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S:I: .DEVELOPMENTAL APPROACH AND TARGETED TREATMENT OF SENSORY ALTERATIONS

Assessing Trial-to-Trial Variability in Auditory ERPs in Autism and Schizophrenia

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Abstract
Sensory abnormalities are characteristic of autism and schizophrenia. In autism, greater trial-to-trial variability (TTV) in sensory neural responses suggest that the system is more unstable. However, these findings have only been identified in the amplitude and not in the timing of neural responses, and have not been fully explored in schizophrenia. TTV in event-related potential amplitudes and inter-trial coherence (ITC) were assessed in the auditory mismatch negativity (MMN) in autism, schizophrenia, and controls. MMN was largest in autism and smallest in schizophrenia, and TTV was greater in autism and schizophrenia compared to controls. There were no differences in ITC. Greater TTV appears to be characteristic of both autism and schizophrenia, implicating several neural mechanisms that could underlie sensory instability.

Keywords Autism · Schizophrenia · Trial-to-trial variability · Inter-trial coherence · Event-related potentials · Auditory

Introduction

Individuals with Autism Spectrum Disorder and individuals with schizophrenia both experience atypical sensory percepts in multiple sensory modalities. Characterizing the exact profile of these sensory irregularities can reveal underlying mechanisms and identify whether they are similar across diagnoses or are specific to one condition. The DSM-V defines autism by social and communication difficulties and unusual behaviors that encapsulate the previous DSM-IV criteria such as repetitive behaviors and a new recognition of unusual sensory behaviors. Schizophrenia, on the other hand, is defined by the presence of delusional and paranoid thinking, and sensory hallucinations. While these definitions make autism and schizophrenia sound distinct from one another, they, in fact, share many behavioral, cognitive, and genetic components (Eack et al., 2013; Sugranyes et al., 2011; King & Lord, 2011; Cheung et al., 2010; Couture et al., 2010), and have even been theorized to be opposite ends of the same spectrum (Crespi et al., 2010). Therefore, identifying the ways in which sensory processing in autism is or is not similar to schizophrenia can help identify mechanisms that might be transdiagnostic and elucidate how they impact symptoms.

In general, individuals with schizophrenia exhibit reduced (hypo-sensitive) sensory processing, particularly in the auditory domain (Rosberg et al., 2008; Moschopoulos et al., 2019). One of the most robust findings in psychiatry is the reduction of the mismatch negativity (MMN) in schizophrenia (Umbricht & Krljes, 2005). MMN is an increased negativity in the event-related potential (ERP; around 120-200ms) after the presentation of a deviant stimulus (Näätänen, 1995). The reduced MMN in schizophrenia is consistent with poorer behavioral measures of auditory performance (Jahshan et al., 2015; Kantrowitz et al., 2015; Shah et al., 2018). In autism, there is some debate as to whether sensory processing is hyper-sensitive (the brain

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over responds) or hypo-sensitive (the brain under responds), including in the auditory domain (Vlaskamp et al., 2017). Auditory scene segregation markers, for example, the object-related negativity (ORN) is smaller in autism than in non-clinical individuals (Lodhia et al., 2014, 2018). The magnitude of the MMN response seems to be dependent on the type of deviant being presented. Frequency and duration deviants elicit a smaller MMN in autism despite a larger P3 response. Pitch deviants, in general, tend to elicit similar or larger auditory MMN amplitudes in autism compared to non-clinical participants, (Kujala et al., 2007; Hudac et al., 2018), and show slower attenuation in ERP responses to pitch too (Millin et al., 2018; Hudac et al., 2018).

While there are few studies that compare sensory processing in autism and schizophrenia directly, those that exist suggest that early responses are smaller in amplitude in schizophrenia compared to autism and non-clinical individuals. This has been shown in fMRI responses to visual, auditory, and somatosensory stimuli (Haigh et al., 2016) and in electroencephalographic (P50) sensory gating responses to the initial stimulus, but normal cross-sensory suppression in the later processing stages of N1 and P2 (Magnée et al., 2009). This differential pattern of sensory processing may be related to the atypical patterns of metabolic glucose rates across the brain in autism and schizophrenia compared to non-clinical individuals (measured using positron emission tomography; PET; Mitelman et al., 2018), atypical resting-state fMRI activity (particularly in sensorimotor, default-mode, and cognitive control networks; Du et al., 2021), and different patterns of white matter diffusion across the brain (Haigh et al., 2019). Autism and schizophrenia have also been associated with an imbalance in neurotransmitters that lead to too much excitation in autism (Wood et al., 2021; He et al., 2021; Umesawa et a., 2020) and too little excitation in schizophrenia (Kantrowitz, 2019; Hoshino et al., 2020).

