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Increased intra-subject variability of neural activity during speech production in people with autism spectrum disorder

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ABSTRACT

Background: Communication difficulties are a core deficit in many people with autism spectrum disorder (ASD). The current study evaluated neural activation in participants with ASD and neurotypical (NT) controls during a speech production task.
Methods: Neural activities of participants with ASD (N = 15, *M* = 16.7 years, language abilities ranged from low verbal abilities to verbally fluent) and NT controls (N = 12, *M* = 17.1 years) was examined using functional magnetic resonance imaging with a sparse-sampling paradigm.
Results: There were no differences between the ASD and NT groups in average speech activation or inter-subject run-to-run variability in speech activation. Intra-subject run-to-run neural variability was greater in the ASD group and was positively correlated with autism severity in cortical areas associated with speech.
Conclusions: These findings highlight the importance of understanding intra-subject neural variability in participants with ASD.

1. Introduction

People with autism spectrum disorder (ASD) present with a wide array of behavioral and neurological traits. The current *Diagnostic and Statistical Manual of Mental Disorders* (American Psychiatric Association, 2013) acknowledged this heterogeneity by removing sub-types (e.g., Asperger's disorder, autistic disorder) in favor of one unifying diagnosis of "autism spectrum disorder" (see Grzadzinski, Huerta, & Lord, 2013). One of the hallmark features for many individuals with ASD is impaired communication abilities, with

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behavioral research indicating that language abilities within this clinical population range from completely non-verbal to verbally fluent (Grzadzinski et al., 2013; Hudry et al., 2010; Stefanatos & Baron, 2011; Tager-Flusberg, Paul, & Lord, 2005). Studies examining the predictive abilities of early speech and language characteristics have found that children later diagnosed with ASD said fewer phrases, produced fewer gestures, were less responsive to people speaking to them, and often displayed a general delay in expressive and receptive milestones (Charman, Drew, Baird, & Baird, 2003; Mitchell et al., 2006; Osterling & Dawson, 1994; Tager-Flusberg et al., 2005). These communication differences have been seen as early as 12–14 months of age (Landa & Garrett-Mayer, 2006; Mitchell et al., 2006), with reduced expressive and receptive language abilities continuing to be noted into adolescence and adulthood (Blume, Wittke, Naigles, & Mastergeorge, 2021; Kjelgaard & Tager-Flusberg, 2001; for review see, Magiati, Tay, & Howlin, 2014; Tager--Flusberg et al., 2005). However, one of the complex aspects of examining individuals with ASD is the heterogeneous presentation of communication skills (Charman et al., 2003; Franchini et al., 2018; Mody et al., 2013; Ramos-Cabo, Vulchanov, & Vulchanova, 2019; Tager-Flusberg & Joseph, 2003). Thus, previous work has proposed focusing on both behavioral and neuroimaging paradigms to elucidate the nature of speech and language deficits in individuals with ASD. The addition of neuroimaging paradigms to the more classical behavioral experiments allows for examination of the neural underpinnings of communication differences seen in this population (Mody et al., 2013; Tager-Flusberg et al., 2005).

Previous neuroimaging studies of communication in participants with ASD have primarily focused on speech and language *perception* (see for review: Herringshaw, Ammons, DeRamus, & Kana, 2016), with significantly fewer studies examining speech and language *production* (Baxter et al., 2019; Beacher et al., 2012; Kenworthy et al., 2013; Kleinhans, Müller, Cohen, & Courchesne, 2008; Knaus, Silver, Lindgren, Hadjikhani, & Tager-Flusberg, 2008; Müller et al., 1998 ; Müller et al., 1999; Pang et al., 2016; Yeung, Lee, & Chan, 2019). A subset of these production studies used covert (i.e., silent) language generation tasks with paradigms that examined category and letter fluency (Baxter et al., 2019; Beacher et al., 2012) and semantic processing (Knaus et al., 2008). These functional magnetic resonance imaging (fMRI) studies found increased activation in language areas involved in semantic processing and word generation in participants with ASD (Beacher et al., 2012; Knaus et al., 2008) and pointed to overall differences in the relationships among regions associated with language in participants with ASD (Baxter et al., 2019; Knaus et al., 2008). However, both verbal fluency and semantic processing require relatively high language and executive functioning abilities. As participants in the ASD and NT groups were matched on these abilities, results from these studies cannot easily be extended to individuals with ASD with more disordered language or executive function abilities (Baxter et al., 2019; Beacher et al., 2012; Knaus et al., 2008). In addition, the covert language generation task has significant limitations as participant accuracy, attention, and compliance cannot be verified during the acquisition.

Overt speech and language tasks have previously been evaluated in verbally fluent individuals with ASD using fMRI (Kenworthy et al., 2013; Kleinhans et al., 2008), functional near-infrared spectroscopy (Yeung et al., 2019), position emission tomography (Müller

Table 1
Participant demographics.

		NT	ASD
Sex			
	Males	7	12
	Females	5	3
Age (years)			
	Mean (SD)	17.1(1.1)	16.7(2.3)
	Range	14.8 – 19.2	13.8 – 21.1
Handedness[a]			
	Mean (SD)	17.1(13.7)	14.5(14.8)
	Range	-24 – 24	-23 – 24
ADOS Calibrated Severity Score[b]			
	Mean (SD)	1.2(0.4)	8.2(1.4)
	Range	1 – 2	6 – 10
Nonverbal IQ standard score			
	Mean (SD)	112.9(13.3)	111.9(26.3)
	Range	88 – 138	65 – 160
PPVT[c] standard score			
	Mean (SD)	116.0(14)	98.9(30.0)
	Range	90 – 138	39 – 135
Words per Minute			
	Mean (SD)	–	44.2(29.7)
	Range	–	11.4 – 134.6
Number of Different Words per Minute			
	Mean (SD)	–	10.3(4.4)
	Range	–	4.9 – 20.6

Abbreviations: L = left; R = right; NT = neurotypical controls; ASD = autism spectrum disorder; SD = Standard deviation; ADOS = Autism Diagnostic Observation Schedule; PPVT = Peabody Picture Vocabulary Test; IQ = intelligence quotient

[a]Handedness was evaluated with a modified version of the Dean Laterality Preference Schedule (Piro, 1998), a parental questionnaire in which parents responded to the hand preferences of their child for different activities.

[b]One NT subject was lost to follow-up before ADOS was administered.

[c]PPVT score was not available for one participant with ASD due to an error during administration in which a basal floor was not established.

et al.,1998;Müller et al.,1999), and magnetoencephalography (Pang et al., 2016). Similar to findings from covert paradigms (Baxter et al., 2019; Beacher et al., 2012), category and letter fluency tasks indicated differences in the functional organization of language and executive function regions in participants with ASD as compared to neurotypical (NT) peers (Kenworthy et al., 2013; Kleinhans et al., 2008; Yeung et al., 2019). Müller and colleagues also suggested participants with ASD had differences in the functional organization of language areas when examining findings from sentence generation and repetition tasks (Müller et al., 1998: Müller et al., 1999). However, the tasks used in prior research all required relatively high language and cognitive abilities and were only evaluated in verbally fluent participants with ASD. Therefore, this earlier research cannot be generalized to individuals with ASD who have reduced verbal abilities.

