Altered maturation and atypical cortical processing of spoken sentences in autism spectrum disorder

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Abstract

Autism spectrum disorder (ASD) is associated with widespread receptive language impairments, yet the neural mechanisms underlying these deficits are poorly understood. Neuroimaging has shown that processing of socially-relevant sounds, including speech and non-speech, is atypical in ASD. However, it is unclear how the presence of lexical-semantic meaning affects speech processing in ASD. Here, we recorded magnetoencephalography data from individuals with ASD (N=22, ages 7–17, 4 females) and typically developing (TD) peers (N=30, ages 7–17, 5 females) during unattended listening to meaningful auditory speech sentences and meaningless jabberwocky sentences. After adjusting for age, ASD individuals showed stronger responses to meaningless jabberwocky sentences than to meaningful speech sentences in the same left temporal and parietal language regions where TD individuals exhibited stronger responses to meaningful speech. Maturational trajectories of meaningful speech responses were atypical in temporal, but not parietal, regions in ASD. Temporal responses were associated with ASD severity, while parietal responses were associated with aberrant involuntary attentional shifting in ASD. Our findings suggest a receptive speech processing dysfunction in ASD, wherein unattended meaningful speech elicits abnormal engagement of the language system, while unattended meaningless speech, filtered out in TD individuals, engages the language system through involuntary attention capture.

Keywords: autism, auditory, speech, language, magnetoencephalography, event-related fields

Abbreviations: ADOS, Autism Diagnostic Observation Schedule; ASD, autism spectrum disorder; ASPS, Auditory Sensory Profile Score; ERF, event-related field; HPI, head position indicator; ICA, independent component analysis; ICSS, Inhibition Contrast Scaled Score; MEG, magnetoencephalography; NVIQ, nonverbal IQ; ROI, region of interest; SCSS, Switching Contrast Scaled Score; SRS, Social Responsiveness Scale; TD, typically developing; TFCE, threshold-free cluster enhancement; tSSS, temporal signal space separation; VIQ, verbal IQ

1 Introduction

Autism spectrum disorder (ASD) is associated with speech and language impairments (Mody et al., 2013; Tager-Flusberg et al., 2005), with receptive language deficits proposed to be particularly characteristic of the disorder (Charman et al., 2003; Hudry et al., 2010; Luyster et al., 2008). While receptive language deficits in ASD have been reported at different linguistic levels, including phonology and syntax, the most consistent findings are arguably related to semantic processing (Boucher, 2012). These speech and language impairments greatly impact the lives of ASD individuals, and childhood language skills in ASD have been shown to predict adaptive behaviours (everyday life skills) and social outcomes, such as inter-personal relationships, later in life (Magiati et al., 2014).

Behaviorally, aberrant speech processing in ASD has been reported by many previous studies. For example, compared to typically developing (TD) peers, infants with ASD or those at increased risk for ASD have been shown to exhibit lack of orientation to speech (Bebko et al., 2006; Curtin and Vouloumanos, 2013; Nadig et al., 2007; Paul et al., 2007). Similarly, preschool children with ASD demonstrate an auditory preference for synthesized non-speech over meaningful speech (Kuhl et al., 2005), and young adults with ASD have poorer perception of speech in noisy acoustic conditions compared to their TD peers (Alcántara et al., 2004). Despite the known behavioral abnormalities, the neural mechanisms underlying speech and language impairments in ASD are not fully understood.

{reviewer 1, comment 3} Compared to TD individuals, weaker cortical responses to socially-relevant sounds, including both speech and non-speech vocal sounds, yet similar responses to various non-vocal sounds, have been demonstrated in ASD by studies using several different neuroimaging techniques, including electroencephalography (EEG; Kuhl et al., 2005), positron emission tomography (PET; Boddaert et al., 2004, 2003), and functional magnetic resonance imaging (fMRI; Gervais et al., 2004; Lai et al., 2011). Moreover, studies using sentence congruence or picture-word priming paradigms have found differences between ASD and TD groups in the context-sensitive N400 component with both EEG (DiStefano et al., 2019; Pijnacker et al., 2010) and magnetoencephalography (MEG) recordings (Ahtam et al., 2020; Braeutigam et al., 2008), thus suggesting altered semantic processing in ASD. Although these studies have demonstrated differences between ASD and TD in the neural processing of social sounds and violations of semantic context, they have not specifically investigated the effect of semantic meaningfulness on the neural processing of speech.

A parallel line of investigation of speech processing in ASD has focused on whether the speech-selective auditory impairments in ASD may be driven at least in part by aberrant attentional orienting (for review, see Kujala et al., 2013). Supporting the role of attentional deficits, **{r1, c3}** EEG-recorded cortical

responses reflecting involuntary attention switching (P3a) have been shown to be diminished to speech-sound changes in speech streams, yet normal or enhanced to acoustic changes in non-speech sound streams (Čeponiene et al., 2003; Lepistö et al., 2007, 2005). The results from neuroimaging studies showing differing processing of social compared to non-social sounds are compatible with the view that ASD individuals have an attentional bias towards socially-irrelevant sounds. However, they do not exclude sensory or perceptual deficits, as some language-relevant regions, such as superior temporal cortex, have dual roles in both low-level speech perception and higher-order attentional processes (Redcay, 2008). A more recent **{r1, c3}** fMRI-study examining attentional capture in ASD reported that, compared to TD peers, children and adolescents with ASD exhibited reduced target-related bottom-up activation of the ventral attentional network, involving regions in the frontal and inferior parietal cortices, with the level of activity reduction associated with ASD symptomatology (Keehn et al., 2016). Instead, to-be-ignored distractors captured attention in ASD. These results were interpreted to imply that ASD individuals do not filter out socially-irrelevant information in the auditory domain.

To date, the brain-based neural signatures of differences in auditory speech processing in ASD compared to TD have predominantly been investigated using prelexical speech sounds or monosyllabic single words. An exception is **{r1, c3}** an fMRI-study of speech processing in ASD and TD toddlers, that found no significant differences between the neural processing of meaningful and meaningless speech (Lombardo et al., 2015). Investigation of speech abnormalities in ASD using full sentences is important for several reasons. **{r1, c3/4}** First, in typical adults, neural responses in canonical language regions have been shown to be strongest for natural language (e.g., intact sentences) and diminished for linguistically degraded inputs (e.g., scrambled or jabberwocky sentences) by studies using various neuroimaging methods, including fMRI (Fedorenko et al., 2010), MEG (Hultén et al., 2019), and electrocorticography (ECoG; Fedorenko et al., 2016). Furthermore, sentence-level processing involves a more comprehensive set of linguistic computations than single sounds or words, and thus makes it possible to gain insights into naturalistic language processing in ASD. Tracking these rapid linguistic computations is best achieved by using neuroimaging methods with high temporal resolution. Furthermore, the temporal component associated with processing sentences vs. words is lost when only shorter units of speech are considered. To date, there are very few studies tapping into the temporal dimension of the neural substrates of auditory speech processing in ASD, using high-temporal resolution neuroimaging and full sentences.

Here, we investigated how the neural processing of speech in children and adolescents with ASD is affected by semantic meaningfulness, capitalizing on the high temporal and good spatial resolution of MEG. To assess the neural processing of meaningful speech, we compared cortical responses to the

unattended processing of naturalistic auditory speech sentences and their meaningless jabberwocky counterparts (Perrachione et al., 2015), where the words have been replaced by pronounceable pseudowords (Fig. 1). Based on the studies described above, we hypothesized that here too, even for unattended stimuli, we will find greater response in the TD group to meaningful speech compared to meaningless jabberwocky in language-relevant brain regions. We further hypothesized that, in the ASD group, we would find the opposite response pattern and that this atypical processing would be associated with reduced inhibition of attentional orienting. Finally, based on the multitude of studies showing abnormal maturation trajectories of brain measures during adolescence in ASD (Alaerts et al., 2015; Kitzbichler et al., 2015; Luna et al., 2007; Nomi and Uddin, 2015), we hypothesized that the maturational trajectory of speech processing would be flatter in the ASD than in the TD group. We tested these hypotheses using MEG data from N=22 ASD and N=30 TD participants, 7 to 17 years old.