One emerging finding of sensory processing in autism, is greater trial-to-trial variability in sensory responses (Milne, 2011; Dinstein et al., 2012; Haigh et al., 2014) suggesting that the processing of sensory information is unreliable from one time to the next. For example, P1 in the visual ERP was more variable in adults with autism compared to non-clinical adults to the same stimulus (Milne, 2011). This pattern of greater trial-to-trial variability was reported in visual, auditory, and in somatosensory responses in the same individuals with autism compared to non-clinical individuals (Dinstein et al., 2012), and also, albeit to a lesser extent, in individuals with schizophrenia compared to non-clinical individuals (Haigh et al., 2016). Furthermore, greater variability has been reported in behavioral responses to sensory stimuli, for example, when judging tactile roughness in adults with autism compared to non-clinical adults (Haigh et al., 2015). This instability in sensory signaling could lead to unstable sensory environments that could contribute to or exacerbate the behavioral characteristics that are associated with autism (Bazelmans et al., 2019; Dinstein et al., 2015; Haigh, 2018). For example, if processing of speech is unstable, then detecting the subtle changes in emotion that impact speech might be missed. This could lead to misinterpretation of social situations and encourage social withdrawal as a result.

The majority of the findings reporting on the greater trial-to-trial variability in sensory responses in autism have focused on fluctuations in the amplitude of the response. This would suggest that the sensory responses are sometimes too strong and other times are too weak. Few have focused on timing discrepancies. Instability in the timing of sensory processing would suggest that the integration and syncing of multiple streams of information would be degraded and could similarly lead to difficulties interacting in complex sensory environments. One study focused on inter-trial coherence (ITC) measures, which capitalizes on phase coherence of different frequencies in electroencephalography (EEG) waves after a stimulus presentation, and on event-related spectral perturbations (ERSPs), which assess the change in power over different frequencies. Interestingly, Butler et al. (2017) reported that there were no significant differences in ITC between adults with autism and matched non-clinical participants in their visual responses to achromatic checkerboard annuli presented 100 times within a block for 1000-1100ms. In fact, they reported that the responses were unexpectedly stable across theta, alpha, and beta bands. Similarly, Edgar et al. (2016) found no significant differences between autism and non-clinical groups in ITC or in ERSPs in a 40 Hz gamma power in an auditory steady-state paradigm using amplitude modulated pure tones of 500 Hz. These findings highlight a key question as to whether the instability in sensory responses is specific to amplitude fluctuations and/or phase fluctuations. When assessing ITC in schizophrenia, the majority of findings report reduced ITCs specifically in theta in visual (oddball chromatic compared to standard achromatic checkerboards presented at ~0.83 Hamilton et al., 2020) and in auditory responses (to 'ah' vocalizations every 1–2 s: Roach et al., 2021), but there are also reports of reduced auditory-evoked gamma-band ITC during oddball MMN paradigms (Parker et al., 2019; recent-onset: Koshiyama et al., 2018) and to 40 Hz clicks under eyes open and eyes closed conditions (Wang et al., 2018). There is some debate as to whether auditory ERSPs are reduced in schizophrenia (Parker et al., 2019; Koshiyama et al., 2018; state-dependent: Wang et al., 2018) or are not different between groups (Roach et al.,2021). Therefore, we have chosen to compare and contrast both amplitude and timing measures ofbetween-trial variability to identify which is atypical in autism, and whether the findings are specific to autism or also present in schizophrenia.

Owing to the significant overlap in behavioral and genetic descriptions in autism and schizophrenia, identifying exactly the ways in which the underlying neural mechanisms are similar or different may be key to differentiating their psychophysiology. In the current study, we compared adults with autism, adults with schizophrenia, and matched non-clinical adults on their auditory responses. We chose to focus on electrophysiological (EEG) responses to capitalize on the high timing resolution so as to compare TTV in the amplitude of ERPs and variability in event-related oscillations by measuring ITC. The original data from the autism and non-clinical groups have been the focus of another manuscript by Haigh et al. (2022). The schizophrenia data were collected as part of the same study.

