Lower cortical activation and altered functional connectivity characterize passive auditory spatial attention in ASD

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Abstract

Autism Spectrum Disorder (ASD) is a developmental condition characterized by difficulties in social interaction, communication and sensory processing. The ability to orient towards sounds is a key component of social interactions, yet auditory spatial attention remains relatively understudied in ASD, despite some prior research indicating differences in this domain. Here, we investigate the neural signatures associated with passive auditory spatial attention in children with ASD (n = 21, ages 6-17) relative to age- and IQ-matched typically developing (TD) children (n = 31), using source-localized magnetoencephalography (MEG). Participants listened passively, while watching a silenced movie, to non-social auditory stimuli designed to either remain lateralized to one hemifield (*stay* trials), or to change in location from one side to the contralateral hemifield (*jump* trials). Linear mixed effect modeling showed lower cortical activation in the auditory cortex in the ASD group in response to *jump* trials, relative to the TD group. Additionally, functional connectivity analyses showed higher alpha-band functional connectivity in the ASD group between auditory cortex seeds and frontoparietal regions known

to be recruited during auditory spatial attention. Right prefrontal alpha-band connectivity estimates were associated with worse behaviorally assessed auditory processing scores and increased ASD symptomatology. Our results align with the hypothesis that auditory spatial attention generally, and specifically orientation to sounds even when experienced passively, differs in ASD individuals.

Introduction

Autism Spectrum Disorder (ASD) is a developmental condition characterized by a complex set of behavioral and sensory symptoms, the core of which is differences in social communication (Ben-Sasson et al., 2019; Grzadzinski et al., 2013; Haesen et al., 2011; Hedger et al., 2020; O. Miguel et al., 2017). Among its sensory manifestations, differences in processing of auditory stimuli have been consistently documented among individuals with ASD (Alho et al., 2021; Alho, Khan, et al., 2023; Alho, Samuelsson, et al., 2023; Bharadwaj et al., 2022; DePape et al., 2012; Gonçalves & Monteiro, 2023; Haesen et al., 2011; Mamashli et al., 2017; Marco et al., 2011; O'Connor, 2012; Port et al., 2015, 2017; Schafer et al., 2020).

Auditory spatial attention, i.e. our ability to perceive and track the location of sounds in space, is a complex phenomenon involving several stages of sensory and cognitive processing. For a sound to be successfully located in space, sensory encoding of acoustic features, specifically the relative timing and amplitude differences between ears, needs to be integrated with efficient selective attention and object recognition processes.(Fritz et al., 2007; Kayser et al., 2005; van der Heijden et al., 2019). This integration allows for environmentally adequate behavioral responses to be generated. In addition to primary and secondary auditory areas in the superior temporal gyrus (STG), fMRI research has shown that locating a sound in space recruits a frontoparietal network of cortical regions (Degerman et al., 2006; Deouell et al., 2007; Haist et

al., 2005; Kong et al., 2014; Smith et al., 2009; Zatorre et al., 1999). These regions include the ventrolateral prefrontal cortex (vlPFC), the dorsolateral prefrontal cortex (dlPFC), the precentral sulcus and gyrus, the central sulcus, the postcentral sulcus and gyrus, and the inferior and superior temporal lobes (IPL/SPL). Unsurprisingly, these areas overlap with well-defined functional networks observed in resting state fMRI data, including the ventral and dorsal attention networks, and the frontoparietal executive control network (Hames et al., 2016; Sadaghiani & Kleinschmidt, 2016; Supekar et al., 2013).

Research to date has shown that during auditory spatial attention tasks, individuals with ASD show poorer behavioral performance, measured as higher reaction times and reduced accuracy rates, when required to localize sounds in space (Soskey et al., 2017; Teder-Sälejärvi et al., 2005). While previous studies using electroencephalography (EEG) and magnetoencephalography (MEG) have established a range of differences in early sensory encoding of auditory stimuli in ASD (Bruneau et al., 1999; Jansson-Verkasalo et al., 2005; Orekhova et al., 2009; Roberts et al., 2010; Russo et al., 2009), these have been mostly documented in the context of general auditory processing. One study that directly investigated neural signatures in the context of auditory spatial attention in individuals with ASD showed that poorer behavioral performance in ASD individuals during auditory spatial attention tasks is accompanied by a lower amplitude of the N1 and the P3 components, two Event-Related Potentials (ERP) associated with early sensory encoding and attentional processing, correspondingly (Teder-Sälejärvi et al., 2005). Another study that also focused on auditory spatial attention in ASD found that individuals with an ASD diagnosis showed an absence of the Object-Related Negativity, an ERP component thought to reflect auditory segregation, as well as a reduced amplitude of the P400, an attention-dependent ERP response thought to reflect

perceptual decision making (Lodhia et al., 2018). Notably, despite its importance for everyday life and communication, auditory spatial attention remains understudied in ASD.

To address this gap in the literature, we investigated cortical responses in ASD and Typically Developing (TD) individuals, ages 6 to 17, to direct manipulations of spatial lateralization cues in sound. Using source-localized MEG signals, we focused on evoked responses and functional connectivity from the auditory cortex to characterize the cortical signatures of differences in passive auditory spatial orienting in ASD. We also conducted correlation analyses to investigate possible associations between brain function and clinically relevant behavioral measures of ASD.