The current study uses fMRI to evaluate brain activity during single-word productions in participants with ASD and NT controls. This work sought to capture the heterogeneity of autism spectrum disorder by evaluating participants with ASD whose language abilities ranged from low verbal abilities to verbally fluent. We hypothesized that participants with ASD and NT controls would differ in their activation patterns during word production. We anticipated that participants with ASD who had reduced verbal abilities would have less activation in regions typically associated with speech and language production. Additionally, we hypothesized that the distribution of neural activation within the ASD group would be more variable than among the NT group, reflecting the increased range of verbal abilities in participants with ASD.

2. Material and methods

2.1. Participants and behavioral measures

Twenty people with ASD ($M = 16.4$ years, range = 11.8 – 21.1 years, 13 male, 7 female) and thirteen NT controls (M = 17.2 years, range = 14.8 – 19.2 years, 8 male, 5 female) were successfully scanned and were included in the current study. Six of these participants (NT = 1, ASD = 5) were excluded from analysis due to excessive scan-to-scan motion (> 0.5 millimeters (mm); N = 4), less than 50 useable scans after outlier scans were removed during preprocessing (N = 1), or poor fMRI image quality (N = 1). Demographics for the remaining 15 participants with ASD and 12 NT controls included in the analysis are in Table 1. Evaluation of group characteristics indicated there were no significant group (NT, ASD) differences in age ($t(25) = 0.55$, $p = 0.59$) or handedness ($t(25) = 0.46$, $p = 0.65$). Approval for this study was granted by the Boston University institutional review board and the Massachusetts General Hospital human research committee. Participants and/or guardians gave informed consent before participating in this study.

ASD diagnoses were confirmed by the Autism Diagnostic Observation Schedule (ADOS: Lord, Rutter, DiLavore, & Risi, 2001) and the Autism Diagnostic Interview (Rutter, LeCouteur, & Lord, 2003). Participants with ASD were given either ADOS module 2 (adapted version, N = 1), ADOS module 3 (N = 3), or ADOS module 4 (N = 11) based on the clinical impression of the trained research administrator. One NT participant was lost to follow-up before the ADOS was administered; the remaining 11 NT participants were given ADOS module 4. ADOS Calibrated Severity Scores (ADOS-CSS) scores were used as a metric of autism severity, as they are robust to differences in age, ADOS module, and language abilities (Gotham, Pickles, & Lord, 2009). All participants were administered the Peabody Picture Vocabulary Test (PPVT: Dunn & Dunn, 2007) to evaluate receptive language capabilities. Nonverbal intelligence quotient (IQ) was evaluated either by the Leiter-3 (N = 1, participant with ASD who had low verbal abilities: Roid & Miller, 1997) or Perceptual Reasoning Index of the Wechsler Abbreviated Scale of Intelligence-II (N = 14 participants with ASD, N = 12 NT; Wechsler, 1999), consistent with previous work (Plesa Skwerer et al., 2019). Average measures of nonverbal IQ, $t(25) = 0.12$, $p = 0.91$) and PPVT standard score ($t(24) = 1.80$, $p = 0.08$) did not significantly differ between the groups, however, the range of both measures was greater in the ASD group (Table 1). Although there were no significant group differences in PPVT scores, there was a trend for lower PPVT scores in the ASD group as compared to the NT group ($p = 0.08$). To ensure this trend was not impacting the results, between-group neuroimaging analysis (described below) was completed both with and without the inclusion of PPVT as a covariate.

For the ASD participants, ADOS sessions were transcribed using Systematic Analysis of Language Transcripts (SALT) conventions and software (Miller & Chapman, 2008). Two measures were derived from the SALT summary: Words per Minute (number words the participant used divided by the total elapsed time) and Number of Different Words per Minute (number of total novel root words divided by the total elapsed time). Both measures excluded "mazes" (e.g., repetition, reformulations, Miller & Chapman, 2008). Pearson's correlations examined relationships between Words per Minute, Number of Different Words per Minute, and age. Since the focus of the current study was on the behavioral relationships in the ASD group, ADOS sessions were not transcribed for the NT group. Furthermore, correlations within this group were unlikely to be informative due to the reduced anticipated variability of these behavioral measures.

2.2. Preparation and MRI acquisition

2.2.1. Participant preparation

Based on the recommendation of the clinical staff familiar to the participants, 13 of the 15 ASD and 4 out of 12 control participants

underwent a training process to familiarize them with the scanning procedure. This included time in a mock scanner, during which participants heard recordings of the scanning sequence sounds and example auditory stimuli. In addition, those participants practiced being still, repeating a word after it was presented, remaining silent during pauses, and viewing example pictures that could be used as visual stimuli in the task. Many of these participants also underwent a trial scan in the scanner, practicing the paradigm in the same environment where the experimental task would occur. Participants who were able to tolerate the scanning sounds, repeat the stimulus word after prompt, and remain relatively still, were moved on to the experimental session.[3]

2.2.2. MRI acquisition

All imaging sequences were acquired with a Siemens MAGNETOM Skyra 3 T scanner at the Athinoula A. Martinos Center for Biomedical Imaging at Massachusetts General Hospital (Charlestown, MA). The scanner was equipped with a 20-channel head/neck coil. High-resolution T1-weighted MPRAGE sequences (voxel size: 1 mm^3, 43 sagittal images, TR: 3000 milliseconds (ms), TE: 30 ms, flip angle: 85°) and functional gradient-echo EPI scans (46 horizontal slices, in-plane resolution: 3.0 ×3.0 mm^2, slice thickness: 3 mm with no gap, minimum TR: 8 seconds (s) , TA: 3 s, TE: 30 ms, flip angle = 90°) were acquired for each participant. Functional volumes were acquired with a sparse-sampling paradigm (Hall et al., 1999), allowing for both stimuli presentation and participant production to be performed in relative quiet. Each participant completed between three and four runs, with each run consisting of 30 trials and taking approximately 6 minutes to complete. During each trial, a single functional volume was acquired. See the section below for trial and run details.

2.2.3. Stimuli selection and experimental task

Each trial of the fMRI experiment involved the production of a single word that was presented to the participant both auditorily and visually (as a high-quality color image; Moreno-Martínez & Montoro, 2012). Visual stimuli were pictures of twenty-four one-syllable words (Table 2) with an average expressive age of acquisition of 1.97 years (range: 1.36–2.63 years; Moreno-Martínez & Montoro, 2012). Two female, native English-speaking, clinical staff members recorded productions of each word to be used for auditory stimuli. All recordings were duration and intensity normalized. A matched baseline stimulus was created for each of the 24 stimulus words. Each visual baseline stimulus was created from a visual phase spectrum scrambled image of the visual stimulus. Each auditory baseline stimulus consisted of multi-talker babble shaped by the envelope of the auditory stimulus.