EEG data were collected during a roving MMN paradigm (Garrido et al., 2008), where tones were presented three or nine times before the pitch changed and the deviant tone became the standard. As this is a pitch deviant paradigm, we predicted that the adults with autism would produce a larger MMN and schizophrenia a smaller MMN than non-clinical participants (in line with previous findings when examining the clinical groups separately; autism: Kujala et al., 2007; Hudac et al., 2018; schizophrenia: Umbricht & Krjles, 2005). We also predicted that TTV would be largest in autism and smallest in non-clinical individuals, reflecting differences in the amplitude of the responses across trials, but that ITC measures would not differ (partially replicating the findings by Butler et al., 2017), suggesting that the timings of the auditory responses are similar in the non-clinical and autism groups. The important question is how the adults with schizophrenia will compare to the other two groups. Following the TTV findings in auditory fMRI responses, the schizophrenia group are expected to show slightly greater TTV than the non-clinical group but not significantly so (Haigh et al., 2016). This study will determine whether this is the case in faster electrophysiological responses. ITC measures, however, are predicted to be reduced in schizophrenia compared to autism and non-clinical groups. Owing to the inconsistencies in ERSP findings in both autism and schizophrenia, we do not predict any significant group differences here. Directly comparing TTV and ITC in the same study will highlight whether autism and/or schizophrenia exhibit instability in their auditory responses, and if so, whether the instability is due to magnitude or timing variability.

Methods

Participants

Twenty-four adults with autism, 12 adults with schizophrenia, and 28 non-clinical adults participated. Owing to artefact rejection criteria (detailed below), three adults with autism and one non-clinical adult were excluded from analysis. Demographic information of the participants who were included in the analysis are shown in Table 1. None of the participants reported any hearing or vision loss, a recent significant head injury, or were pregnant. Protocols were approved by an Institutional Review Board and participants gave their informed consent to take part. They were paid $50 for their time.

The adults with autism met DSM-IV or DSM-V criteria for autism. Clinical diagnosis was confirmed with the Autism Diagnostic Observation Schedule (ADOS) (Lord et al., 1989) and carried out by experienced clinical interviewers.

Table 1 Demographic information for the autism, schizophrenia, and non-clinical groups, and IQ and MATRICS scores for the autism and schizophrenia groups

	Autism	Schizophrenia	Non-clinical	p value
Gender (M/F)	16/5	9/3	16/9	p = .544
Age (years)	29.52 (7.47)	29.00 (6.84)	33.58 (8.21)	p = .219
IQ	111.14 (15.35)	107.09 (10.48)		p = .007
BACS	30.74 (31.59)	28.41 (33.34)		p = .853
Processing speed	44.70 (35.40)	30.48 (29.53)		p = .250
Attention vigilance	47.03 (33.77)	38.45 (22.84)		p = .415
Working memory	53.01 (36.99)	41.51 (25.65)		p = .341
Verbal learning	43.16 (31.91)	24.63 (17.82)		p = .060
Visual learning	61.27 (31.06)	31.56 (27.60)		p = .014
Reasoning and problem solving	52.63 (34.10)	55.18 (32.89)		p = .845
Social cognition	42.36 (27.13)	52.61 (32.32)		p = .394

The sum is shown for gender (male/female). Means are shown for the rest of the demographics

T-tests were used to compare groups, except gender which was compared using a chi square and age which was compared using a one-way ANOVA

BACS Brief assessment of cognition in schizophrenia

IQ for all adults with autism was over 85 (details in Table 2). The Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (Nuechterlein et al., 2006, 2008; Kern et al., 2008; Green et al., 2014) was used to assess the effects of psychiatric condition (originally psychosis) on cognition. The following subscales were assessed: Brief Assessment of Cognition in Schizophrenia (BACS), processing speed, attention vigilance, working memory, verbal learning, visual learning, reasoning and problem solving, and social cognition (see Table 1).

The adults with schizophrenia met the DSM-IV criteria for schizophrenia and diagnosis was confirmed with the Structured Clinical Interview for DSM-IV (SCIP-IV) by experienced clinical interviewers at Western Psychiatric Hospital. All schizophrenia participants had a minimum IQ of 95 and had at least 5 years of illness. Eight participants reported being on antipsychotic medication (see details in Table 3). Individuals with schizophrenia completed the same MATRICS assessment as the individuals with autism and the same eight subscores were calculated (see Table 1).