Methods

Participants

Thirty-one typically developing (TD, mean age = 13.1 years, SD = 3.4, range = 6-17), and twenty-one children diagnosed with autism spectrum disorder (ASD, mean age = 13.5, SD = 2.7, range 7-17) participated in this study (table 1). All participants met an IQ cutoff of full-scale IQ ≥ 70, as measured by the Kaufman Brief Intelligence Test II (KBIT, Kaufman & Kaufman, 2004). Participants were right-handed except two ASD individuals, determined using the Dean Questionnaire (Dean, 1988). All participants had normal hearing, defined as pure tone thresholds better than or equal to 15 dB in both ears at octave frequencies between 250 Hz and 8 kHz, tested in a soundproof room using an audiometer. Informed consent was provided by parents or legal guardians, in addition to participants' assent, according to protocols approved by the Institutional Review Board of the Massachusetts General Hospital.

All ASD individuals had a formal clinical diagnosis and met criteria on the diagnostic Autism Diagnosis Observation Schedule, Version 2, (ADOS-2, Lord et al., 2000), administered by trained research personnel with demonstrated inter-rater reliability, the diagnostic Social Communication Questionnaire, Lifetime Version (SCQ Lifetime, Rutter et al., 2003), and quantitative Social Responsiveness Scale (SRS, (Constantino & Gruber, 2012)). All participants were also administered the Sensory Profile Questionnaire (ASPS) (Brown & Dunn, 2002). ASD participants who met ADOS-2 criteria but had a borderline ADOS-2 score, did not meet a cutoff of ≥ 15 on the SCQ, or a total t-score < 59 on the SRS, were further evaluated by expert clinician (RMJ) to confirm the ASD diagnosis. A diagnosis of Fragile X syndrome, tuberous sclerosis, and other known risk factors, such as gestation for less than 36 weeks, were criteria for exclusion from participation in the study.

All TD subjects were below SCQ thresholds. Parental report was used to rule out the possibility of any neurological/psychiatric condition (including psychotic episodes, seizures, clinical EEG abnormalities, Tourette syndrome, or any other tics), or substance abuse in the last six months. Participants with Tourette syndrome or tic disorders were excluded from both groups. Due to high comorbidity with ASD, participants with a diagnosis of ADHD, depression, anxiety or language delay were excluded from the TD group, but not from the ASD group.

	ASD (N = 21, 4 females)			**TD (N = 31, 4 females)**			
	N	*Mean (SD)*	*Range*	*N*	*Mean (SD)*	*Range*	**p-value**
Age	21	13.5 (2.7)	7-17	31	13.1 (3.4)	6-17	0.640
NVIQ	17	102.8 (15.1)	59-130	20	112.4 (16.4)	83-147	0.083
VIQ	17	98.8 (19.1)	61-139	20	114.2 (13.8)	86-139	0.009
ADOS	21	11.2 (3.1)	7-18	-	-	-	-
SCQ	19	18.0 (8.9)	0-31	30	3.4 (3.2)	0-12	< 0.001
SRS	20	71.9 (16.0)	40-95	29	43.4 (6.0)	34-62	< 0.001
ASPS	20	12.2 (4.1)	5-20	30	17.2 (2.5)	12-20	< 0.001

Table 1. Characterization of participants. P-values are shown for independent samples t-tests for the difference of means across groups. NVIQ (non-verbal IQ), VIQ (Verbal IQ), ADOS (Autism Diagnostic Observation Schedule), SCQ (Social Communication Questionnaire), SRS (Social Responsiveness Scale), ASPS (Auditory Sensory Profile Score).

Stimuli and procedures

The auditory stimuli consisted of 1200 ms broadband (0.5-2.5 kHz) noise bursts (Figure 1a), presented in 200 trials. Stimuli were designed with a 400 microsecond Interaural Time Delay (ITD) between the stereo channels, thus generating a left- or right-lateralized percept depending on the direction of the ITD. In each trial, the broadband noise was amplitude modulated at either 25 Hz or 43 Hz (Ahlfors et al., 2024). To manipulate the ITD, discontinuities of ±400 µs were introduced in the noise carriers in each channel 550 ms after stimulus onset. Crucially, the discontinuities were designed to coincide with a trough of the amplitude modulation to render them monaurally imperceptible. In half the trials, the 400- µs discontinuities occurred in the same direction in both ears, thus holding the ITD constant for the full duration of the trial (Figure 1b). For the other half of the trials, carrier discontinuities were introduced in opposite directions, thus switching the ITD polarity and creating a percept of a spatial jump in the location of the sound from one hemifield to the contralateral side midway through the trial (Figure 1c).

The subjects listened passively to the auditory stimuli while watching a silent movie with no subtitles. Participants were explicitly asked to ignore the auditory stimuli. After rejection of bad epochs (see below for details), the mean total number of trials was 177 per participant. The mean number of trials across groups did not differ significantly (ASD jump = 181.6, SD = 20.2; ASD stay = 180.0, SD = 22.6; TD jump = 175.5, SD = 19.8, TD stay = 176.2, SD = 19.2). The

interstimulus interval was uniformly distributed between 300 and 400 ms. Stimuli were presented at 65 dB-SPL via MEG compatible earphones.