For the experimental task, 5 of the possible 24 stimulus words were selected for each participant. The stimuli recorded by the clinical staff member the participant was most familiar with were selected. Stimulus words were pseudo-randomly chosen for the majority of participants, with the average age of acquisition for target words (Table 2) balanced across the ASD and NT groups. Word selections for ASD participants with low verbal abilities were conducted by clinical staff members to ensure the target word was one the participant could reliably produce. Each of the five selected words had an accompanying *speech* and a *baseline* stimulus. During a run, participants were presented with each of the five words three times as a *speech* trial (visual and auditory stimulus) and three times as a *baseline* trial (visual and auditory baseline stimulus). Trial order within the run was chosen from one of four previously created pseudorandom lists in which no more than four trials of the same type (i.e., speech or baseline) were produced sequentially. Visual stimuli were projected onto a screen the participant could view from within the scanner via a mirror attached to the head coil. Auditory stimuli were played over MRI-compatible, pneumatic over-the-ear headphones or over the scanning room's PA system if the participant did not tolerate headphones. Participants' productions were recorded with a fiberoptic MR-compatible microphone (Fibersound model FOM1-MR-30 m); signals were sent to a Lenovo ThinkPad and recorded at a sampling rate of 44.1 kilohertz in MATLAB (The Mathworks Inc, 2017). After scanning, audio recordings were evaluated for each participant, and trials were manually eliminated if the participant did not produce the target word during a *speech* trial or spoke during a *baseline* trial.

During a given *speech* or *baseline* trial, the participant was presented with the visual and auditory stimuli simultaneously for 0.5 s (Fig. 1). The visual stimulus remained on the screen for three additional seconds, prompting the participant to repeat the word out loud. Then one of ten randomly chosen grey-scale abstract silent filler videos with slowly moving shapes or lines played for 7.5 s to keep the participant's attention and minimize motion during the acquisition of functional volume. The scanner was triggered between 4.5 and 5 s (randomly jittered) after the participant's speech onset to acquire the peak of the hemodynamic response (Belin, Zatorre, Hoge, Evans, & Pike, 1999). Triggering the scanner relative to the start of speech onset accommodated the range of verbal abilities of the participants and removed the potential impact of varying participant reaction times. Due to differences in participants' speech onsets, trials lasted between 10 and 13 s. Trials over 14 s were treated as production errors and excluded from the analysis. During baseline trials, the timing of the scanning onset was based on the average duration of speech onset during speech trials. A person familiar to the participants with ASD (either a member of the clinical staff or a family member) was present in the room for the experiment, providing them with reminders to stay still and when to speak during the task.

[3] Fifteen additional participants were enrolled in the current study but were not included in the analysis or Table 1. Reasons for exclusion were: unsuccessful participation in the mock and/or trial scans, which resulted in a failure to advance to the experimental stage (N = 10), inability to complete the experimental task due to behavioral difficulties or request to stop (N = 3), experimental errors during the task that required an early stop and unusable data (N = 2).

Table 2
Speech stimuli.

Stimuli (average age of acquisition)[a]			
Hand (1.37)	Chair (1.74)	Cow (2.00)	Train (2.34)
House (1.43)	Pencil (1.79)	Horse (2.00)	Church (2.39)
Bed (1.47)	Fork (1.79)	Duck (2.03)	Lamp (2.43)
Foot (1.49)	Shoe (1.86)	Ant (2.03)	Glove (2.49)
Cat (1.58)	Socks (1.86)	Pear (2.05)	Drum (2.58)
Arm (1.62)	Car (1.90)	Grapes (2.29)	Boat (2.63)

[a]Average age of acquisition in years from Moreno-Martínez and Montoro (2012) derived from a picture-naming task.

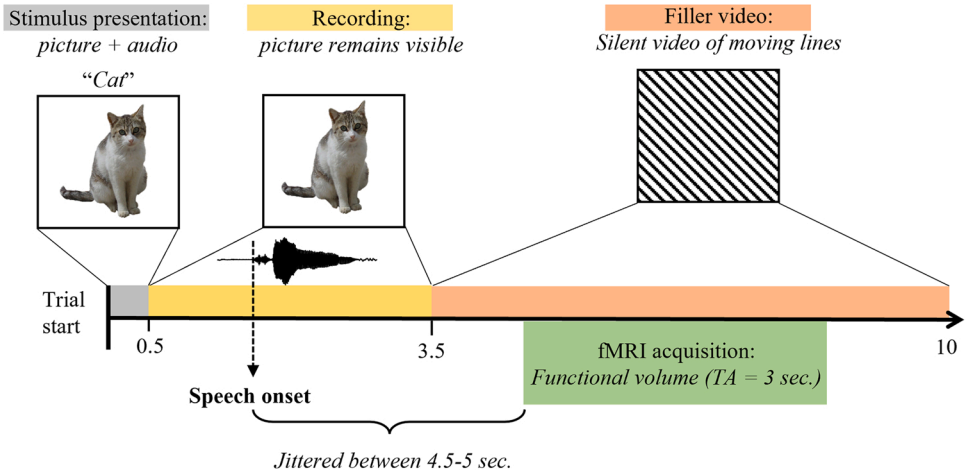

Fig. 1. A task schematic for a sample speech trial. The participant was presented with the picture and audio representation of the target stimuli for 0.5 s. Following the auditory prompt, the visual prompt remained on the screen for three seconds while the participant repeated the target word. The visual prompt was removed after three seconds and replaced with a silent filler video of moving lines or shapes to keep the participant still for the remainder of the trial. The functional volume was acquired over a 3-second period, starting 4.5 – 5 s after speech onset. During baseline trials (not pictured), the visual and auditory baselines were presented simultaneously for 0.5 s, the visual picture stimuli remained on the screen for an additional 3 s, and then the silent filler video of moving lines or shapes was shown for the remainder of the trial. Scanning onset during baseline trials was based on the average duration of speech onset during speech trials.

2.3. MRI Analysis

2.3.1. Preprocessing and participant-level blood oxygen-level dependent (BOLD) activation

Functional data were processed using tools from the following software packages that were integrated into a single MATLAB-based processing stream: SPM12 (Statistical Parametric Mapping, v12; www.fil.ion.ucl.ac.uk/spm/), FreeSurfer (Fischl et al., 2002; Fischl, Sereno, Tootell, & Dale, 1999, www.freesurfer.net), Artifact Detection Tools (ART; www.nitrc.org/projects/artifact_detect/), and the CONN toolbox (Whitfield-Gabrieli & Nieto-Castanon, 2012). FreeSurfer was used to remove non-brain components of the T1 structural volumes, segment the brain into gray matter, white matter, and cerebral spinal fluid components and to generate a reconstruction of the cortical surfaces of each hemisphere. 18 anatomically defined cortical regions of interest (ROIs) that are involved in speech and language production were labeled in each hemisphere (black outlines, Fig. 2) for the purpose of ROI-based analysis of functional data (see below). ROIs were mapped from FreeSurfer's *fsaverage* surface template to the co-registered individual cortical surface reconstructions.

