses to PPAF may be a sensitive index of genetic liability to ASD. Variable response patterns to PPAF in the speech task between the BAP(+) and BAP(−) groups suggest potential differences in the incorporation of feedback in subgroups of parents, highlighting the need for further investigation in a larger sample of parents to tease out potentially variable expression of genetic liability to ASD evident in feedforward and feedback mechanisms during speech. Given parallel findings in vocal responses to PPAF in the ASD and ASD parent group, associations between vocal response magnitudes and prosodic abilities highlight the important contribution of audio-vocal integration to prosodic atypicalities related to ASD and the BAP. Findings may have treatment implications as well, with the association of vocal response magnitudes and prosodic atypicalities suggesting that treatments that emphasize development of feedforward mechanisms may be fruitful for impacting prosodic atypicalities in individuals with ASD. An important limitation of this work includes the relatively small sample size for ERP recording and limited sample sizes to assess potential sex differences in ASD and the BAP, making it important to replicate these findings in larger samples assessing ERP to PPAF in males and females with ASD and their parents. Such work aimed at understanding feedforward motor control in ASD may further elucidate our understanding of whether both feedforward and feedback systems in this population are independently affected and thus clarify targets for further interrogation in studies of underlying biology and treatment. Furthermore, while the present study highlights differences in audio-vocal integration, it did not assess contributions of auditory perceptual acuity to compensatory vocal responses. For instance, increased pitch discrimination may contribute to increased vocal response magnitudes. Although not all individuals with ASD exhibit increased auditory perceptual acuity, it will be important for future studies to disentangle effects of auditory perceptual acuity and atypical audio-vocal integration.

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## Conflict of Interest

The authors declare that they have no disclosures or conflict of interest.

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