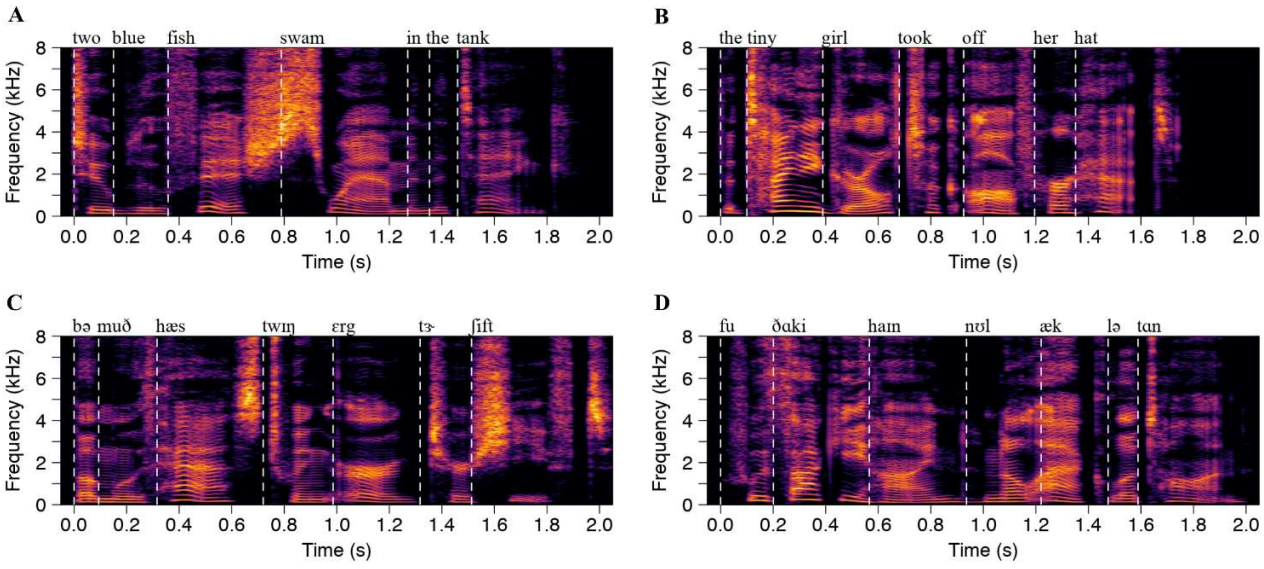

Figure 1: Spectrograms of stimuli used in the experimental paradigm. (**A**) First speech sentence. (**B**) Second speech sentence. (**C**) First *jabberwocky* sentence (corresponding to **A**). (**D**) Second *jabberwocky* sentence (corresponding to **B**). Transcriptions of the sentences are written above the spectrograms. The participants watched a silenced movie while the sentences were being played in random order via earphones.

2 Material and methods

2.1 Participants

{r1, c10; r2, c6} The participants were 23 individuals between ages 7 to 17 diagnosed with autism spectrum disorder (ASD), and 33 age-matched typically developing (TD) individuals. Data from one ASD and three TD individuals were excluded from the final analysis due to excessive continuous motion not correctable using the MNE-Python Maxwell filtering routine (Taulu and Kajola, 2005) or due to insufficient number of trials collected (as collection was stopped due to excessive motion), resulting in a final sample of 22 ASD and 30 TD participants. Sample characteristics are summarized in Table 1 **{r2, c3}** (see also histogram of age distribution in Fig. S1). All participants were right-handed and **{r1, c11}** had normal hearing, clinically defined as pure-tone thresholds better than 15 dB hearing level in both ears at octave frequencies between 250 Hz and 8 kHz, tested in a soundproof room using an audiometer. All participants also confirmed hearing the stimuli well in each ear prior to the onset of the paradigm. Participants with ASD had a prior clinical diagnosis of ASD and met a cutoff of $\geq$15 on the Social Communication Questionnaire, Lifetime Version, and ASD criteria on the Autism Diagnostic Observation Schedule (ADOS; Lord et al., 2000) administered by trained research personnel who had established inter-rater reliability. Individuals with autism related medical conditions (e.g., Fragile-X syndrome, tuberous sclerosis) and other known risk factors (e.g., gestation <36 weeks) were excluded from the study. **{r1, c10}** See SI.M.1 and Fig. S2 for a full description of medications use, and corresponding analysis showing the results were independent of medication use.

All TD participants were below threshold on the Social Communication Questionnaire and were confirmed to be free of any neurological or psychiatric conditions, and of substance use for the past 6 months, via parent-reports and self-reports. Verbal IQ (VIQ) and nonverbal IQ (NVIQ) were assessed using the Kaufman Brief Intelligence Test – II (Kaufman, 2004) for 17 ASD and 18 TD participants, and using the Differential Ability Scales – II (Elliot, 2007) for 5 ASD and 12 TD participants. Handedness information was collected using Dean Questionnaire (Piro, 1998). The Social Responsiveness Scale parent report (SRS-2; Constantino and Gruber, 2012), which was designed as a quantitative measure of autism-related symptoms, was collected from all participants.

Additionally, Sensory Profile Questionnaire (Brown and Dunn, 2002) data were collected for 20 ASD and 28 TD participants. For the correlations between MEG data and behavioral scores, we focused specifically on the score from the Auditory section of the Sensory Profile, referred to as ASPS (Auditory Sensory Profile Score) in the text. Lastly, a subset of participants (16 ASD and 24 TD) completed the INN

(Inhibition-Naming), INI (Inhibition-Inhibition), and INS (Inhibition-Switching) sections of the NEPSY-II evaluation (Korkman et al., 2007). **{r1, c12}** The INN involves naming the stimuli (circles and squares) and constitutes a baseline test for processing speed. In the INI, the participant is instructed to respond "square" when they view a circle and "circle" when they view a square, thereby inhibiting the "correct" response. In the INS, the participant has to switch the response according to what color the shape is (e.g., when circles are white, call them squares but when the circles are black, call them circles). The Inhibition Contrast Scaled Score (ICSS – INI/INN) was introduced to control for naming speed. Low ICSS score indicates that the participant performed poorly on the inhibitory task relative to the initial naming speed. Similarly, the Switching Contrast Scaled Score (SCSS) was introduced to provide a more direct measure of attentional switching, by controlling for the level of inhibitory skills. Low SCSS score indicates that the participant performed poorly on the switching aspect of the test relative to his or her level of inhibitory control. The ICSS and SCSS scores range from 1 to 19. Our hypothesis focused on the ICSS, whereas the SCSS was used as a secondary control for our hypothesis; **{r1, c13}** this is because the participants were instructed to ignore the sound stimuli (see section 2.3), which requires the inhibition of attention. We therefore hypothesized that the neural measures would correlate with the ICSS, i.e., inhibition of attention, but not with the SCSS, as attentional switching was not required. All research was in compliance with the Massachusetts General Hospital Institutional Review Board (MGH IRB), and all participants were consented in accordance with the Declaration of Helsinki and the approved protocol. Parents provided informed consent according to protocols approved by the MGH IRB.

	ASD (N=22, 4 females)			**TD** (N=30, 5 females)			
	N	**mean (SD)**	**range**	**N**	**mean (SD)**	**range**	**p-value**
Age	22	13.5 (2.9)	7-17	30	13.4 (3.3)	7-17	0.86
NVIQ	22	104.5 (15.8)	59-136	30	114.5 (14.0)	93-147	0.02
VIQ	22	100.4 (15.5)	61-123	30	114.6 (14.4)	71-140	0.002
ASPS	20	24.4 (7.2)	13-38	28	35.1 (4.3)	23-40	< 0.001
NDIS	16	7.8 (3.4)	2-14	24	10.8 (3.6)	3-17	0.01
NSS	15	9.4 (1.7)	5-13	23	10.7 (3.2)	4-17	0.19
SCQ	20	18.9 (7.0)	8-31	29	3.7 (3.2)	0-12	< 0.001
SRS	22	93.6 (30.0)	12-128	-	-	-	-
ADOS	22	10.9 (3.8)	3-18	-	-	-	-

Table 1: Characterization of the participants. The p-values are from two-sample t-tests (two-tailed) for the difference in means between the ASD and TD groups. **NVIQ**: Nonverbal IQ; **VIQ**: Verbal IQ; **ASPS**: Auditory Sensory Profile Score; **ICSS**: NEPSY-II Inhibition Contrast Scaled Score; **SCSS**: NEPSY-II Switching Contrast Scaled Score; **SCQ**: Social Communication Questionnaire lifetime score; **SRS**: Social Responsiveness Scale total score; **ADOS**: Autism Diagnostic Observation Schedule score.

2.2 Group difference in NVIQ, VIQ, and sample size

The two groups differed in both VIQ and NVIQ. While the group difference in VIQ is likely a manifestation of the ASD phenotype, the significant group difference in NVIQ is a possible confounding variable. Furthermore, we had a different number of participants in each group. While we controlled for both NVIQ and VIQ in our group comparisons, as a further control, we created a subsample with the same number of participants per group (N=21), and with no difference in NVIQ (Table S1). We then repeated the region of interest (ROI) analysis (Fig. 5) on this subsample and found that they were similar to the main results (Fig. S3), thus further confirming that the group differences we observed were not likely to be the result of group differences in sample size or in NVIQ.