Functional images from each participant were realigned to the participant's mean image and unwarped (correction of susceptibility distortion-by-motion interactions) using the SPM12 realign and unwarp procedure (Andersson, Hutton, Ashburner, Turner, & Friston, 2001). Outlier scans were detected with ART based on thresholds for motion displacement (2 mm for scan-to-scan head-motion) and global signal change (z-score of 9 for scan-to-scan global signal change). Functional volumes from each subject were then co-registered with their high-resolution T1 structural images and resliced using the SPM12 affine inter-modality coregistration procedure with a normalized mutual information cost function (Collignon et al., 1995; Studholme, Hawkes, & Hill, 1998). The functional data were then resampled at the location of the FreeSurfer *fsaverage* surface template tessellation, averaged across 10 intervals along the normal between the white matter and pial surfaces of each subject-specific cortical surface, and smoothed using iterative diffusion smoothing with a series of 40 discrete diffusion steps (approximately equivalent to an 8 mm full-width half-maximum two-dimensional Gaussian smoothing kernel; Hagler, Saygin, & Sereno, 2006). A two-sample t-test examined group differences in scan-to-scan average motion during the fMRI task.

Blood oxygen-level dependent (BOLD) responses during speech and baseline trials were estimated using participant-specific

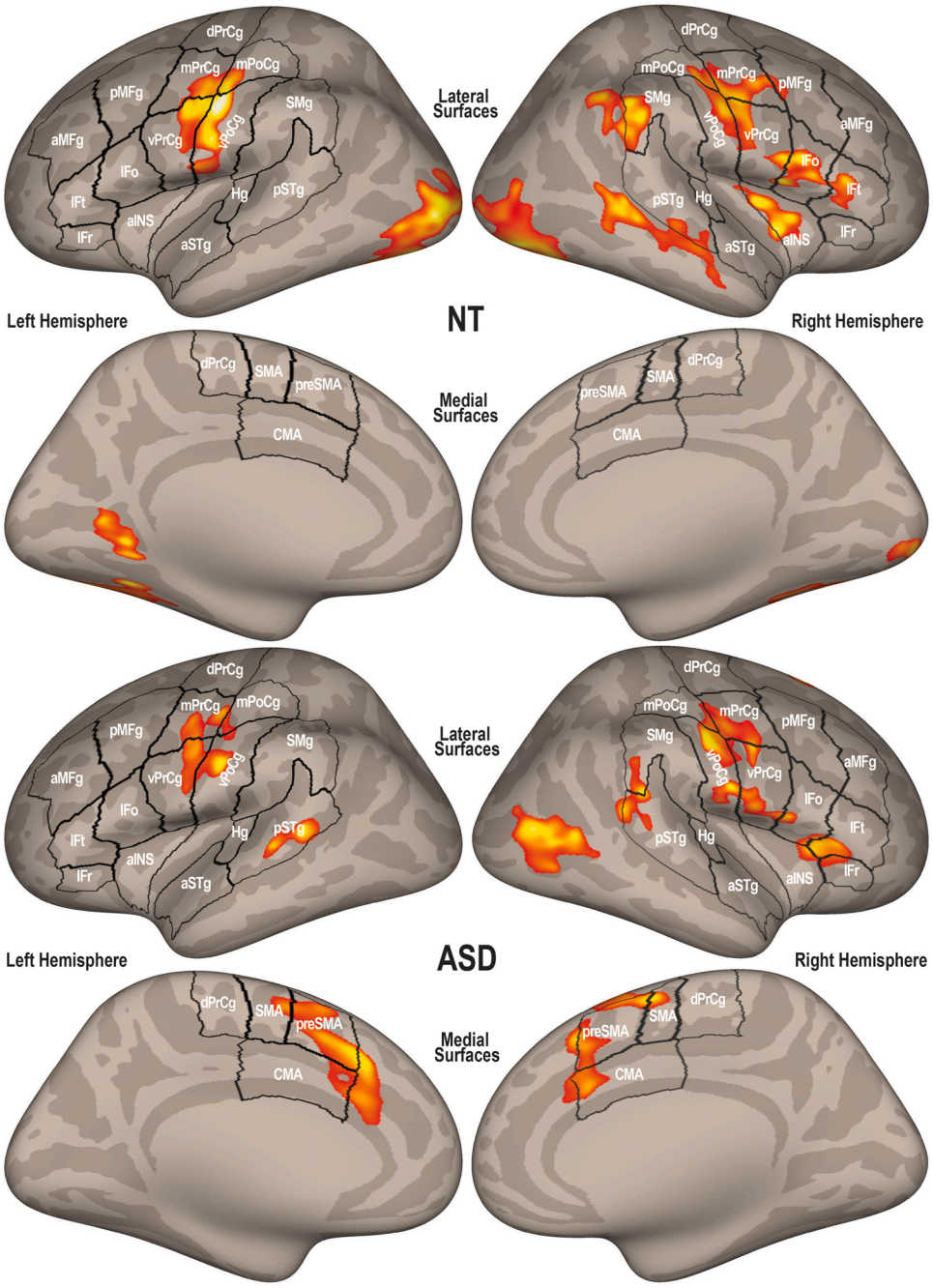

Fig. 2. Areas with significant *speech – baseline* BOLD activation within the neurotypical (NT) and persons with autism spectrum disorder (ASD) groups after controlling for motion. Significant voxels shown with a cluster threshold of $p < 0.05$ and a voxel threshold of $p_{unc} < 0.01$. A direct comparison of *speech – baseline* activity in the two groups showed no significant differences. Overlay of black lines indicates speech and language network regions of interest. Abbreviations: NT = neurotypical controls; ASD = autism spectrum disorder; aINS = Anterior insula; aMFg = Middle frontal gyrus, anterior division; aSTg = Superior temporal gyrus, anterior division; CMA = Cingulate motor area; dPrCG = Precentral gyrus, dorsal division; Hg = Heschl's gyrus; IFo = Inferior frontal gyrus, pars opercularis; IFr = Inferior frontal gyrus, pars orbitalis; IFt = Inferior frontal gyrus, pars triangularis; mPoCG = Postcentral gyrus, medial division; mPrCG = Precentral gyrus, medial division; preSMA = Pre-supplementary motor area; pMFg = Middle frontal gyrus, posterior division; pSTg = Superior temporal gyrus, posterior division; SMA = Supplementary motor area; SMg = Supramarginal gyrus; vPoCG = Postcentral gyrus, ventral division; vPrCG = Precentral gyrus, ventral division.