None of the non-clinical participants had a neurological or psychiatric diagnosis and were not taking any psychotropic medications at the time of the experiment. They were either students from the University or residents in the surrounding area. As the non-clinical participants were not recruited through a clinic, they did not complete a MATRICS assessment.

Table 2 Demographic information for the autism group

Participant	ADOS communication	ADOS stereotypical	IQ	Age	Gender
1	3	7	92	28	F
2	8	9	111	21	M
3	4	10	87	44	M
4	4	7	104	29	M
5	4	6	123	28	M
6	3	11	97	26	F
7	2	7	123	38	F
8	2	5	128	32	M
9	4	4	128	41	M
10	3	8	123	29	M
11	4	7	111	26	M
12	4	5	127	23	M
13	4	7	125	37	M
14	2	5	107	22	M
15	3	5	89	26	M
16	3	4	88	31	M
17	2	6	120	36	F
18	4	9	95	24	F
19	5	5	100	41	M
20	5	9	127	19	M
21	4	4	129	19	M

Table 3 Demographic information for the schizophrenia group

Participant	Medication (Generation)	BPRS	IQ	Age	Gender
1		–	100	41	Male
2	Second	37	109	30	Female
3	Second	38	101	28	Female
4		52	114	37	Male
5	Second	38	99	25	Male
6	Second	48	104	30	Male
7	Second	33	121	37	Male
8		39	107	46	Male
9	Second	47	99	32	Male
10	Second	60	95	32	Female
11		–	–	24	Male
12	First	30	129	41	Male

Type of antipsychotic medication is listed. For one individual with schizophrenia, the Brief Psychiatric Rating Score (BPRS) and IQ were missing. For another individual with schizophrenia, just the BPRS was missing

EEG Data Acquisition

Data were collected using a 64-channel BioSemi Active2 EEG system (Amsterdam, Netherlands) with a nylon cap to hold the electrodes in place in a standard 10–10 electrode montage. Seven additional electrodes were used: two electrodes were added to the mastoids, one to the collarbone to detect heartbeat, and four were placed around the eyes to monitor eye movements (one above the right eye, one below the right eye, and on the outer canthi of each eye). All electrodes were recorded relative to the CMS and DRL electrodes. Data were digitized at 512 Hz with a 24-bit A/D conversion.

Stimuli

All of the tones were generated in MATLAB and presented using the PsychToolbox extension (Brainard, 1997, Kleiner et al., 2007, Pelli & Vision, 1997). Tones were presented for 50ms every 330ms and included a 5ms ramp up and ramp down to avoid high frequency artifacts from the earphones at 1046.5 Hz (C6), 1108.73 Hz (C#6), or 1244.51 Hz (D#6). Each pitch was presented either three or nine times consecutively before changing pitch. Tones were sampled at 48 kHz with 16-bit resolution. The use of a roving paradigm was to examine deviance detection while controlling for stimulus-specific differences—the deviant tone becomes the standard tone before the presentation of the next deviant.

The manipulation of the tone train length was to examine the effects of adaptation on the MMN as part of a larger study (see Haigh et al., 2022; see Fig. 1 for an example of the stimulus paradigm).

Procedure

Tones were presented over Etymotic insert earphones while EEG was recorded. To ensure that any fluctuations in attention did not drive the variability in EEG responses, participants were instructed to ignore the tones and to attend to the fixation cross that was presented in the center of the screen. Participants were seated approximately 1 m from the screen. They were asked to keep their eyes on the central fixation cross at all times and to press the spacebar whenever they saw the black fixation cross flash white (16.6% of trials). A one-way analysis of variance (ANOVA) showed that there was no significant difference between groups in their reaction time ($F(2,57) = 2.37$, $p = .103$) nor in the number of responses made ($F(2,57) = 2.97$, $p = .059$).

To verify that any group differences in EEG responses were not due to an inability to perceptually distinguish between different pitches, all participants took part in a brief behavioral pitch discrimination task: pairs of 50 ms tones were presented 500 ms apart and participants had to respond as to whether the tones sounded as though they had the same pitch (50% of trials) or if they sounded different. Five tones were used (1046.5 Hz, 1062.2 Hz, 1077.9 Hz, 1108.73 Hz, 1244.51 Hz) providing 10 pitch changes. Each tone pair was presented four times. Percent correct and reaction time for each pitch difference were recorded. Responses showed that all three groups had similar pitch discrimination functions, although the autism and schizophrenia groups were slightly slower at responding (see Supplementary Materials for more information).