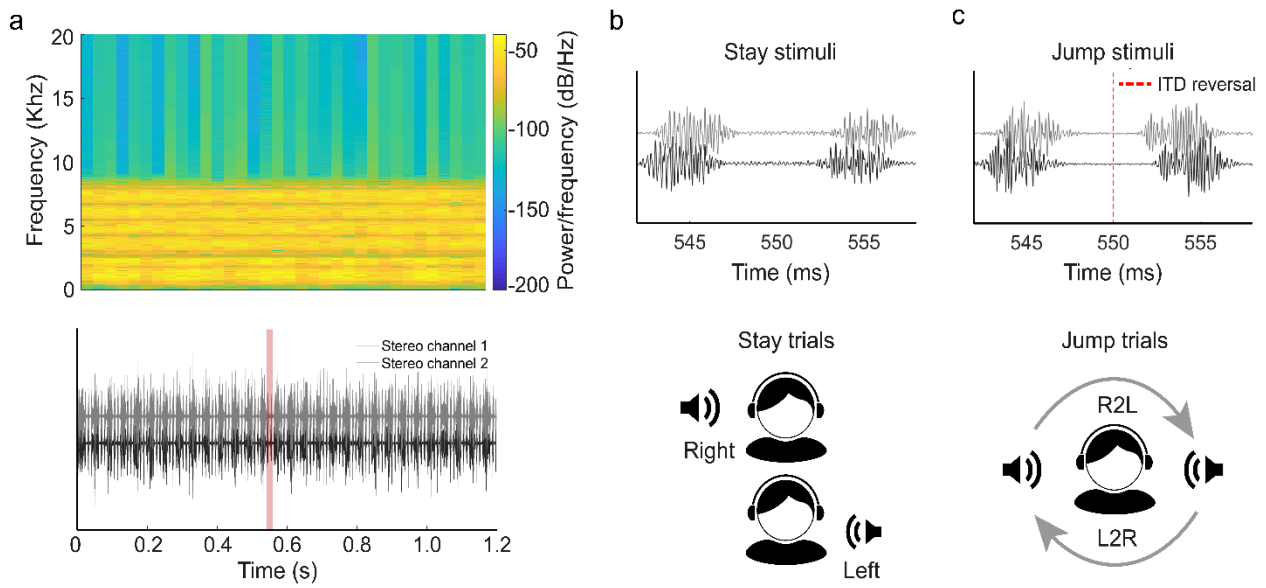

Figure 1. Stimuli and schematic representation of conditions. **a.** Spectrogram (top) and soundwave (bottom) of the auditory stimuli in the stay condition. The red shaded area in the bottom panel represents the time window from which panels in b and c (top) were extracted. **b.** For stay events, the directionality of the ITD was kept constant between the two stereo channels (top). Stimuli were presented with either left- or right-leading ITD (bottom), with equal probability. **c**. For jump events, the polarity of the ITD was reversed at 550ms (dotted line, top). The sound was initially presented with either left- or right-leading ITD, with equal probability. The ITD reversal created a percept of a spatial jump in the lateralization of the sound, right-to-left (R2L) or left-to-right (L2R) side (bottom).

MEG Data acquisition

MEG data was acquired using a 306-channel Vector-View Magnetoencephalography system with 204 planar gradiometer and 102 magnetometer sensors (MEGIN Oy, Finland) inside a magnetically shielded room (IMEDCO, Switzerland). Signals were bandpass filtered between 0.1 and 330 Hz and sampled at the rate of 1,000, or 3,000 Hz and then downsampled to 1000 Hz. Head position was recorded during data acquisition using four head position indicator (HPI) coils attached to the scalp. The location of the HPI coils, the nasion, preauricular points, and

additional points in the scalp surface were digitized using a Fastrack digitizer (Polhemus) system. The digitization information was used to co-register the MEG and MRI data for source modeling analyses. Electrocardiography (ECG) and electro-oculography (EOG) electrodes were used to detect heartbeat, saccades, and blinks. Five minutes of empty-room data were recorded at the end of the session to measure the instrumentation and environmental noise levels in the MEG sensors on the data acquisition date.

Structural MRI

T1-weigthed magnetization-prepared rapid gradient echo (MPRAGE) structural images were acquired using a 3T Siemens MRI scanner and a 32-channel head coil. Reconstruction of cortical surface, cortical volume and anatomical parcellation was conducted using FreeSurfer (Dale et al., 1999; Fischl, Sereno, & Dale, 1999).

MEG data preprocessing

MEG data was preprocessed and analyzed using MNE-Python (Gramfort et al., 2013). Noisy MEG channels were visually identified and excluded from further analyses. Temporal Signal Space Separation (tSSS, Taulu & Simola, 2006) was implemented to compensate for head movements and minimize noise from sources outside of the virtual sphere circumscribing the MEG sensors. Next, data was bandpass filtered between 0.1 and 144 Hz, and notch filters were applied at 60 Hz and 120 Hz to remove line noise and its harmonics. Signal Space Projection (SSP, Uusitalo & Ilmoniemi, 1997) was used to remove cardiac and oculomotor artifacts by computing projections from the bandpass filtered (1-35 Hz) signal. The data were then epoched from -400 ms to 1400 ms with respect to sound onset and detrended to remove slow drifts.

Epochs were excluded if the signal exceeded a peak-to-peak threshold of 4000 fT for magnetometer channels and 5000 fT/cm for planar gradiometer channels.

Source localization

The planar gradiometer signals were used to calculate source estimates on the FreeSurfer-reconstructed cortical surfaces for each individual. The forward solution was computed using a single-compartment boundary element model (BEM, Hamalainen & Sarvas, 1989). Inner skull surface triangulations were generated from MRI structural data using the watershed algorithm. The cortical current distributions were obtained using the dynamic Statistical Parametric Mapping (dSPM, Dale et al., 2000) with a loose orientation constraint of 0.2 and depth weighting of 0.8 (Lin et al., 2006). To reduce the contribution of instrumentation and environmental artifacts to the MEG signals, a noise covariance matrix was obtained from empty room recordings. The noise covariance matrix was used to construct the inverse operator (Hämäläinen & Ilmoniemi, 1994) with a regularization parameter set to 0.1, and to noise-normalize the source estimates (Dale et al., 2000).

Regions of interest

Regions of interest (ROIs) in auditory cortex were identified for each subject's anatomical surface reconstruction by visually examining the time course activations in response to ITD reversals. ROIs corresponding to peak earliest activations were then manually delineated for each individual participant, in both the right and the left hemisphere. Figure 2 shows the overlap probability for left and right auditory ROIs across all subjects. ROI size was not significantly different across groups (ASD mean = 63.1 vertices, TD mean = 64.5 vertices, $t = -0.21$, $p = 0.83$.