2.3 Stimuli and paradigm

Two phonetically rich English sentences ("*Two blue fish swam in a tank*" and "*The tiny girl took off her hat*") and their jabberwocky counterparts (where the words were replaced by pseudowords), were used as stimuli (Fig. 1). The English sentence stimuli (referred to as "*speech*" in the text) were taken from the IEEE sentences ("IEEE Recommended Practice for Speech Quality Measurements," 1969). The jabberwocky sentences (referred to as "*jabberwocky*" in the text) were taken from a corpus derived from the IEEE sentences (Perrachione et al., 2015). **{r1, c15}** The *jabberwocky* sentences were created by re-arranging the phonemes from the *speech* sentences while adhering to the phonotactic rules of English. The corresponding *speech* and *jabberwocky* sentences had the same number of phonemes and syllables.

An ANOVA revealed no difference in the duration of individual phonemes between the conditions (*speech* vs. *jabberwocky*; $F_{1,32} = 1.38$, $p = 0.25$), and no condition × phoneme interaction ($F_{22,32} = 0.79$, $p = 0.71$). Also, the phoneme and biphone positional probabilities (Vitevitch and Luce, 2004) of the pseudowords in the *jabberwocky* sentences were matched with the words in the *speech* sentences (phonemes: $F_{1,27} = 0.004$, $p = 0.95$; biphones: $F_{1,27} = 0.87$, $p = 0.36$). Low-level acoustic cues in the stimuli were controlled by having the same speaker, a highly trained phonetician (TKP), produce all the *speech* and *jabberwocky* sentences.

The stimuli were presented binaurally through insert earphones (Etymotic, Elk Grove Village, IL) at 75 dB sound pressure level. To direct attention away from the stimuli, the participants watched a movie with the sound off and were instructed to ignore the sound stimuli. The advantage of such passive paradigm is that it ensures reliable and comparable responses regardless of the ability of the participant to maintain attention during the paradigm.

Each sentence was presented 40 times in the paradigm, totalling 80 *speech* trials and 80 *jabberwocky* trials **{r1, c8}** (for the exact number of trials per condition per participant, see Fig. S4). The stimuli were presented in random order with a 700–800 ms randomly varying inter-stimulus interval. The paradigm also included two categories of sinewave speech (60 repetitions each), and two categories of noise stimuli (40 repetitions each) randomly presented along with the *speech* and *jabberwocky* stimuli, not discussed here. The paradigm was presented in three runs, each lasting about 6 min.

2.4 Structural MRI data acquisition and processing

T1-weighted magnetization-prepared rapid gradient echo (MPRAGE) structural images were acquired using a 3T Siemens Trio MRI scanner (Siemens Medical Systems, Erlangen, Germany) and a 32-channel head coil (in-plane resolution 1x1 mm; slice thickness 1.3 mm, TR 2530 ms; TI 1100 ms; TE 3.39 ms; flip angle 7°). Cortical reconstructions and parcellations were generated using FreeSurfer (Dale et al., 1999; Fischl et al., 1999).

2.5 MEG data acquisition

The MEG data were acquired with a whole-head 306-channel VectorView neuromagnetometer (MEGIN Oy, Finland) inside a magnetically shielded room (IMEDCO, Switzerland). The channels of this instrument are arranged in 102 sensor triplets with two orthogonal planar gradiometers and one magnetometer. The signals were band-pass filtered at 0.1–200 Hz prior to sampling at 1000 Hz. The position of the head was continuously recorded during the data acquisition using four head position indicator (HPI) coils attached to the scalp (Uutela et al., 2001). Locations of the HPI coils, three anatomical landmarks (nasion and auricular points), and multiple additional scalp surface points were digitized using a Fastrak digitizer (Polhemus) to allow coregistering the MEG and MRI data. Electrocardiography (ECG) and electro-oculography (EOG) signals were recorded to detect heartbeats, eye movements, and eye blinks. Additionally, 5 min of data were recorded without the subject present at the end of each session to estimate the noise covariance matrix for MEG source analysis.

2.6 MEG data preprocessing, artifact correction, and epoching

Bad MEG channels were first detected using visual inspection. To compensate for head movements during the recording, and to reduce artifacts originating both from external sources outside the MEG sensor array and from the space between the brain and the MEG sensor array, we applied temporal Signal

Space Separation (tSSS; Taulu and Kajola, 2005; Taulu and Simola, 2006) as implemented in the MNE-Python Maxwell filtering routine. The default parameters were used (inside expansion order of 8, outside expansion order of 3, subspace correlation limit of 0.98, and raw data buffer length of 10 s). Fine calibration and cross talk correction data specific to the recording site were applied.

Independent component analysis (ICA) was applied to the tSSS-processed data to reduce systematic physiological artifacts, such as eye blinks and heart beats. More specifically, FastICA (Hyvärinen, 1999) was used to decompose MEG signals into maximally independent components. The ICA decomposition was estimated on band-pass filtered (1 Hz highpass, 40 Hz lowpass) data. Segments where signal amplitude exceeded 4000 fT/cm and 4000 fT on the gradiometers and magnetometers, respectively, were excluded from the estimation. The ICA components corresponding to ECG or EOG activity were identified based on Pearson correlation and visual inspection of scalp topographies corresponding to each of the components.

The epochs of MEG data started 200 ms before and ended 2000 ms after the stimulus onset. The data were low-pass filtered at 40 Hz and baseline corrected using the prestimulus data. Event-related fields (ERFs) were derived by averaging across epochs for both conditions.

2.7 Source estimation

The cortical surface reconstruction provided by FreeSurfer was decimated to a grid of 10,242 dipoles per hemisphere. The forward solution was computed using a single-compartment boundary-element model (BEM; Hämäläinen and Sarvas, 1987). The inner skull surface triangulations were generated from the MRI data using the watershed algorithm. The cortical current distribution was estimated using minimum-norm estimate (MNE) solution (Hämäläinen and Ilmoniemi, 1994) with a loose orientation (Lin et al., 2006a) of 0.2 and depth weighting (Lin et al., 2006b) of 0.8. The noise covariance matrix used in the inverse operator was estimated from the empty room data.

2.8 Spatio-temporal clustering analysis

For the spatio-temporal clustering analysis, the whole-brain data from 0 to 2000 ms after stimulus onset were downsampled temporally to 100 Hz and spatially to 1284 dipoles. Focusing on the temporo-parieto-frontal language networks (Fedorenko et al., 2010; Fedorenko and Thompson-Schill, 2014), the medial wall, limbic lobe, and occipital lobe as defined by a FreeSurfer automatic parcellation were excluded from the analysis, resulting in 400 dipoles per hemisphere. Thus, the spatio-temporal clustering employed a

total number of 80,000 (200 time points × 400 dipoles) data points per hemisphere. As loose dipole orientation was used, the dipole activity was derived as the length of the dipole vector.

2.9 Region of interest (ROI) analysis

The ROIs were defined by first delineating the three regions in the anterior temporal, middle/posterior temporal, and inferior parietal cortices showing the strongest group × condition interaction in the spatio-temporal clustering analysis (see Fig. 2A). We then used an automatic algorithm to split the two large regions in the temporal cortex into four smaller, roughly equal-sized ROIs along the sulci. This was done to increase the spatial specificity and to avoid signal cancellation due to sources on the opposite walls of sulci (Ahlfors et al., 2010). The resulting five ROIs were morphed from the FreeSurfer average brain to the individual brain. A response time course from each ROI was extracted by applying singular value decomposition (SVD) to the vertex time courses within the ROI and taking the first right-singular vector (i.e., first principal component). The time course was scaled to match the average power of the vertex time courses. Sign flips were applied to the vertex time courses whose direction was opposite to the dominant direction within the ROI to prevent the phase from randomly changing by 180 degrees from one vertex time course to the next.

2.10 Statistical analysis

In the spatio-temporal clustering analysis, a nonparametric two-sample permutation test with spatio-temporal threshold-free cluster enhancement (TFCE; Smith and Nichols, 2009) was used to compare the ERFs between groups. To identify brain regions exhibiting significant group (ASD vs. TD) × condition (*speech* vs. *jabberwocky*) interaction, contrast between *speech* and *jabberwocky* ERFs were input to the two-sample permutation test. The test was run separately for each hemisphere as there are no interhemispheric spatial-adjacency-based clusters.

In the TFCE procedure, cluster-level statistic for each data point is derived by calculating a weighted average between the cluster extent (i.e., number of connected above-threshold data points) and the cluster height (i.e., the statistical value of the data point) according to the formula:

$$\mathrm{TFCE} = \int_0^h e(h)^E \, h^H \, dh$$

where *h* is the height of the given data point. In practice, the integral is estimated numerically using a standard Riemann sum (Smith and Nichols, 2009). The default values of E = 0.5 and H = 2 were used. A reference distribution for the TFCE outputs was derived by permuting the group labels and repeating the TFCE procedure 5000 times. A corrected *p*-value for each data point was calculated as the proportion of permutations where the TFCE output was greater than or equal to the original TFCE output. The null hypothesis of no difference between the groups was rejected at $p < 0.05$.