General Linear Models (GLM) in SPM12. Because images were collected in a sparse sequence with a relatively long TR, the BOLD response for each trial (event) was modeled as an individual epoch. Each model included two regressors (*speech* and *baseline*) identifying the corresponding trials for each condition, concatenated across all runs in order to maximize power while controlling for potential differences in the number of valid trials per run. Invalid trials, identified as production errors or as motion or signal outliers by ART, were modeled as separate regressors removing any variability in the BOLD signal resulting from these trials. Additional regressors of non-interest for each individual run included two regressors modeling constant and linear effects of time (e.g., signal drift) as well as six regressors modeling residual subject-motion effects (3 translation and 3 rotation parameters estimated during the functional realignment step). For each participant, the GLM was estimated at each vertex, resulting in two surface maps (one for each hemisphere) of the model regressor coefficients for each condition. The condition estimates were then contrasted to yield effect-size maps of the *speech – baseline* contrast. The mean speech-baseline effect size within each structural ROI was also calculated for each participant.

2.3.2. Group-level analyses: speech – baseline contrasts

A whole-brain vertex-wise analysis examined differences in *speech – baseline* contrasts both between (NT vs ASD), and within each group. Contrasts were evaluated at a whole-brain level using a nonparametric permutation analysis (Bullmore et al., 1999) with an uncorrected vertex height threshold of $p < 0.01$ and a false discovery rate (FDR) corrected cluster-mass threshold of $p_{fdr} < 0.05$ across the entire cortical surface.

BOLD activity levels within a set of pre-defined anatomical ROIs involved in speech production (black outlines in Fig. 2) were calculated. ROIs were created by combining ROIs describe in Tourville and Guenther (2003), using the parcellation system designed for speech studies. An FDR threshold of $p < 0.05$ was used to evaluate significance in each hemisphere. This ROI-based analysis provides a more statistically sensitive measure of activity in regions previously associated with speech production in exchange for some loss of spatial resolution compared to vertex-wise analysis. Relationships between behavioral measures and activity levels in these ROIs were also examined within the ASD group. The relationship between average BOLD activation within each ROI and ADOS-CSS and Number of Different Words per Minute were examined after controlling for motion.

2.3.3. Variability of activation in speech network ROIs

A linear mixed model (LMM) was used to evaluate group differences in run-to-run variability in the degree of BOLD activation. First, a new set of subject-specific GLMs were defined and used to estimate *speech* and *baseline* effects separately for each run. After this, a LMM was defined to model the resulting subject- and run- specific *speech - baseline* contrast values, with *ROIs* and *motion* included as fixed effects and *participants* included as a random effect. The resulting LMM covariance parameters were evaluated, with the standard deviation of the estimated *participants'* random effect providing information on inter-subject run-to-run variability while the standard deviation of the residual of the error term provided information on intra-subject run-to-run variability in degree of activation. A subsequent LMM included *PPVT* as an additional fixed effect to the above model when examining group differences. The relationship

Table 3
Significant clusters of activation in the *speech – baseline* contrast after controlling for motion. Location of each peak in MNI space.

		Location (MNI space)				
Group	*ROI*	*x*	*y*	*z*	*Size (voxels)*	*p-fdr*
NT						
	OC (L)	-38	-88	6	3402	< 0.001
	vPoCG (L)	-52	-12	32	2757	0.002
	dPrCG (R)	54	-7	29	2468	0.002
	OC (R)	38	-78	-12	1364	0.017
	IFo (R)	45	11	4	1292	0.017
	SMg (R)	63	-35	43	1029	0.031
	pITg (R)	57	-43	5	910	0.039
	aINS (R)	40	8	-2	702	0.057
ASD						
	vPoCG (R)	59	-6	39	2580	0.009
	vPoCG (L)	-62	-5	29	2403	0.009
	FMC (L)	-5	24	39	1964	0.013
	OC (R)	53	-68	16	1712	0.014
	vPoCG (R)	65	-5	11	1367	0.025
	SFg (R)	7	24	48	1101	0.032
	pCO (R)	66	-31	26	1093	0.032
	IFt (R)	37	25	9	994	0.035
	PO (R)	5	-4	68	885	0.041
	pSTg (L)	-58	-44	8	779	0.041

Abbreviations: MNI = Montreal Neurological Institute; L = left; R = right; NT = neurotypical controls; ASD = autism spectrum disorder; ROI = Region of interest; aINS = Anterior insula; dPrCG = Precentral gyrus, dorsal division; FMC = Frontal medial cortex; IFo = Inferior frontal gyrus, pars opercularis; IFt = Inferior frontal gyrus, pars triangularis; OC = Occipital Cortex; pCO = Central operculum, posterior division; pITg = Inferior temporal gyrus, posterior division; PO = Parietal operculum; pSTg = Superior temporal gyrus, posterior division; SFg = Superior frontal gyrus; SMg = Supramarginal gyrus; vPoCG = Postcentral gyrus, ventral division.

between intra-subject run-to-run variability and behavioral measures was further examined within each group (ASD, NT). Partial correlations between intra-subject run-to-run variability and ADOS-CSS, after controlling for motion, was completed in both groups. An additional partial correlation between intra-subject run-to-run variability and Number of Different Words per Minute was completed in the ASD group.

3. Results

3.1. Behavioral measures

Within the ASD group, Words per Minute and Number of Different Words per Minute were significantly positively correlated ($r = 0.87$, $p < 0.001$). Words per Minute was significantly positively correlated with age ($r = 0.60$, $p = 0.02$), while Number of Different Words per Minute and age were not correlated ($r = 0.30$, $p = 0.28$). As Number of Different Words per Minute provides information on semantic complexity and proficiency (e.g., Miller, 1991) and was not correlated with age in the current participants, Number of Different Words per Minute was used as a proxy for verbal abilities. The ASD group produced an average of 10.3 different words per minute (range: 4.9 – 20.6), with eight participants producing less than ten different words per minute. Average scan-to-scan motion measures were extracted for each individual. Average motion was significantly greater in the ASD group (0.87 mm) compared to the NT group (0.45 mm; ($t(25) = 3.45$, $p = 0.002$). Therefore, motion was included as a covariate of non-interest in subsequent analyses.

3.2. Speech – baseline BOLD activation

Within-group *speech – baseline* BOLD activations with a cluster threshold of $p_{fdr} < 0.05$ and a voxel threshold of $p_{unc} < 0.01$ for the ASD and NT groups are shown in Fig. 2, with clusters listed in Table 3. Although visual inspection of Fig. 2 might suggest differences in brain activity during speech in the ASD versus NT groups, both the whole-brain voxel-wise analysis and the ROI-based analysis indicated no significant differences between the ASD and NT groups in BOLD activity for the *speech - baseline* contrast after controlling for motion ($p_{fdr} > 0.05$) as well as after controlling for motion and PPVT ($p_{fdr} > 0.05$).

Evaluation of activation indicated that both groups showed strong activity in the middle and ventral sensory-motor cortex, which includes motor (precentral gyrus) and somatosensory (postcentral gyrus) representations of the speech articulators (Guenther, 2016). Activity was also found in right premotor cortex, right inferior frontal gyrus, and insular cortex, regions that have been associated with sensory feedback control (Guenther, Ghosh, & Tourville, 2006) and prosodic processing (Geiser, Zaehle, Jancke, & Meyer, 2008) in speech. The ASD group had significant activity in the left higher order auditory cortical areas (posterior superior temporal gyrus). Neither group had activity in the primary auditory cortex (Heschl's gyrus). A major contributing factor to the relatively low auditory

Table 4
ROIs with significant *speech – baseline* activity within the ASD and NT groups after controlling for motion.