Table S1, Supplemental Materials). Evoked responses were computed by extracting the mean dSPM activation across all vertices within each auditory ROI.

In addition to auditory areas, studies of spatial auditory attention using fMRI reported the recruitment of a frontoparietal network during auditory spatial attention tasks. Areas within this network include the dorsolateral Prefrontal Cortex (dlPFC), the ventrolateral Prefrontal Cortex (vlPFC), the precentral/central sulci, the pre/postcentral gyri, the Superior Parietal Lobe (SPL) and the Inferior Parietal Lobe (IFL). These target regions were therefore grouped into frontal, central and parietal ROIs for subsequent functional connectivity analyses (Table S2, supplemental materials), using Freesurfer cortical parcellations (Destrieux et al., 2010).

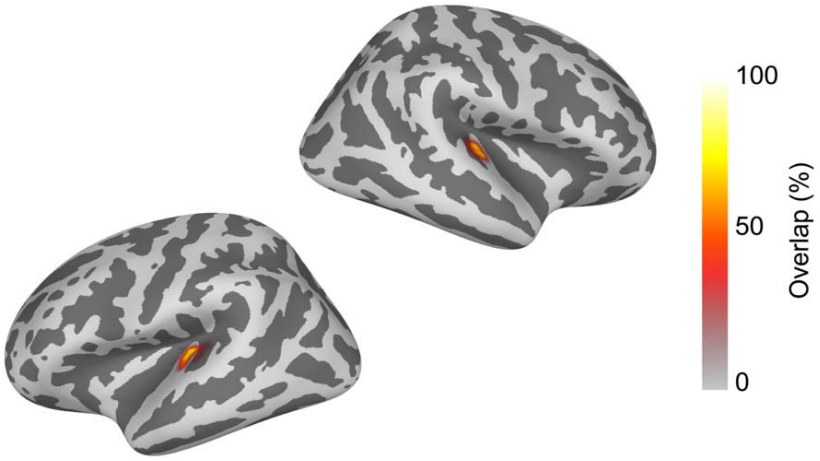

Figure 2. Anatomical overlap across all subjects for the manually drawn, left and right auditory ROIs. These ROIs were identified on the basis of cortical activations in response to ITD reversals in the Jumps condition. Overlap is presented in a common cortical space (Freesurfer's fsaverage cortical surface).

Functional connectivity analyses

We computed seed-based functional connectivity for each condition (*stay* and *jump*) from the left and right auditory cortices with the regions of interest outlined above, including the dlPFC and

vlPFC (superior, middle and inferior prefrontal sulci, middle and inferior prefrontal gyri), central regions (precentral and central sulci, precentral and postcentral gyri) and parietal regions (postcentral and intraparietal sulci, superior and inferior parietal sulci), bilaterally. The seed time courses for functional connectivity analyses corresponded to the auditory cortical activations in response to *jump* trials. Functional connectivity was quantified using the Phase Lag Index (PLI), a measure of phase synchronization that penalizes zero-lag estimates, thus effectively controlling for spurious connectivity due to field spread of MEG signals (Stam et al., 2007). Data was resampled to 250 Hz, and the PLI was computed for each trial between the right and left seed ROI time course and the time course at each vertex, using the wavelet method (spanning four cycles) between 4 and 30 Hz, for a 2000-ms window between -400 and 1400 ms. PLI estimates in the jump condition were then normalized with respect to the *stay* condition to obtain a *z*-scored PLI value, hereafter referred to as zPLI (see supplementary materials). The zPLI estimate is a *z* value which reflects the extent to which connectivity during *jump* trials deviates with respect to the baseline condition (i.e. *stay*), while additionally controlling for the non-normal distribution of connectivity estimates and the difference in trial number across subjects and conditions (Khan et al., 2013; Maris et al., 2007).

Cluster-based permutation statistics within anatomical ROIs

Clusters of vertices showing a significant difference in connectivity across groups within the target regions of interest were identified using cluster-based permutation statistics (Maris & Oostenveld, 2007). This test was conducted for the alpha band (8 – 12 Hz) by averaging functional connectivity estimates over the time dimension between 550 and 850 ms, a time window corresponding to the onset and offset of brain activation to *jump* trials. This statistical test was implemented for each seed (left and right) and target ROI (prefrontal, central and

parietal) separately, using a one-way ANOVA with a cluster-forming threshold of F = 10.54 (corresponding to a p value = 1e-06) and 1000 permutations. Clusters were identified based on spatial adjacency. To achieve this, data from each participant was morphed to a FreeSurfer average cortical representation with 10,242 vertices per hemisphere (Fischl, Sereno, Tootell, et al., 1999). Cluster size was then estimated for each surviving cluster and results were filtered to keep only the top 5% biggest clusters. Finally, clusters were sorted by their statistical significance, which was obtained by summing F values at each vertex within the formed cluster, and only the most significant cluster per seed and anatomical ROI was considered for further analyses. As a post-hoc control analysis, we repeated the same functional connectivity analysis pipeline using Coherence, and repeated the same cluster-based statistical analyses using the coherence metrics instead of the PLI metrics. This was done to ensure the robustness of cluster identification approach. This resulted in two ROIs that showed significant group difference across both functional connectivity metrics, and those are the ones reported in the results section. Cluster based permutation statistics were implemented using MNE-python (Gramfort et al., 2013).