In the ROI analysis, group × condition interactions were tested with mixed-design ANOVA, differences in ERFs between groups were tested with two-sample t-test (two-tailed), and differences in ERFs between conditions within group were tested with paired-samples t-test (two-tailed). The ERF-values were extracted by averaging over the ROI-specific significant group × condition interaction time window (see Fig. 3B). Linear regression was used to adjust the ERFs for age in within-group comparisons, and for age, NVIQ, and VIQ in the ANOVA and between-group comparisons. For the visualizations, the residuals were normalized between 0 and 1.

Correlations between age and ERFs, and between behavioral measures and ERFs, were tested within the spatial and temporal extents of the significant group × condition interaction by calculating Pearson correlation for each vertex within the spatial extent of the significant interaction using the ERFs averaged within the temporal extent of significant interaction. For increased spatio-temporal specificity, we used the ROI-specific time window of significant interaction (see Fig. 3B) for averaging the ERFs for a given vertex. The resulting correlation maps were thresholded at $p < 0.05$ and clusters smaller than 20 vertices were excluded.

The correlation between age and ERFs was adjusted for NVIQ and VIQ, and the correlation between behavioral measures and ERFs was adjusted for age, NVIQ, and VIQ. This was done by regressing these covariates out from both the ERFs and ages/behavioral scores before partitioning the data into TD and ASD groups. Differences in correlations between groups, and between ERFs within group, were assessed using Fisher's r-to-z transformation.

3 Results

3.1 Group differences in event-related fields (ERFs)

We began by investigating whether the neural processing of speech in ASD is affected by its meaningfulness, i.e., presence vs. lack of lexical-semantic information, using a spatio-temporal clustering analysis on *speech-jabberwocky* contrast ERFs within each hemisphere. We found a significant group difference for the *speech-jabberwocky* contrast in a 840–1540 ms window post stimulus onset in multiple left-hemisphere cortical regions related to language processing (Fig. 2), and no significant group differences in the right hemisphere, or in earlier responses in either hemisphere. More specifically, the minimum p-value in the spatio-temporal clustering analysis within the first 500 ms after stimulus onset was p = 0.14, and p = 0.51 within the first 250 ms post onset. That said, an additional analysis on only the first 500 ms, to focus on low-level differences, did reveal small group differences in a 0–250 ms time window **{r1, c1}** (see SI.R.2, and SI Table S2, for details). For all subsequent analyses, we focused on the cortical regions and time window illustrated in Fig. 2.

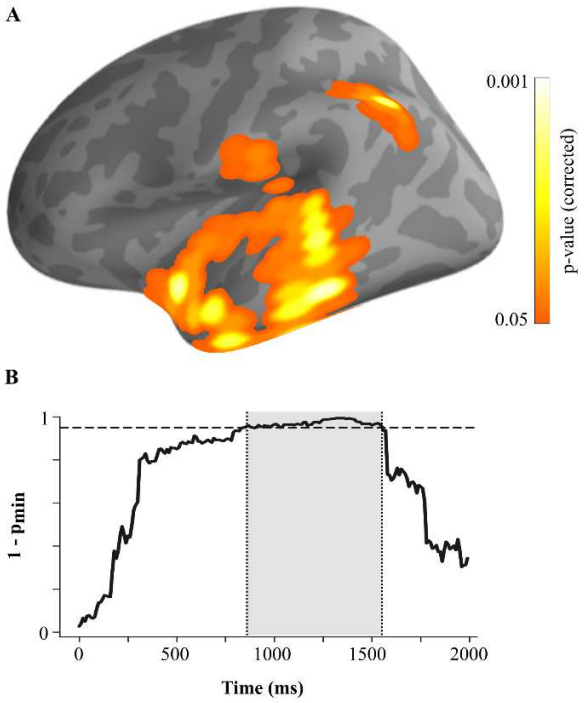

Figure 2: Delineation of significant group differences in the spatio-temporal domain. (**A**) The spatial extent of statistically significant group × condition (speech vs. jabberwocky) interaction depicted on inflated left hemisphere of the brain. Permutation p-values smaller than 0.05 (corrected) are color-coded on a red-yellow scale, with brighter colour indicating a more significant interaction. (**B**) The $1 - p_{min}$ of the group × condition interaction at each time point. The shaded area shows the time window (840 – 1540 ms after stimulus onset) with statistically significant interaction.

To further refine these analyses, we divided the cortical areas that showed a significant group × condition interaction into five ROIs, roughly following the known functional neuroanatomy of cortical speech

processing (Fedorenko and Thompson-Schill, 2014; Hickok and Poeppel, 2007; Rauschecker and Scott, 2009): anterior superior temporal, anterior middle temporal, posterior superior temporal, posterior middle temporal, and inferior parietal (Fig. 3A). We then defined the time windows with a significant group × condition interaction for each ROI (Fig. 3B).

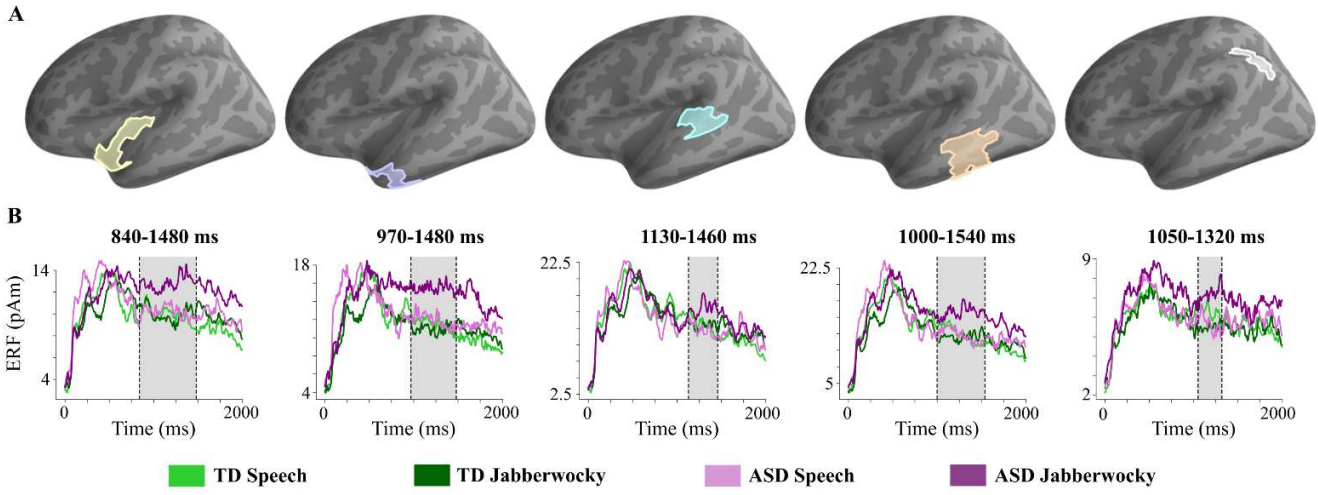

Figure 3: ERFs to *speech* and *jabberwocky* stimuli in TD and ASD in each ROI. (**A**) ROIs depicted on an inflated brain surface. From left to right: anterior superior temporal (yellow), anterior middle temporal (blue), posterior superior temporal (cyan), posterior middle temporal (orange), and inferior parietal (white). (**B**) ERFs from the ROIs for 2000 ms post stimulus onset. The grey areas indicate temporal extents of statistically significant group × condition interaction. The exact times for each grey window are indicated in the subplot's title.

3.2 Correlation between ERFs and age

There is a substantial body of evidence showing age effects for language in the age range (7–17) of the present sample (Skeide and Friederici, 2016). In parallel, there is also a growing number of studies showing abnormal maturational trajectories in this age range in ASD **{r2, c2}** (for review, see Edgar, 2020), both from our group (Khan et al., 2015; Mamashli et al., 2021, 2018) and others (Alaerts et al., 2015; Luna et al., 2007; Wallace et al., 2010). We therefore chose to first assess the effect of age on the ERFs, in each group. Furthermore, because the groups were not matched on either NVIQ or VIQ, we also adjusted for these values. Note that typically only NVIQ is considered as a covariate, because VIQ is considered part of the ASD phenotype (Joseph et al., 2002); however, to ensure that any observed differences are not due to differences in verbal abilities, we chose to nonetheless adjust for VIQ as well.

{r1, c17} Rather than repeating the correlation test for each ROI, we identified (corrected) clusters showing significant correlation between the ERFs and age within the area showing significant group × condition interaction; in other words, while the results are displayed within each of the ROIs, only one spatial mask was used for the analysis, and therefore the results are corrected for multiple comparisons spatially.

Three significant clusters emerged within the five ROIs that showed a negative correlation between age and *speech* ERFs in the TD group (Fig. 4A-C). Correlation between age and *jabberwocky* ERFs resulted in one significant cluster in the TD group, overlapping with the cluster in Fig. 4B. No significant clusters were found in the ASD group.