Group	ROI	Effect size (beta)	T value	p-fdr
NT	aINS (L)	0.110	3.084	0.021
	aINS (R)	0.126	3.058	0.021
	aSTg (L)	0.108	3.108	0.021
	CMA (L)	0.165	2.877	0.026
	IFo (R)	0.177	3.831	0.009
	IFt (R)	0.181	3.527	0.015
	mPrCG (L)	0.239	2.610	0.045
	mPrCG (R)	0.331	3.311	0.017
	pSTg (R)	0.155	2.555	0.047
	vPoCG (L)	0.292	4.532	0.005
	vPoCG (R)	0.318	2.961	0.024
	vPrCG (L)	0.207	3.418	0.016
	vPrCG (R)	0.243	4.101	0.007
ASD	mPrCG (L)	0.218	2.745	0.040
	mPrCG (R)	0.285	3.237	0.020
	preSMA (L)	0.217	3.288	0.020
	preSMA (R)	0.223	3.480	0.020
	pSTg (L)	0.119	2.741	0.040
	pSTg (R)	0.152	2.958	0.030
	SMg (R)	0.116	2.652	0.045
	vPoCG (L)	0.223	3.611	0.020
	vPoCG (R)	0.302	3.323	0.020
	vPrCG (L)	0.167	3.029	0.029
	vPrCG (R)	0.194	3.557	0.020

Abbreviations: L = left; R = right; NT = neurotypical controls; ASD = autism spectrum disorder; ROI = region of interest; aINS = Anterior insula; aSTg = Superior temporal gyrus, anterior division; CMA = Cingulate motor area; IFo = Inferior frontal gyrus, pars opercularis; IFt = Inferior frontal gyrus, pars triangularis; mPrCG = Precentral gyrus, medial division; preSMA = Pre-supplementary motor area; pSTg = Superior temporal gyrus, posterior division; SMg = Supramarginal gyrus; vPoCG = Postcentral gyrus, ventral division; vPrCG = Precentral gyrus, ventral division.

cortical activity in this study is that subjects could not hear their own speech well as they were wearing ear protection that blocked the sound of their voice. The delay between the stimuli presentation and MRI acquisition may have also contributed to the lack of activation noted in these auditory areas. Furthermore, participants also heard an auditory sound during the *baseline* task, which likely contributed to the lack of *speech – baseline* differences in the primary auditory cortex. The more sensitive ROI-based analysis did reveal activity in bilateral posterior superior temporal gyrus in both groups (Table 4). The vertex/voxel-wise results showed activity in the pre-supplementary motor area and cingulate motor area in the ASD group but not the control group; however, the ROI-based analysis revealed significant activity in both groups in pre-supplementary motor area and cingulate motor area. Outside of the speech network, activity is seen in occipital cortical areas involved in visual processing, likely due to the visual aspect of stimulus presentation.

Within the ASD group, there were no significant relationships between *speech – baseline* activation and either ADOS-CSS or Number of Different Words per Minute after controlling for motion. Exploratory uncorrected analyses indicated there was a positive relationship between ADOS-CSS and *speech-baseline* activation within the right anterior insula ($\beta = 0.059$, $p_{unc} = 0.036$), right inferior frontal gyrus, *pars opercularis* ($\beta = 0.088$, $p_{unc} = 0.005$), right postcentral gyrus, ventral division ($\beta = 0.099$, $p_{unc} = 0.047$), and right precentral gyrus, ventral division ($\beta = 0.064$, $p_{unc} = 0.014$). Furthermore, there was a positive relationship between Number of Different Words per Minute and *speech – baseline* activation in the left superior temporal gyrus, anterior division ($\beta = 0.016$, $p_{unc} = 0.020$), and negative relationships between Number of Different Words per Minute and *speech-baseline* activation in the precentral gyrus, dorsal division ($\beta = -0.022$, $p_{unc} = 0.032$).

3.3. Variability analysis

There were no significant group differences in inter-subject run-to-run variability after controlling for motion ($t(25) = 0.29$, $p = 0.78$) or after controlling for motion and PPVT ($t(24) = 0.99$, $p = 0.70$) In contrast, there was a significant group difference in intra-subject run-to-run variability after controlling for motion ($t(25) = 5.68$, $p < 0.001$, Fig. 3) and after controlling for motion and PPVT ($t(24) = 6.18$, $p < 0.001$). Greater intra-subject variability was found in the ASD group as compared to the NT group (Fig. 3).

Average run-to-run intra-subject variability was significantly correlated with ADOS-CSS in the ASD group after controlling for motion ($r = 0.70$, $p = 0.005$, Fig. 4). Average run-to-run intra-subject variability in the NT group was not significantly correlated with ADOS-CSS after controlling for motion ($r = 0.10$, $p = 0.77$). There were no significant correlations in the ASD group between run-to-run intra-subject variability and Number of Different Words per Minute after controlling for motion ($r = -0.05$, $p = 0.87$).

4. Discussion

The main significant group difference found in this study showed that participants with ASD had increased intra-subject neural variability across experimental runs as compared to the NT group. However, this increased intra-subject variability was not attributable to overall group variability, as the ASD and NT groups had comparable measures of inter-subject neural variability. Furthermore, in participants with ASD, there was a significant correlation between increased autism severity measures and increased intra-subject neural variability. These findings suggest that brain activity during speech production in participants with ASD is more variable, with less consistent activation in the speech network of people with increased autism severity scores.

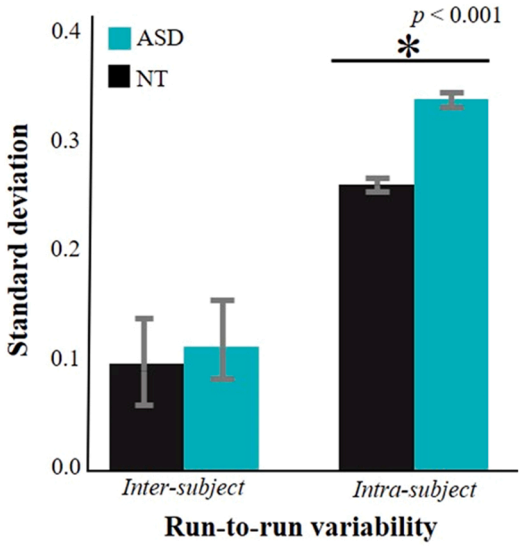

Fig. 3. Run-to-run variability for the neurotypical (NT, black bars) and persons with autism spectrum disorder (ASD, green bars) groups. Average inter- and intra-subject variability shown with 95% confidence intervals. Intra-subject variability was significantly different between the ASD and NT groups.