Linear mixed effect modelling

Brain responses to *jump* trials were investigated using Linear mixed effect (LME) modeling with the LME4 package (Bates et al., 2015) in R version 2023.6.1. The predicted variable was the brain response to *jump* trials, quantified as the Area Under the Curve (AUC) at the activation post jump onset. For this, the onset and offset latencies of brain activations with respect to peak latencies in response to *jump* trials were visually identified and recorded for each subject. This time window did not significantly differ across groups (t=1.70, p =0.091. Table S3, Supplementary Materials). The AUC for *stay* trials was obtained using the same subject-specific

time window as for *jump* trials. Fixed effects included group (ASD, TD), condition (*stay*, *jump*), and hemisphere (left, right). To control for the within-subject nature of the task, a random effect for subject was included.

Brain-behavior correlations

Spearman correlation was estimated between normalized functional connectivity estimates extracted from the two surviving statistically significant ROIs that showed significant group differences (see Results) and the two quantitative behavioral measures: the Social Responsiveness Scale (SRS) total t score, a quantitative measure of Autism severity, and the Auditory Sensory Profile Score (ASPS), a quantitative measure of auditory sensory processing in ASD. The ASPS was quantified as the average of the first five questions of the auditory section of the Sensory Profile (parent report), which measures auditory processing atypicality in terms of sensitivity to and distraction by noise. These questions are categorically different from questions 6-8, which are related to social communication (e.g., ignoring what parents say or not responding to their name being called, question 6-7) and to enjoying or seeking to produce strange noises question 8), rather than to more basic auditory processing. Multiple comparisons were addressed by adjusting *p* values using the False Discovery Rate (FDR).

Results

Evoked responses in the auditory cortex

Both ASD and TD individuals showed stronger activations during *jump* trials compared to *stay* trials (i.e., a jump-evoked response). AUC values between onset and offset of peak activations during *jump* trials for both conditions are presented in Table 1.

	AUC - Jump				AUC - Stay			
	Left		Right		Left		Right	
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*
TD	1267.09	835.24	1321.34	864.35	538.77	451.13	532.25	382.52
ASD	845.09	730.18	950.64	434.52	430.63	326.76	503.19	301.30

Table 1. Area Under the Curve (AUC) for TD and ASD individuals at peak between onset and offset of brain activations to *jump* trials.

Figure 3 shows the mean source time course for ASD and TD individuals in left and right auditory ROIs. Mixed effect modeling confirmed a significant effect of group (F (194.10) = 7.84, p = 0.006), condition (F (165.53) = 52.31, p = 1.67e-11) as well as a statistically significant interaction between group and condition (F (165.53) = 3.97, p = 0.048). There was no significant effect of hemisphere in predicting the AUC in brain activations (F (165.53) = 0.47, p = 0.49). Post-hoc pairwise comparisons showed that, within each group, mean AUC values for *jump* trials were significantly higher than *stay* trials (ASD: t(171) = 3.39, p = 9.0e-04, TD: t(171) = 7.26, p < 1.0e-4, insets in Figures 3a and 3b). Across groups, AUC values during *jump* trials were significantly higher for the TD group compared to the ASD group (t (185) = 3.39, p = 9.0e-05) in both left (Figure 3c) and right (Figure 3d) auditory ROIs. Maximum Likelihood Estimation analyses confirmed that the model outperformed a null (intercept-only) model in predicting evoked responses to jumps $\chi^2(7) = 62.78$, p = 4.19e-12, BIC = 3209.95, $R^2_{conditional} = 0.32$, $R^2_{marginal} = 0.24$).

Activations in response to ITD reversals peaked on average at 734 ms in the left auditory cortex (SD = 52 ms) and at 724 ms in the right auditory cortex (SD = 48 ms) in the ASD group. In the TD group, the left hemisphere responses peaked at 742 ms (SD = 50 ms) whereas and the right hemisphere responses peaked at 739 ms (SD = 51 ms). There was no statistically significant difference in peak latency across the two groups.

Functional connectivity between auditory areas and frontoparietal ROIs

Next, we investigated whether the spatial jump was also associated with different alpha-band functional connectivity dynamics, using zPLI, which corresponds to the PLI estimates for the *jump* condition normalized by PLI for the *stay* condition. The seed time courses were the bilateral activations observed in left and right auditory cortices within the manually outlined ROIs, and the target regions were the prefrontal, central and parietal anatomical ROIs defined on the basis of previously reported fMRI findings (see Methods and Supplemental Materials). Based on our prior studies where across-group differences were modulated by functional connectivity in the alpha (8-12 Hz) band (Alho, Khan, et al., 2023; Alho, Samuelsson, et al., 2023; Khan et al., 2013; Mamashli et al., 2021), here too we chose to focus on zPLI estimates in the alpha frequency between 550 and 850 ms, a time window corresponding to the onset-to-offset of the evoked response to the jump event.