Within these significant clusters, age was significantly negatively correlated with the *speech* ERFs in the TD group (Fig. 4D-F). In the two superior temporal clusters, the correlation between the *speech* ERFs and age was significantly different between the groups (Fig. 4D, E). No such difference was observed in the inferior parietal cluster (Fig. 4F). Instead, correlating age with the *speech* ERFs from this cluster across both groups combined into one revealed significant negative correlation ($r = -0.44$, $p = 0.001$), indicating similar correlation in the TD and ASD groups.

Jabberwocky ERFs extracted from the same clusters in the posterior superior temporal and inferior parietal cortices were significantly correlated with age in the TD group (Fig. 4H, I). No significant group differences were observed for the *jabberwocky* condition (Fig. 4G-I). A significant negative correlation between age and the *jabberwocky* ERFs was observed in the inferior parietal cluster when calculating across both groups ($r = -0.37$, $p = 0.008$).

The correlations between ERFs and age remained largely unchanged even when NVIQ and VIQ were not considered as covariates (Fig. S5). Given the correlation between the ERFs and age, and given the group differences in NVIQ and VIQ, all subsequent between-group comparisons were adjusted for age, NVIQ, and VIQ.

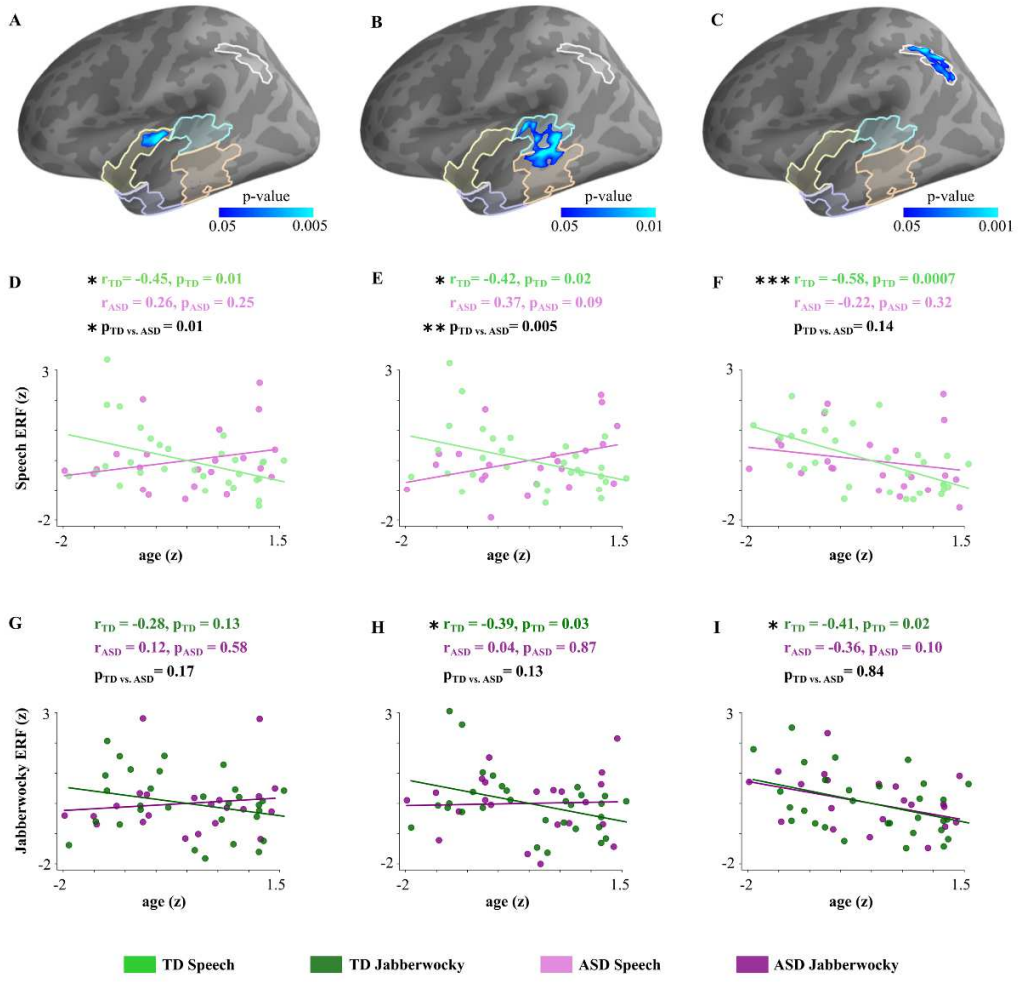

Figure 4: Correlation between ERFs and age, adjusted for NVIQ and VIQ. (**A-C**) Clusters showing significant age vs. *speech* ERF correlation (at $p < 0.05$, cluster-corrected) in the TD group plotted on the left hemisphere inflated cortical surface with the ROIs underlaid. (**D**) *Speech* ERFs extracted from the cluster in **A** plotted against age in both groups. (**E**) *Speech* ERFs extracted from the cluster in **B** plotted against age in both groups. (**F**) *Speech* ERFs extracted from the cluster in **C** plotted against age in both groups. (**G**) *Jabberwocky* ERFs extracted from the cluster in **A** plotted against age in both groups. (**H**) *Jabberwocky* ERFs extracted from the cluster in **B** plotted against age in both groups. (**I**) *Jabberwocky* ERFs extracted from the cluster in **C** plotted against age in both groups. In **D-I**, Pearson correlation coefficients (r) and p-values for within-group correlations, as well as p-values for the difference in correlations between the groups, are displayed above each plot. The plotted values are the z-scored residuals after regressing out NVIQ and VIQ from both the ERFs and ages of participants. Statistically significant correlations are indicated by asterisks (*p<0.05, **p<0.01, ***p<0.001).

3.3 Within-ROI differences in ERFs

To assess whether there were any differences in ERFs after adjusting for age and the IQs, we next averaged the ROI-specific ERFs over the significant interaction time extents (Fig. 3B) for each participant, and plotted the group means separately for each condition. A significant group × condition interaction was indeed observed in all five ROIs (Fig. 5). Again, the results remained stable also when covariates were considered separately (Fig. S6). Post-hoc between- and within-group comparisons revealed that the group × condition interaction was driven by enhanced responses to the *speech* compared to *jabberwocky* in the TD group in all five ROIs, enhanced responses to *jabberwocky* compared to *speech* in the ASD group in four out of five ROIs, and enhanced responses to *jabberwocky* in the ASD group relative to the TD group in all five ROIs (Table 2). There were no significant differences in the ERFs to the *speech* sentences between the groups. **{r2, c2}** To further test whether the age dependence was uniform across the age range, or alternatively, was driven by the older age group for instance, instead of adjusting for age, we conducted a supplementary analysis with two subsamples – one with ages 7-11, and the other with ages 13-17. The results show the trend did not vary by age group (see Fig. S7).