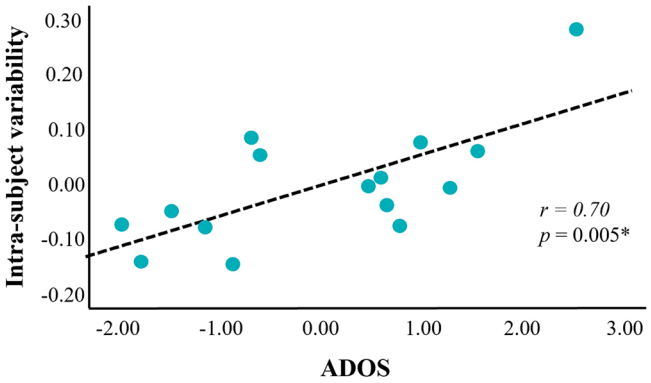

Fig. 4. Partial regression plot showing the relationship between ADOS-CSS and intra-subject variability in *speech – baseline* activity after accounting for the effect of motion. Each circle is the residual for an individual participant in the ASD group; dashed line indicates the linear fit.

This work adds to the growing body of literature emphasizing the importance of understanding intra-subject neural variability in individuals with ASD, as the sole focus on average group values may mask these more nuanced differences (David et al., 2016; Dinstein et al., 2012; Dinstein, Heeger, & Behrmann, 2015; Haigh, 2018; Haigh, Heeger, Dinstein, Minshew, & Behrmann, 2015; Hawco et al., 2020; Magnuson, Iarocci, Doesburg, & Moreno, 2020; Milne, 2011; Müller, Kleinhans, Nobuko Kemmotsu, Karen Pierce, & Courchesne, 2003; Pierce, Müller, Ambrose, Allen, & Courchesne, 2001; Poulin-Lord et al., 2014; Simmons et al., 2009; Vilidaite, Yu, & Baker, 2017; Weinger, Zemon, Soorya, & Gordon, 2014). For example, individuals with ASD had increased neural variability in both sensory (visual, auditory somatosensory; Dinstein et al., 2012; Haigh et al., 2015, 2016; Kovarski et al., 2019; Magnuson et al., 2020; Milne, 2011; Weinger et al., 2014; Yu, Wang, Huang, Wu, & Zhang, 2018) and motor tasks (Dinstein et al., 2010; Müller et al., 2003). To date, only a few studies have reported relationships between intra-subject neural variability and autism severity. Latinus and colleagues (2019) examined the consistency of neural responses to auditory stimuli from trial to trial using electroencephalography. Results indicated two subgroups of ASD, one with similar inter-trial consistency to the control group and a second with reduced inter-trial consistency (i.e., more intra-subject variability). Participants with reduced inter-trial consistency were generally younger and less verbal (Latinus et al., 2019); however, direct correlations between behavioral and neural variability findings were not investigated. Other works examining neural variability during fMRI paradigms have evaluated trial-to-trial variability in sensory perception tasks by calculating signal-to-noise ratios (defined as response amplitude divided by response variability, Dinstein et al., 2012; Haigh et al., 2015). Dinstein and colleagues Dinstein and colleagues (2012) found a trend for a relationship between decreased signal-to-noise ratios and increased autism severity, but this finding was not statistically significant. Additionally, a follow-up replication study did not find a significant relationship between signal-to-noise ratios and autism severity (Haigh et al., 2015). Importantly, participants in both studies were verbally fluent, and thus, the restricted range of autism severity may have precluded significant findings. Participants in the current study had a range of nonverbal IQ and verbal abilities; this more extensive range of functional abilities may have provided enough power to observe the significant relationship between increased autism severity and increased intra-subject variability.

The direct impact of neural variability on speech and language production has not been fully ascertained; however, below we discuss some potential reasons for a relationship between increased neural variability in the speech network and lower verbal abilities. Dinstein and colleagues posit that increased intra-subject variability in sensory areas of the brain may result in an unpredictable, and unreliable, perception of external stimuli (Dinstein et al., 2012; Dinstein et al., 2015; Haigh et al., 2015; Haigh et al., 2016). Within the context of speech and language production, this could translate to unpredictable auditory input in the presence of neural noise, which negatively impacts key processes in language development. This is supported by previous work showing differences in auditory processing in individuals with ASD. For example, minimally verbal and language-impaired individuals with ASD have delayed neural responses to single-word comprehension tasks (Cantiani et al., 2016), auditory tones (Roberts et al., 2011, Roberts et at., 2019), and vowel contrasts (Matsuzaki et al., 2019). Moreover, in minimally verbal and language-impaired individuals with ASD, atypical auditory behaviors were related to the level of neural sensitivity to differences in non-speech sounds (Schwartz, Wang, Shinn-Cunningham, & Tager-Flusberg, 2020a), and auditory deficits were found in difficult listening situations, such as noisy environments (Schwartz, Wang, Shinn-Cunningham, & Tager-Flusberg, 2020b). Language and communication abilities in individuals with ASD are also related to areas of language impacted by auditory perception (e.g., implicit language learning, word segmentation abilities, consonant differentiation, verbal imitation), further suggesting a linkage between auditory perception and language abilities (Arnett et al., 2018; Key, Yoder, & Stone, 2016; Scott-Van Zeeland et al., 2010; Smith, Mirenda, & Zaidman-Zait, 2007). These previous studies indicate that differences in auditory perception abilities (potentially caused by increased neural noise) may be related to verbal abilities in individuals with ASD. This previous work, coupled with the current findings of increased neural variability in individuals with increased autism severity, suggests this relationship warrants further examination.

Another potential explanation is that individuals with ASD and limited verbal abilities have increased neural noise in areas involved in sensorimotor integration, that is, the use of sensory information to inform and guide motor output. This explanation would be consistent with previous findings of differences in sensorimotor behavior in multiple domains in individuals with ASD (Fournier