Data Analysis

EEG data were preprocessed and analyzed using MATLAB (MathWorks) and the EEGLAB (Delorme & Makeig, 2004) and ERPLAB toolboxes (Lopez-Calderon & Luck, 2014). The average signal from the mastoids was used as an offline reference and data were filtered using a 0.1–100 Hz Butterworth zero-phase filter. Noisy electrode channels were identified manually and were interpolated (0.8% of electrodes from the autism group, 0.2% from the schizophrenia group, and 0.4% of electrodes from the non-clinical group). There was no significant difference in the number of electrodes interpolated across groups ($F(2,61) = 0.66$, $p = .522$). An independent component analysis (ICA) was used to manually identify and remove components that contained blinks, eye movements, and heartbeat. The data were then epoched relative to the onset of the tones.

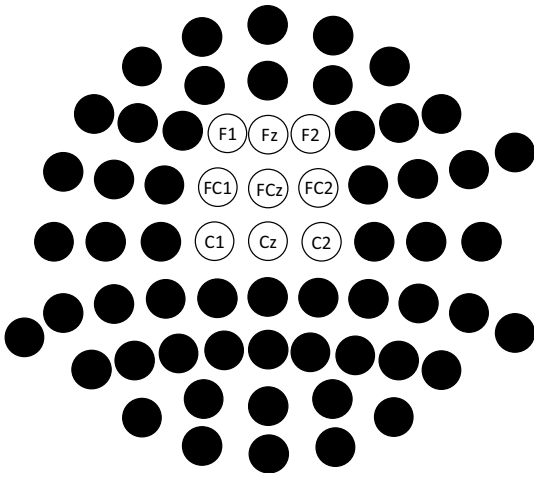

Fig. 2 Location of electrodes (open circles) used in the analyses

ERP Amplitudes and Trial-to-Trial Variability (TTV)

Epochs were extracted from 50ms before the onset of the tone to 330ms after the onset of the tone (maximum time before the next tone was presented) and baseline corrected from −50 ms to 0. Any epochs that contained signal that exceeded ± 100μV were automatically rejected from analysis. All epochs were then filtered with a low-pass 20 Hz filter to ensure accurate identification of the MMN.

To assess group differences in the amplitude of MMN, epochs from the last tone from each train were averaged together (regardless of pitch or tone train length) to create the standard response. To create the deviant response, the first tone from each tone train were then averaged together. The standard waveform was then subtracted from the deviant. The subtraction waveforms for electrodes F1, Fz, F2, FC1, FCz, FC2, C1, Cz, and C2 are shown in Fig. 3. These electrodes were chosen as the auditory MMN signal is maximal at FCz (see Salisbury et al., 2016). To ensure that the results are not due to a single electrode, a grid of 3 × 3 electrodes was selected to ensure signal reliability (see Fig. 2 for location of electrodes). The mismatch