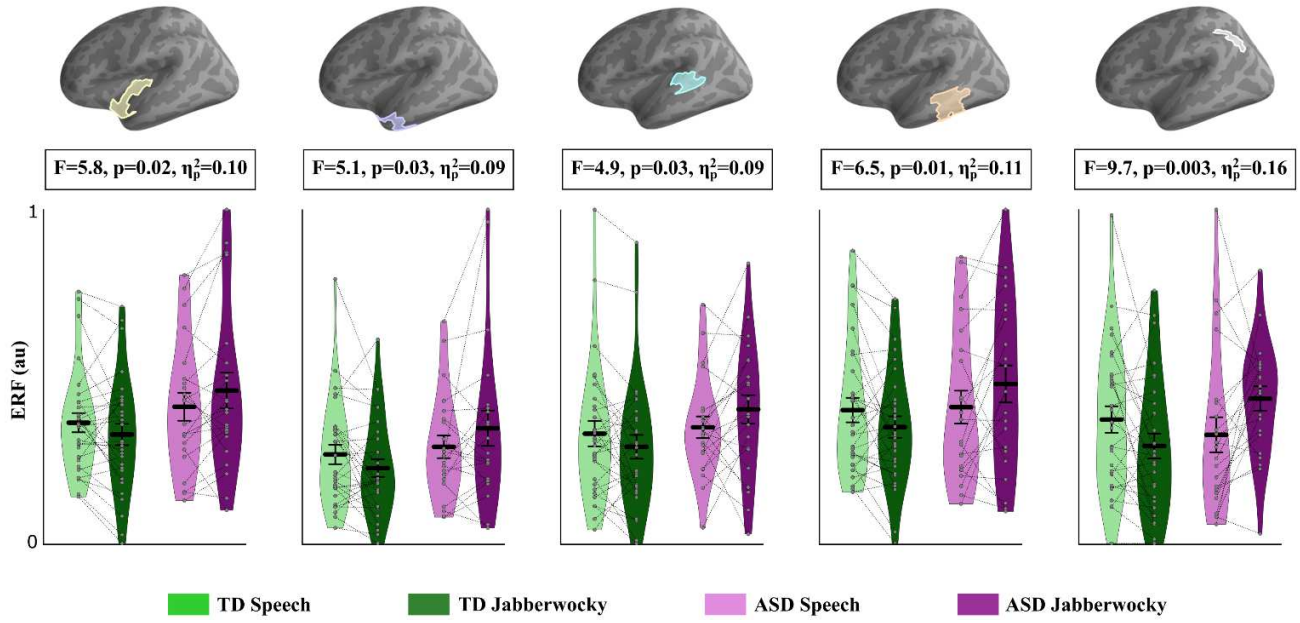

Figure 5: Group × condition interaction in each ROI. Plots of group mean ERFs (thick horizontal black line) with kernel density estimation (KDE) of the underlying distribution separately for *speech* and *jabberwocky* conditions. The KDEs are limited within the range of the observed data. The ERFs were averaged over the ROI-specific significant group × condition interaction time window. Individual responses are overlaid on the KDE plot with the change between *speech* and *jabberwocky* ERFs indicated by a connecting line. Error bars around the mean represent standard error of the mean. NVIQ, VIQ, and age of the participants were regressed out from the ERFs and the residuals were normalized between 0 and 1. The F-statistic, p-value, and effect size (partial eta squared, η_p^2) for the group × condition interactions are shown above each plot. The observed effects sizes varied from medium (0.6–0.14) to large (>0.14).

	TD vs. ASD						Speech vs. Jabberwocky					
	Speech			Jabberwocky			TD			ASD		
ROI	t(50)	p	d	t(50)	p	d	t(29)	p	d	t(21)	p	d
aST	-0.97	0.34	0.28	-2.23	**0.03***	0.64	2.43	**0.02***	0.31	-2.52	**0.02***	-0.33
aMT	-0.51	0.61	0.15	-2.17	**0.03***	0.62	2.37	**0.03***	0.35	-1.82	0.08	-0.35
pST	-0.37	0.71	0.11	-2.03	**0.05***	0.58	2.29	**0.03***	0.28	-2.15	**0.04***	-0.43
pMT	-0.15	0.88	0.04	-2.13	**0.04***	0.61	2.48	**0.02***	0.38	-2.45	**0.02***	-0.39
iP	0.71	0.48	-0.20	-2.65	**0.01***	0.76	2.82	**0.01****	0.50	-2.94	**0.01****	-0.65

Table 2: Results from t-tests for between- and within-group differences in the ERFs in the ROIs, showing t-values, p-values, and Cohen's d effect sizes for each comparison. For the between-group comparisons, the ERFs were adjusted for age, NVIQ, and VIQ. For the within-group comparisons, the ERFs were adjusted for age only. Numbers in parentheses after the t-values indicate degrees of freedom. Statistically significant correlations are in bold, with the level of significance indicated by asterisks (*p<0.05, **p<0.01). aST: anterior superior temporal; aMT: anterior middle temporal; pST: posterior superior temporal; pMT: posterior middle temporal; iP: inferior parietal.

3.4 Correlation between ERFs and behavioral scores

Lastly, to determine whether the atypical responses in the ASD group corresponded to behaviorally assessed ASD traits, we tested for correlations between behavioral scores and the ERFs, starting with the *speech-jabberwocky* contrast ERFs. **{r1, c17}** Again, rather than repeating the correlation test for each ROI, we identified (corrected) clusters showing significant correlation between the ERFs and behavioral scores within the area showing significant group × condition interaction. In the ASD group, a significant correlation was found in the inferior parietal cortex between the *speech-jabberwocky* contrast ERFs and scores for volitional attentional inhibition, measured using the ICSS (Fig. 6A). Post-hoc test revealed that the ICSS correlated with the *speech* and *jabberwocky* ERFs extracted from the cluster in the ASD group (Fig. 6B; $z = 3.56$, $p = 0.0004$); a reduced score on attentional inhibition corresponded to an increase in the ratio of *jabberwocky* vs. *speech* ERFs. Also, the correlations between ICSS and *speech-jabberwocky* contrast ERFs were significantly different between the TD and ASD groups ($z = 3.22$, $p = 0.001$), with opposite directions of correlations for *speech* and *jabberwocky* ERFs between the groups (Fig. 6B, C). As a further control to our hypothesis, we tested for correlations when SCSS, rather than ICSS, was used. As predicted, we found no significant correlation between the ERFs and SCSS.

We then correlated the behavioral scores separately with the *speech* ERFs and with the *jabberwocky* ERFs. In the ASD group, the severity of auditory sensory processing abnormalities, measured using the

ASPS, correlated positively with the *speech* ERFs in the anterior superior temporal cortex (Fig. 6D). ERFs extracted from the cluster showed positive correlation for both *speech* and *jabberwocky* ERFs (i.e., more severe auditory sensory processing abnormalities corresponded to weaker ERFs to both *speech* and *jabberwocky* stimuli; Fig. 6E). No significant correlations were observed between the ERFs and ASPS in the TD group in this region (Fig. 6F). ASD severity, measured using the SRS scores, correlated with *speech* and *jabberwocky* ERFs in three clusters in the mid-to-anterior temporal cortex (Fig. 6G). More specifically, in all three of these clusters both *speech* and *jabberwocky* ERFs were significantly negatively correlated with SRS, i.e., more severe ASD corresponded to weaker ERFs to both *speech* and *jabberwocky* stimuli, with the most significant correlations in the anterior superior temporal cluster (Fig. 6H).

{r2, c3} To address the possibility that statistical outliers were driving some of the significant correlations within the ASD group (i.e., Fig. 6B, E, H), we recalculated the correlations using the Theil-Sen estimator (Sen, 1968; Theil, 1950), which is robust against outliers. The NDIS correlations in Fig. 6B remained significant ($r_S = 0.57$, $p_S = 0.02$; $r_J = -0.23$, $p_J = 0.39$; $p_{S\ vs.\ J} = 0.001$). Similarly, the correlations between ASPS and *speech* ERFs (Fig. 6E; $r = 0.53$, $p = 0.02$), and SRS and *speech* ERFs (Fig. 6H; $r = 0.50$, $p = 0.02$) remained significant. In contrast, the correlations between ASPS and *jabberwocky* ERFs (Fig. 6E; $r = 0.36$, $p = 0.12$), and SRS and *jabberwocky* ERFs (Fig. 6H; $r = 0.35$, $p = 0.11$) did not reach significance. For correlations between ERFs and behavioral scores without NVIQ and VIQ as covariates, see Fig. S8.