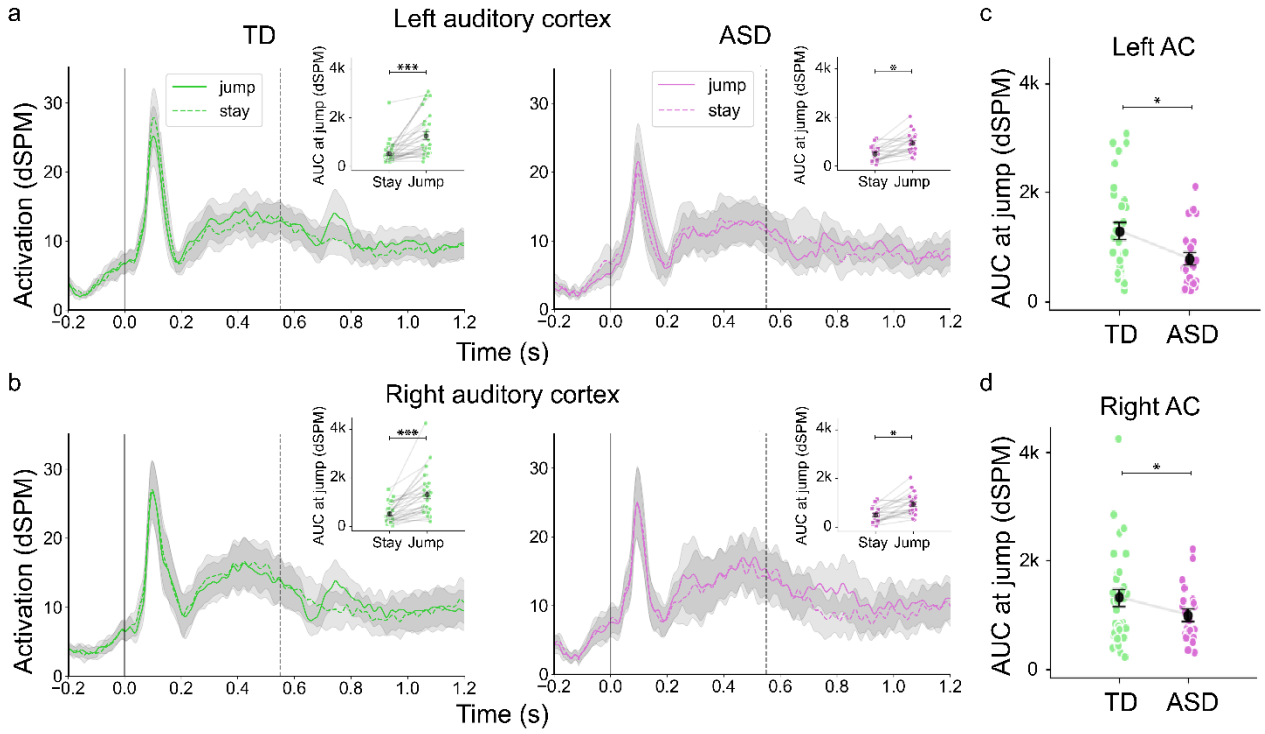

Figure 3. Evoked activations in auditory cortical ROIs. **a.** and **b.** Activations in the left (**a**) and right (**b**) auditory cortices for the TD (green) and ASD (purple) groups in response to jump (solid lines) and stay (dotted lines) trials. Solid vertical line at time zero represents sound onset. Dotted vertical line at 0.55 s represents the onset of and ITD reversal in the jump condition. Gray shades indicate the 95% confidence interval. **c**. and **d**. Mean AUC values for *jump* trials for the TD (green) and ASD (purple) groups. Whiskers indicate the Standard Error of the Mean (SEM). *** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$.

Non-parametric cluster-based permutations tests showed two statistically significant clusters where alpha-band connectivity differed between the two groups. The first cluster ($n_{vertices}$ = 16, F = 44.29, p = 0.0010, Figure 4a, left panel) showed significant connectivity differences across groups between the left auditory seed and dorsolateral portions of the prefrontal cortex (dlPFC). Within this cluster, alpha-band connectivity was significantly lower during *jump* trials compared to *stay* trials (median zPLI = -0.037, SD = 0.022) for TD individuals (t (30) = -10.28, p = 1.23e-10, Figure 4b, left),), but higher during *jump* trials compared to *stay* trials (median zPLI = 0.021, SD = 0.027) for the ASD group (t (20) = -2.71, p = 0.015, Figure 4b, right). Additionally, prefrontal zPLI estimates significantly differed across groups (t(50) = -8.25, p = 1.23e-10, Figure 4b).

The second cluster ($n_{vertices}$ = 17, F = 67.25, p = 0.0010, Figure 4c, left panel) showed significant connectivity differences across groups between the left auditory seed and portions of the left superior postcentral sulcus and superior parietal gyrus. Within this cluster, alpha-band connectivity was significantly lower during *jump* trials compared to *stay* trials (median zPLI = -0.06, SD = 0.02) for TD individuals (t (30) = -16.38, p = 1.49e-15, Figure 4d, left), but zPLI estimates during *jump* trials did not significantly differ from the *stay* condition (t(20) = 1.34, p = 0.19) for the ASD group (median zPLI = 0.01, SD = 0.02, Figure 4d, right).). Parietal functional connectivity within this parietal cluster was also significantly different across groups (t(50) = -11.19, p = 1.44e-14, Figure 4d). All reported *p* values from comparisons of MEG measures between the two groups are FDR-adjusted.