et al., 2010; Glazebrook, Gonzalez, Hansen, & Elliott, 2009; Hayes et al., 2018; Unruh et al., 2019). Thus, if children had increased neural noise in areas involved in sensorimotor integration, they may have difficulty producing reliable and consistent speech. This deficit is one of the hypothesized mechanisms behind the speech motor planning disorder, childhood apraxia of speech (CAS), a disorder with a high comorbidity with ASD (Beiting & Maas, 2021; Belmonte et al., 2013; Chenausky, Brignell, Morgan, & Tager-Flusberg, 2019; Prizant, 1996; Shriberg, Paul, Black, & Van Santen, 2011; Tierney et al., 2015). Recently, Chenausky and colleagues (2021) examined individuals with ASD within the framework of the neurocomputational model of speech production, Directions into Velocities of Articulators (DIVA) (Guenther, 2016; Tourville & Guenther, 2011). DIVA proposes that typical speech development involves learning the relationship between motor movements and their subsequent speech outcomes, using this information to create articulatory maps for later productions. Terband and colleagues used DIVA to simulate pediatric motor speech disorders and proposed two potential subgroups (Terband, Maassen, Guenther, & Brumberg, 2014). The first subgroup was simulated to have deficits in somatosensory perception and sensorimotor integration. They hypothesized that the lack of accurate knowledge about the state of the articulators would cause speech production to be highly variable. In this subgroup, the intact auditory perception would detect the speech production errors and lead to continual attempts to correct them. Yet, the deficits in somatosensory perception would make these correction efforts difficult and result in variable speech production. The second subgroup was simulated to have noise in areas for somatosensory perception, auditory perception, and sensorimotor integration. The hypothesized speech outcome in this simulation was reduced variability, as there would be no errors detected by either the auditory or somatosensory domains (Terband et al., 2014). Chenausky and colleagues (2021) tested these model-driven hypotheses by examining speech output from minimally verbal individuals with ASD and suspected motor speech disorders. They found evidence that some participants had speech indicative of deficits in somatosensory perception and sensorimotor integration. Other participants displayed speech that suggested deficits in auditory perception, somatosensory perception, and sensorimotor integration. These findings support the potential relationship between motor speech deficits and verbal abilities, while further highlighting the heterogeneity of children with ASD. Although speech production was not directly examined in the current study (i.e., only a small subset of single, familiar words was produced), verbal abilities rely on both language abilities and speech production abilities. For example, speech production abilities, such as consonant inventory and phonetic repertoire were found to be significant predictors of expressive language abilities in minimally verbal individuals with ASD (Saul & Norbury, 2020). Thus, the speech motor impairments found in some individuals with ASD may be accounting for their reduced verbal abilities. Continued work is needed to explore the impact of auditory processing, sensorimotor integration, and motor control in minimally verbal and language-impaired individuals with autism.

Unlike the group differences found in neural variability, there were no significant group differences in neural activation during the speech production task, unlike some previous overt speech and language tasks (Kenworthy et al., 2013; Kleinhans et al., 2008; Müller et al., 1998; Müller et al., 1999; Pang et al., 2016; Yeung et al., 2019). One potential reason for the lack of a group difference in the current work is due to the heterogeneity of the ASD participants. Previous studies on speech production in participants with ASD examined more homogeneous groups, evaluating primarily verbally fluent participants with tasks that required relatively high language and cognitive abilities. Thus, although the number of participants was similar between the current study and many of the previous studies examining overt speech production (Kenworthy et al., 2013; Kleinhans et al., 2008; Müller et al., 1998; Müller et al., 1999), a larger group size may have been required due to the heterogeneity of the participants with ASD in the current study. Furthermore, although the exploratory analysis examining the relationship between ROI activation and behavioral measures did not reach significance, the uncorrected findings suggested a relationship between increased autism severity with greater activation in the right motor and premotor regions. As this result was found in multiple contiguous ROIs in the right motor and premotor areas, this suggests further analysis with a larger group is needed to examine this potential relationship. Another potential reason for the lack of group differences is the different speech production tasks used in the current study compared to previous work. Many of these previous studies used tasks that required higher language and cognitive abilities, such as category or letter fluency (Kenworthy et al., 2013; Kleinhans et al., 2008; Yeung et al., 2019) and sentence generation (Müller et al., 1998, Müller et al., 1999). These language generation tasks would not be possible for many of the language-impaired participants in the current study. Therefore, although there may be differences between verbal participants with ASD and NT controls in higher-level language and cognitive tasks, these findings do not directly transfer to the methodology and participants in the current study, which focused on the highly simplified task of single-word production.

This study is one of the first to complete an fMRI speech production task with participants with ASD whose verbal abilities range from low verbal abilities to verbally fluent; eight out of the fifteen participants with ASD produced fewer than ten novel words per minute during the ADOS interview analyzed for each participant. This was accomplished by following general guidelines outlined for collecting high-quality data from participants with ASD (Tager-Flusberg et al., 2017) and adapting the imaging sessions to fit the individual's needs. These adaptations included: (1) participants had sessions to familiarize them with the scanner and the task, (2) selection of a simple task using words familiar to the participant, (3) the use of auditory and visual prompts, with auditory prompts recorded by a known clinical staff member, and (4) the use of a voice-triggered sparse-sampling protocol which allows for speech production in relative quiet and avoids the influence of speech initiation reaction time. Our results indicate that minimally verbal or language-impaired individuals with ASD can be successfully imaged during a speech production task. Future work can use these fundamentals to continue to examine speech and language production in this population.

4.1. Limitations

To successfully scan participants with reduced language and cognitive abilities, necessary adaptations were made to the acquisition protocol that may have impacted the results. Some participants were sensitive to noise or tactile sensation, requiring the stimuli to be

played over the loudspeaker rather than into headphones. Although this change may have affected the quality of the auditory portion of the presented stimulus, this concern is mitigated due to the following aspects of the protocol: stimuli were selected to be familiar words, and auditory presentations were accompanied by visual representations of the target word. Another potential confound is participants with ASD were accompanied by a familiar adult in the scanner room, whereas NT participants were not. This was necessary in order to assist the participants with ASD in sitting through the scanning session and participating in the task. However, it is possible that these differences during acquisition may have masked any group differences in speech-related BOLD activity, and further work is needed to examine this potential impact. An additional point of consideration is although motion was included as a covariate of non-interest, scans with over 2 mm of motion were removed, and participants with over 1.5 mm of average scan-to-scan motion were excluded, this may not have been enough to control for group motion effects. Although we attempted to control for motion during practice, acquisition, and analysis, we acknowledge that motion may continue to be a confounding variable. Finally, the relatively small sample size of the current study is a limitation. Although this was one of the first studies to examine the neural correlates of speech production in low verbal participants with ASD, the primary finding of intra-subject variability coupled with the smaller sample size suggests that further work is needed to evaluate neural variability in ASD in a larger group of participants.

4.2. Conclusion

This study was designed to provide insight into the neural correlates of speech production in participants with ASD across a wide range of speech and language capabilities. Findings indicated that there were no overall differences in speech-related neural activation between ASD and NT groups, and neural activity levels were not significantly related to behavioral presentation in ASD. However, significantly increased intra-subject neural variability was found in ASD as compared to NT participants. Furthermore, increased intra-subject variability was significantly correlated with increased autism severity as measured by the ADOS-CSS within the ASD group. Together these results support a growing literature showing higher intra-subject variability in brain activity in participants with ASD and suggest that novel insights into ASD can be gained through further study of the cause and impact of intra-subject neural variability.

CRediT authorship contribution statement

Heller Murray: Writing – original draft, Data curation, Formal analysis. **Segawa:** Conceptualization, Methodology, Investigation. **Karahanoglu:** Investigation. **Tocci:** Investigation. **Tourville:** Methodology, Software, Investigation, Data curation, Writing – review & editing. **Nieto-Castanon**: Software, Data curation, Formal analysis, Visualization. **Tager-Flusberg:** Funding acquisition, Writing – review & editing, Supervision. **Manoach:** Funding acquisition, Writing – review & editing, Resources, Supervision. **Guenther:** Funding acquisition, Conceptualization, Writing – review & editing, Supervision.

Conflict of Interest

The authors have no real or potential conflicts of interest to declare that are relevant to the content of this article.

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