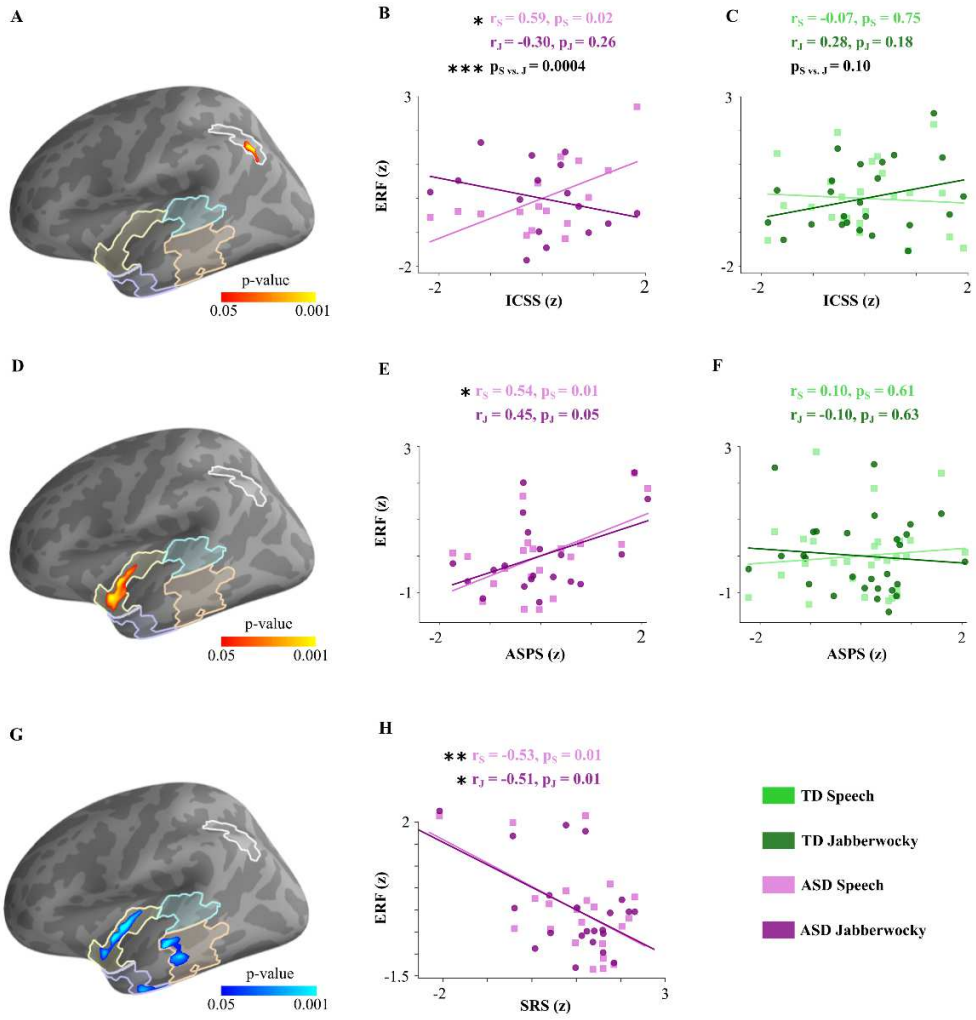

Figure 6: Correlation between ERFs and behavioral scores, adjusted for age, NVIQ, and VIQ. (**A**) Cluster showing significant ICSS vs. *speech-jabberwocky* contrast ERF correlation in the ASD group. (**B**) *Speech* and *jabberwocky* ERFs extracted from the cluster in **A** plotted against ICSS in the ASD group. (**C**) *Speech* and *jabberwocky* ERFs extracted from the cluster in **A** plotted against ICSS in the TD group. (**D**) Cluster showing significant ASPS vs. *speech* ERF correlation in the ASD group. (**E**) *Speech* and *jabberwocky* ERFs extracted from the cluster in **D** plotted against ASPS in the ASD group. (**F**) *Speech* and *jabberwocky* ERFs extracted from the cluster in **D** plotted against ASPS in the TD group. (**G**) Clusters showing significant SRS vs. *speech* ERF correlation in the ASD group. (**H**) *Speech* and *jabberwocky* ERFs extracted from the largest cluster in the anterior superior temporal cortex in **G** plotted against SRS in the ASD group. In **A**, **D**, and **G**, significant clusters (at p<0.05, cluster-corrected) are plotted on the left hemisphere inflated cortical surface with the ROIs underlaid. Above each plot, Pearson correlation coefficients (r) and p-values for within-condition correlations are shown. In **B** and **C**, p-values for the difference between the within-condition correlations are also shown. All plotted values are the z-scored residuals after regressing out age, NVIQ, and VIQ from both the ERFs and behavioral scores. **{r1, c17}** Statistically significant correlations are indicated by asterisks: *p<0.05, Bonferroni-corrected over the number of independent behavioral scores (N=2; see SI.R.1); **p<0.05, Bonferroni-corrected over the two independent behavioral scores and the two groups (N=4); ***p<0.05, Bonferroni-corrected over all comparisons irrespective of dependence, i.e., two groups, two conditions, and three behavioral scores (N=10, because SRS scores were not collected for the TD participants). S: *speech*: J: *jabberwocky*.

4 Discussion

The goal of this study was to investigate the neural mechanisms underlying deficits in auditory speech processing in children and adolescents with ASD. More specifically, we investigated how the presence or lack of lexical-semantic information embedded in meaningful sentences and meaningless matched jabberwocky sentences affects the unattended processing of speech in ASD compared to TD peers. Corroborating our hypothesis, our results show that the age-adjusted event-related fields (ERFs) in ASD participants were stronger to meaningless jabberwocky sentences than to meaningful speech sentences in the same canonical language regions in the left temporal and parietal cortices where the TD participants showed stronger responses to meaningful sentences. The maturational trajectories of ERFs to meaningful sentences were, as we hypothesized, atypical in ASD, but only in the temporal regions. In contrast, ERFs to both meaningful and meaningless jabberwocky sentences in the parietal cortex followed similar maturational trajectories for both groups. Furthermore, behavioral scores measuring inhibition of attentional capture correlated differently between ERFs to meaningful and meaningless *speech* in the parietal cortex in ASD. This correlation pattern was significantly different between the ASD and TD groups. Lastly, ERFs in the anterior temporal cortex correlated with both scores measuring ASD symptom severity (SRS) and auditory processing abnormalities (ASPS).

4.1 Differences in ERFs to meaningful vs. meaningless speech in ASD

Our finding of stronger ERFs to meaningless jabberwocky sentences compared to meaningful speech sentences in ASD individuals in the same language-related regions where TD individuals exhibited the opposite pattern demonstrates striking differences in the neural mechanisms of unattended auditory speech processing between these groups. **{r1, c2}** Previous EEG and MEG studies of speech processing in ASD have provided evidence for violations of semantic context based on findings on the context-sensitive N400 component of the event-related potential, which is related to semantic processing, using either sentence congruence (i.e., reading meaningful sentences and sentences with a semantically incongruous final word; Ahtam et al., 2020; Braeutigam et al., 2008; Pijnacker et al., 2010) or picture-word priming paradigms (i.e., picture followed by the expected or unexpected word; DiStefano et al., 2019). That said, these studies focused only on the N400, and therefore did not show the effect of semantic meaningfulness on the auditory processing of speech in ASD throughout the processing of full sentences.

{r1, c19} The diminished brain responses to meaningless jabberwocky sentences in TD individuals aligns with previous studies on speech processing in typical development using various imaging methods, including MEG (Hultén et al., 2019), ECoG (Fedorenko et al., 2016), and fMRI (Fedorenko et al., 2010).

The differences in the processing of meaningful and meaningless speech in the present study were observed towards the end of the sentences, at latencies 840–1540 ms post onset. This is consistent with earlier work showing that sentences are interpreted incrementally (Marslen-Wilson, 1975). Indeed, a study using intracranial recordings demonstrated that activity in left-hemisphere language regions increased monotonically over the course of a sentence, and that this steady increase in activity was absent for jabberwocky sentences and word-lists, indicating that the largest difference in activity between the processing of these stimuli was around the final words (Fedorenko et al., 2016). This supports the interpretation that our findings reflect group differences in higher-order construction of linguistic meaning, rather than in lower-level sensory processing differences due to, for example, acoustic differences in the stimuli.

{r1, c1} As noted, while the most significant results were in the later time window of the response, we found a weak but significant group × condition interaction effect also in the early time window of 0–250 ms after stimulus onset, limited only to the left anterior superior temporal cortex. Specifically, within that time window, we found stronger responses to the meaningful speech in the ASD compared to TD group, and stronger responses to the meaningless jabberwocky compared to meaningful speech in the TD group (see SI.R.2, Table S2). This points towards group differences also in the lower-level auditory processing, and is in line with prior MEG studies reporting speech-induced ERF differences between ASD and TD at early latencies (Yoshimura et al., 2017, 2013). **{r2, c1/5}** It should also be noted that some lower-level abnormalities of ASD have been shown to be driven by language impairments, not the ASD (Oram Cardy et al., 2008; Roberts et al., 2011). While the present results are primarily in higher-level language processing and attentional domains, since they were derived using a language paradigm, specificity to ASD would need to be determined using a language impaired non-ASD group with a matched VIQ distribution. Furthermore, future studies would be needed to determine whether these results extend to children and adolescents with ASD that are on the minimally to moderately verbal range of the ASD spectrum (Matsuzaki et al., 2019; Roberts et al., 2019). Finally, since the present sample consisted of predominantly males, future studies would be needed to determine whether gender has an impact on the results.

4.2 Differences in maturational trajectories of ERFs in ASD

Our results revealed both differences and similarities in the maturational trajectories of speech processing between ASD and TD. The ERFs to meaningful speech correlated negatively with age in the TD group in the left superior temporal and inferior parietal cortices. This correlation was significantly different

between the TD and ASD groups in the superior temporal cortex, but similar in the inferior parietal cortex. The finding of opposite direction correlations in the superior temporal regions between the groups corroborates previous research that has showed different maturational trajectories between ASD and TD generally (Alaerts et al., 2015; Kitzbichler et al., 2015; Luna et al., 2007; Mamashli et al., 2021, 2018; Nomi and Uddin, 2015; Uddin et al., 2013; Vakorin et al., 2017), and also in the auditory domain specifically (Edgar et al., 2015; Gage et al., 2003; Port et al., 2016; Stephen et al., 2017). **{r1, c5}** Based on these studies, the divergence in maturational trajectories may emerge over a wide age range, and the age of divergence likely depends on the paradigm, and may well vary by cortical area as well, even for one paradigm. In typical language development, full maturation of semantic processing at the sentence level takes place over a long trajectory, with first appearance of adult-like functions at about nine years of age (Skeide and Friederici, 2016). The weaker ERFs in older TD individuals to meaningful speech may thus reflect more efficient language processing through synaptic pruning (Changeux and Danchin, 1976). Interestingly, while the superior temporal ERFs to meaningful speech showed different maturational trajectories between the ASD and TD groups, the inferior parietal ERFs to both meaningful and meaningless speech followed similar maturational trajectory across the groups. This suggests that the contribution of the inferior parietal cortex to auditory processing of speech follows typical maturation in ASD. The question then arises as to why abnormal maturation was observed in the superior temporal cortex, but not in the inferior parietal cortex, both of which showed involvement in the processing of the speech stimuli. A possible explanation is provided by the functional segregation: the superior temporal cortex belongs to core language regions, whereas the inferior parietal cortex is a domain-general region that contributes to language processing, among other mental processes, depending on task demands (Fedorenko and Thompson-Schill, 2014). These domain-general processes include, for example, attention and working memory. Our findings, therefore, suggest that abnormal maturation of speech processing in ASD is confined to functionally specialized language areas, and does not impact domain-general areas associated with speech and language processing more broadly. **{r2, c2}** That said, it would be extremely interesting to test whether future studies replicate these findings to toddlers and younger children, a period of accelerated language development.