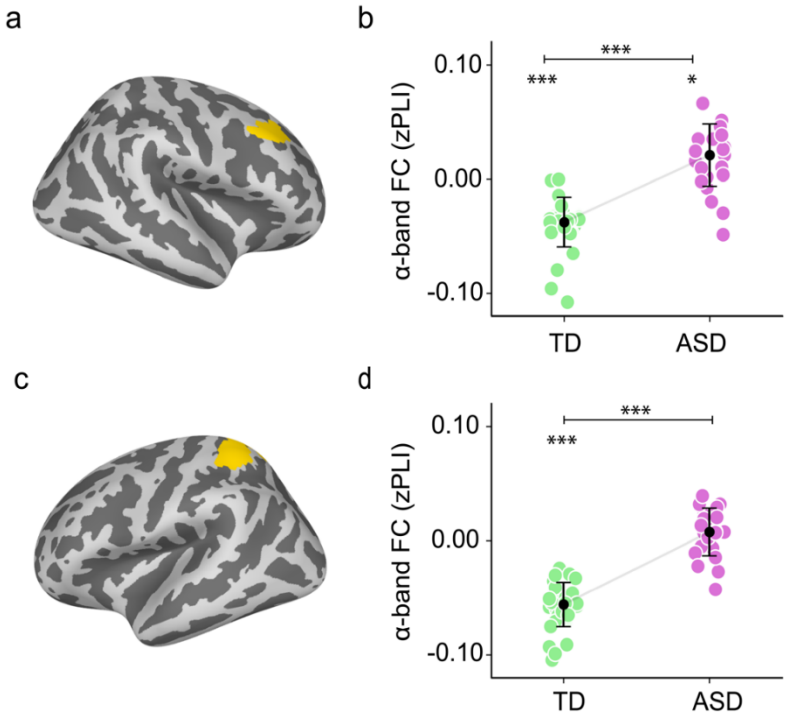

Figure 4. Functional connectivity for the two statistically significant clusters during *jump* trials, normalized by *stay* trials. **a**. and **c**. Anatomical location of the statistically significant clusters in prefrontal (**a**) and the superior parietal regions (**c**). **b**. and **d**. Median alpha-band connectivity estimates obtained from the dlPFC (**b**) and SPL clusters (**d**) for the TD (green) and ASD (purple) groups. Whiskers represent the Standard Error (SE). Asterisks on top of horizontal lines denote significant differences across groups. Asterisks below horizontal lines denote a

Correlations between brain measures and behavioral measures

To test whether the MEG measures correspond to relevant ASD traits, we correlated the magnitude of the evoked responses, as well as estimates of normalized functional connectivity (zPLI) with behaviorally assessed phenotypic measures of ASD severity (SRS t-score) and auditory processing, (the ASPS score). In the TD group, we did not find significant associations between any of the behavioral measures and the evoked responses. Similarly, neither behavioral measure was significantly correlated with zPLI in the TD group.

For the ASD group, higher alpha band functional connectivity in the prefrontal cluster showed positive correlation with autism severity, as measured by the SRS t-score (r(18) = 0.51, p = 0.021 uncorrected, q = 0.08), although this correlation did not survive multiple comparisons correction. Prefrontal connectivity in the alpha band was also negatively correlated with the auditory processing component of the Sensory Profile Questionnaire in the ASD group (r(18) = - 0.63, p = 0.003, q = 0.025). The correlations between the behavioral measures and zPLI are shown in Figure 5. To check for any possible effects of age, we computed post-hoc correlations between age and functional connectivity estimates, and between age and cortical activations. No significant correlation was found between age and these two MEG measures of brain function, meaning age was not a factor in the response patterns and observed group differences.

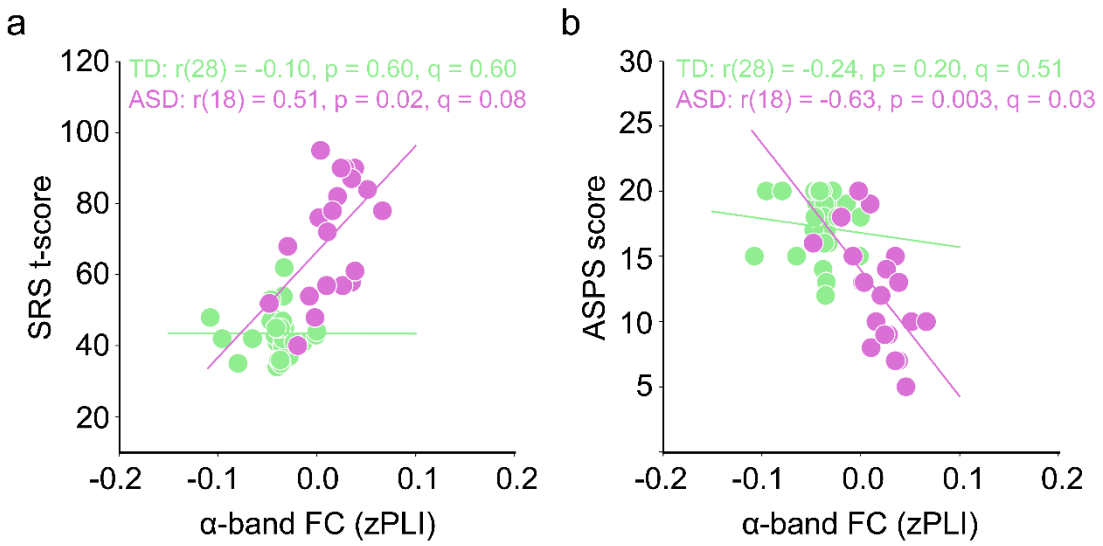

Figure 5. Brain-behavior correlations. **a**. and **b**. Correlation between alpha-band connectivity estimates obtained from the prefrontal cluster and scores in the Social Responsiveness Scale, SRS (**a**) and Auditory Sensory Profile Scores, ASPS (**b**) in the TD group (green). **c**. and **d**. Correlation between alpha-band connectivity in the prefrontal cluster and SRS (**c**) and ASPS scores (**d**) in the ASD group (purple). q values show the adjusted p values after FDR correction.

Discussion

The aim of this study was to investigate passive auditory spatial attention in ASD. Specifically, we examined cortical activations and alpha-band functional connectivity in individuals with ASD and TD individuals in response to changes in sound location (i.e., *jump* trials) under passive listening conditions. ASD individuals showed lower cortical activations in cortical auditory regions and altered alpha frequency band functional connectivity between auditory and frontal areas. Additionally, functional connectivity estimates for the ASD group were significantly correlated with behavioral measures of ASD severity. Our findings provide insight into the differential neural processing of spatial auditory information in ASD and TD groups.