4.3 Correlation between ERFs and attentional inhibition

The stronger ERFs to meaningless jabberwocky compared to meaningful speech sentences in ASD individuals could be explained by the proposed attentional bias towards socially-irrelevant sounds. For example, **{r1, c2/20}** Lepistö et al. (2007) found enhanced EEG-recorded P3a responses reflecting

involuntary attention switching to non-speech compared to speech changes in ASD, while no such effect was found in TD participants. In an analogous way, the meaningless jabberwocky could elicit enhanced responses compared to meaningful speech as a result of involuntary attention switching in the present study. This interpretation is supported by our finding that behavioral scores measuring inhibition of attentional capture (ICSS) correlated differently between left inferior parietal ERFs to unattended meaningful and meaningless sentences in ASD, and that this pattern of correlation was significantly different from that in the TD group. More specifically, a reduced ICSS in ASD corresponded to an increase in the ratio of ERFs to meaningless vs. meaningful sentences. The inferior parietal cortex has been demonstrated to support auditory sentence comprehension (Hartwigsen et al., 2015), but is also strongly associated with reorienting of attention (Gottlieb, 2007) and particularly with bottom-up involuntary attention shifting (Ciaramelli et al., 2008; Huang et al., 2012). Our findings therefore imply that the receptive language system in ASD individuals is less able to supress involuntary attention to meaningless speech. Correspondingly, the opposite correlation pattern in the TD group suggests that, in a typical receptive language system, unattended speech without lexical-semantic information is filtered out and therefore does not capture attention in the same way. These findings are also in line with a recent study showing that ASD individuals exhibited reduced bottom-up activation of the ventral attentional network for behaviorally-relevant target stimuli, yet their attention was captured by to-be-ignored distractors (Keehn et al., 2016). The fact that no such correlations emerged with the SCSS further supports these conclusions. Our results therefore support the view that speech-selective auditory impairments in ASD emerge at least in part due to aberrant attentional orienting (Čeponiene et al., 2003; Lepistö et al., 2007, 2005).

4.4 Correlation between ERFs and ASD severity

Our results are also consistent with abnormal sentence processing in ASD that is independent of attentional capture. The ERFS in the left anterior temporal cortex correlated with scores measuring behaviorally assessed auditory processing abnormalities as well as symptom severity in ASD. In typical adults, auditory processing of phonemes, words, and phrases have been shown to follow an anterior-directed gradient from mid to anterior superior temporal cortex in the left hemisphere (DeWitt and Rauschecker, 2012), with the comprehension of sentence-length stimuli linked to the left anterior temporal cortex (Dronkers et al., 2004; Pallier et al., 2011). The correlation between ASD social-affective symptomology (SRS scores) and ERFs in left anterior temporal cortex therefore points towards an impairment in phrase/sentence processing rather than in lower-level sensory or perceptual processes in

ASD. Although the correlation was strongest for meaningful sentences, a significant correlation was observed also for meaningless sentences, suggesting that, rather than deficits in higher-level sentence comprehension, the impairment could be related to other aspects of speech processing. As an equally strong correlation was observed between the anterior temporal cortical ERFs and scores measuring auditory sensory processing abnormalities (ASPS), the impairment might be associated with more general oversensitivity to sounds in ASD, in line with earlier findings (Ben-Sasson et al., 2009). However, the direction of the correlations (i.e., the more severe ASD and auditory sensory processing abnormalities, the weaker the responses) points more towards language-related neural systems dysfunction instead of general oversensitivity to sounds. This interpretation is supported by earlier work showing temporal cortical hypoactivation to speech specifically in ASD individuals with poor language outcome (Lombardo et al., 2015).

4.5 Limitations

The results of this study need to be interpreted in the context of its limitations. First, the sample size of ASD participants was smaller than that of TD participants, impacting the power of the analyses. That said, the observed medium-to-large effect sizes, consistent trends, and results from the subsample analyses of equal group sizes, increase the confidence in the results. More generally, this limitation is mitigated by the data-driven, assumption-free approach to obtain the main results of this study, where the multiple comparisons problem is addressed with a cluster-level permutation test across space and time, providing a more rigorous and sensitive statistical test compared to parametric tests (Maris and Oostenveld, 2007) especially when the sample size is small (Warner, 2007). Further, the TFCE method used for clustering has been shown to effectively control the type 1 error rate in event-related brain signals (Pernet et al., 2015). Another limitation is that the ICSS scores measuring inhibition of attentional capture were missing on six ASD and six TD participants, weakening the statistical power of this particular analysis. That said, the behavioral data are consistent with the known functional role of the parietal ROI. The consistency of our findings with those from earlier neuroimaging as well as with the phenotype of ASD provide further support to our findings, thus also mitigating these limitations. **{r2, c1}** Lastly, the observed group difference effects are not large enough to provide robust clinical brain measures with high sensitivity and specificity. Indeed, due to the inherent heterogeneity of language function in ASD, it is not clear that any brain measure of language function would ever reach clinical significance. Thus, the value of the presented measures lies with expanding our understanding of the mechanisms underlying ASD, rather than with clinical diagnoses using these measures.

4.6 Conclusions

In summary, our findings demonstrate that ASD individuals show significantly stronger cortical responses to meaningless compared to meaningful speech in the same canonical language regions where TD individuals exhibit stronger responses to meaningful speech. These differences emerge well past the stimulus onset, at around 800–1000ms into the sentence. This divergence in responses as a function of the presence or lack of lexical-semantic information in speech is a striking difference between ASD and TD in the neural mechanisms underlying auditory speech processing. Furthermore, responses in the anterior temporal cortex, implicated in sentence-level processing, correlated with ASD symptom scores in several domains, including social-affective, attention-related, and sensory processing domains, demonstrating the relevance to the ASD phenotype. Correlation between inferior parietal responses and scores measuring inhibition of attentional capture suggests that the stronger responses to meaningless speech in ASD is associated with involuntary attention capture, thus supporting the view that speech-selective auditory impairments in ASD correlate with aberrant attentional orienting. In TD individuals, responses to meaningful speech correlated negatively with age in both temporal and parietal cortices, probably reflecting a maturation process wherein the receptive language system becomes more efficient via synaptic pruning. Such a maturational trajectory was not observed in ASD individuals in the temporal cortical regions. In contrast, the inferior parietal region exhibited similar maturational trajectories between the two groups. This novel finding suggests that speech processing in ASD is associated with abnormal maturation of the core language regions specifically, not peripheral domain-general regions. This also demonstrates that maturational trajectory abnormalities are not universal in ASD, but instead are likely function and brain region dependent. Taken together, our findings point to a dysfunction in receptive speech processing in ASD, driven at least in part by aberrant attentional orienting, wherein unattended semantically meaningful speech elicits abnormal engagement of the receptive language system of the brain while unattended semantically meaningless speech, filtered out in typically developing individuals, engages the language system in individuals with ASD.

Author contributions

Jussi Alho: Formal analysis, Software, Visualization, Writing - Original Draft; **Hari Bharadwaj**: Conceptualization, Investigation, Writing - Review & Editing; **Sheraz Khan**: Conceptualization, Investigation, Writing - Review & Editing; **Fahimeh Mamashli**: Investigation, Writing - Review & Editing; **Tyler K. Perrachione**: Conceptualization, Resources, Visualization, Writing - Review & Editing; **Ainsley Losh**: Investigation, Project administration, Writing - Review & Editing; **Nicole McGuiggan**: Investigation, Project administration, Writing - Review & Editing; **Robert M. Joseph**: Supervision, Writing - Review & Editing; **Matti S. Hämäläinen**: Methodology, Writing - Review & Editing; **Tal Kenet**: Conceptualization, Investigation, Funding acquisition, Supervision, Writing - Original Draft

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Competing interests

The authors declare no competing financial interests.

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