ASD individuals show reduced auditory activation during jump trials compared to TDs

The fact that both groups showed cortical responses to *jump* trials confirms that both ASD and TD individuals were sensitive to acoustic cues indicative of a change in the location of a sound in space. This would be in line with findings which suggest that despite relative differences in performance, both groups can behaviorally locate sounds in space (Lodhia et al., 2018; Soskey et al., 2017; Teder-Sälejärvi et al., 2005). While both groups detected changes in localization, auditory cortical activations were significantly lower in the ASD group, which may be indicative of altered encoding of perceived acoustic features that are important to map sounds in space. These results are in line with previous electrophysiological research, which has shown a smaller amplitude of early and mid-latency auditory components during spatial (Lodhia et al., 2018; Teder-Sälejärvi et al., 2005) and non-spatial auditory processing tasks (Bruneau et al., 1999; Jansson-Verkasalo et al., 2005; Orekhova et al., 2009; Port et al., 2015; Russo et al., 2009; Soskey et al., 2017). They are also in line with postmortem human evidence in ASD of malformed brainstem circuits (i.e., superior olive) that are thought to be the first nuclei along the

ascending auditory pathway to process binaural cues, such as interaural time delays (Kulesza et al., 2011). The significant group-by-condition interaction, where the ASD group exhibited a smaller magnitude of activation during *jump* trials, further supports the notion that individuals with ASD exhibit atypical auditory processing, potentially resulting from altered encoding or binding of relevant acoustic features (Bharadwaj et al., 2022; Gonçalves & Monteiro, 2023; Hames et al., 2016; Keehn et al., 2010, 2017; Lodhia et al., 2018; Marco et al., 2011).

ASD and TD Groups show opposite connectivity patterns in response to jump trials

Our functional connectivity analyses revealed significant differences in temporo-frontal and temporo-parietal alpha-band connectivity between ASD and TD groups, with the ASD group showing stronger connectivity during *jump* trials relative to the TD group. These results suggest that the ASD group may lack the typical modulation of connectivity in response to sensory changes. This could reflect a disruption in the dynamic adjustment of attentional networks required for processing auditory spatial shifts, especially given that this is a passive paradigm, where attention was presumably directed away from the sounds. Atypical functional connectivity involving the auditory cortex, measured with EEG or MEG, has been documented in ASD, by our group and others (Alho, Khan, et al., 2023; Alho, Samuelsson, et al., 2023; Demopoulos et al., 2024; Mamashli et al., 2017). Long-range alpha-band functional connectivity has been previously proposed as a neurophysiological marker of attentional modulation via coordination of temporal windows of neural excitability across cortical space (Klimesch et al., 2007; Palva & Palva, 2011; Sadaghiani & Kleinschmidt, 2016). Higher alpha-band connectivity in the ASD group could therefore be associated with atypical synchronization of attentional networks involved in sensory integration and cognitive control, which are often reported as dysregulated in ASD. The lower connectivity observed in the TD group could reflect a more typical response to

the auditory shift, suggesting more efficient attentional allocation and neural processing. Although not related to functional connectivity, previous studies on auditory spatial attention in ASD have reported lower amplitude of mid-lantency ERP components associated with attention and executive function, namely the P300 and P400 (Lodhia et al., 2018; Teder-Sälejärvi et al., 2005). This lends additional support to the idea that, on top of sensory encoding, attentional processes also differ in ASD during execution of auditory spatial attention tasks.

Prefrontal alpha connectivity in ASD correlates with auditory processing and autism severity

We found that higher temporo-parietal alpha band connectivity was positively correlated with higher manifestations of ASD symptoms as measured by the Social Responsiveness Scale (SRS). Although this correlation did not survive correction for multiple comparisons, the trend is consistent with other studies showing a correlation between functional connectivity of auditory cortex with both cerebral and cerebellar ROIs and ASD symptoms severity (Alho, Samuelsson, et al., 2023; Sharda et al., 2018; Wilson et al., 2022).

Additionally, higher alpha-band connectivity between auditory and the prefrontal regions was negatively correlated with behaviorally assessed auditory processing symptoms, as measured by the Auditory Sensory Profile Score (ASPS) in the ASD group, potentially indicating that higher connectivity is linked to poorer auditory integration of spatial cues. This is also in line with previous work in our group, showing that increased connectivity between auditory and parietal regions is associated with poorer auditory processing skills, as measured by the ASPS (Alho, Khan, et al., 2023).

The finding of higher alpha-band functional connectivity in ASD during spatial attention tasks is in line with similar findings observed in resting state which propose alpha-band

hyperconnectivity as a characteristic feature of ASD (Demopoulos et al., 2024; Orekhova et al., 2014; Wang et al., 2020). These findings highlight the potential impact of prefrontal and parietal regions on auditory processing in ASD.

Limitations

This study has two limitations that should be addressed in future research. First, the relatively small sample sizes of the ASD and TD groups limit the power of the findings. While the findings align well with prior studies, future studies with larger cohorts will be important for further confirming the observed group differences in cortical activations and connectivity patterns, as well as to potentially uncover additional differences. Second, because our results were obtained during passive listening conditions, we lack task-relevant behavioral correlates that allow us to rule out the possibility that participants with ASD actively engaged auditory attention differently from the TD participants. Future studies with an active spatial auditory attention task and behavioral assessments of spatial auditory attention will be needed to elucidate any behavioral differences between the groups, and links between these differences and cortical measures.

Conclusion

The results presented here provide novel insights into the neural mechanisms underlying auditory spatial attention in ASD. We found that ASD was associated with lower auditory cortical activations and altered alpha-band functional connectivity between auditory cortex and frontal and parietal regions, in response to shifts in the spatial location of sounds. The neurophysiological measures were correlated with measures of ASD symptoms extent and behaviorally assessed auditory processing, in the ASD group, thus confirming their relevance to the ASD phenotype. Future directions include the evaluation of these metrics with an active,

rather than passive, auditory spatial attention paradigm, and extending it to larger samples as well as to related conditions, so as to elucidate the specificity of the results to ASD.

Conflict of interest

The authors declare no conflict of interest.

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