Fig. 1 Example of the roving pitch paradigm used

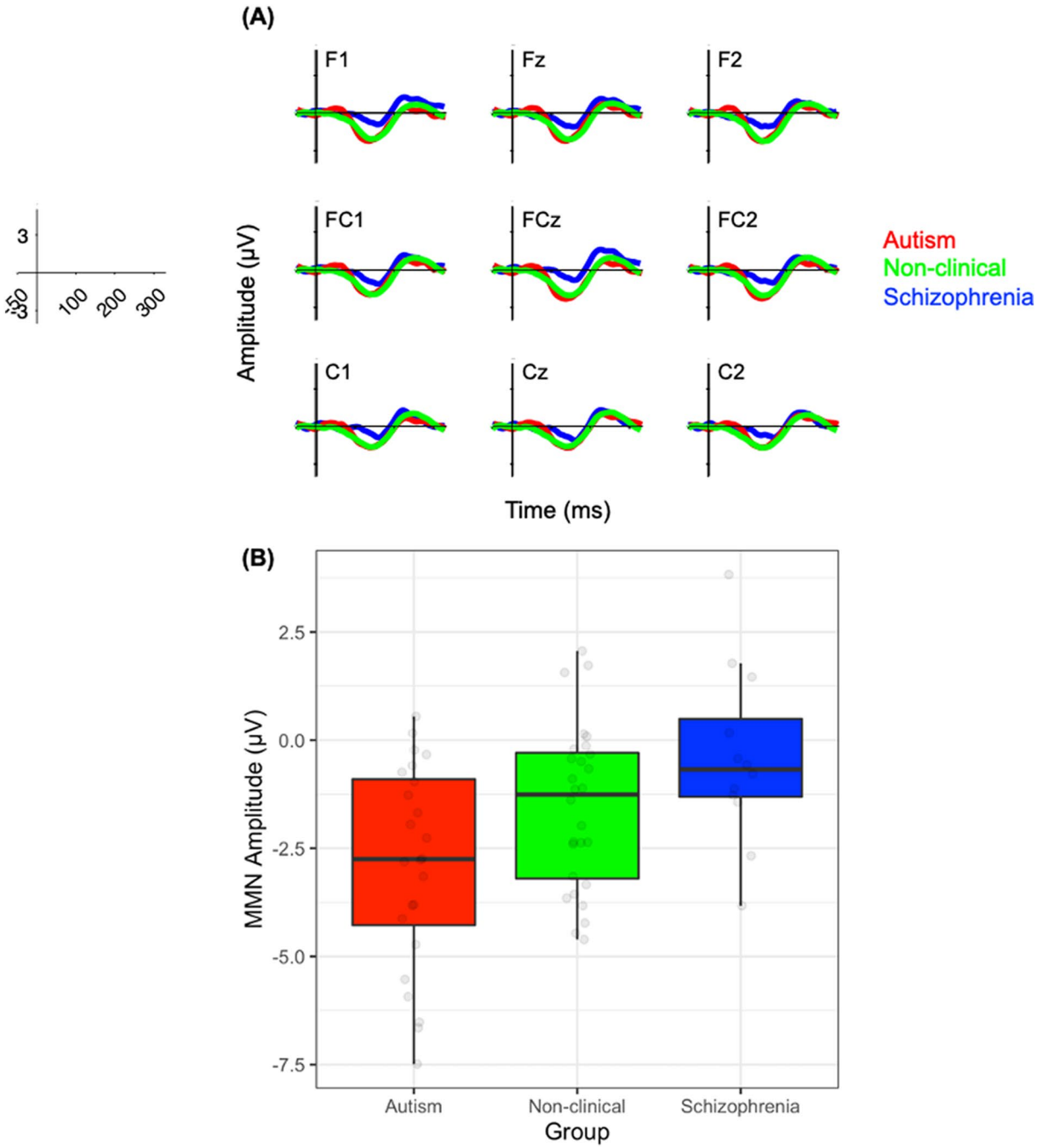

Fig. 3 **A** Subtraction waveforms in autism (red), non-clinical (green), and schizophrenia groups (blue) all electrodes included in the analysis. **B** MMN amplitudes for autism, non-clinical, and schizophrenia groups from electrode Fz where the group difference was maximal

negativity amplitude was calculated by averaging the response 110–130 ms after stimulus-onset, where the peak was maximal for all participants.

To assess TTV in responses, the standard error of the mean (SEM) was calculated for each data point over all epochs to generate a measure of between trial variability. This was calculated separately for each participant. The SEM was averaged over 110 ms (the beginning of the N1) to the end of the epoch (330 ms) for all tone presentations for each participant and for each channel.

To ensure that all epochs contained clean noise-free data, one autism participant's data were removed from analysis owing to > 50% of epochs being rejected for containing signal ± 100 μV, and two autism and one

non-clinical individual's data were removed for having TTV values > 3SD away from their group mean. These participants were removed from all analyses.

Due to the random presentation order of the tone trains, the number of tones presented varied between 2126 and 2994. On average, 1.15% of trials were rejected according to the artifact rejection criteria (autism = 2.06%, non-clinical = 0.63%, schizophrenia = 0.72%). Independent samples t-tests were used to compare groups on the number of epochs rejected and there were no significant differences detected (autism vs. non-clinical $p = .244$; autism vs. schizophrenia $p = .274$; schizophrenia vs. non-clinical $p = .788$). This resulted in between 292 and 429 standard trials and an equivalent number of deviants. Independent samples t-tests showed that there were no significant differences between groups in the number of standard trials (autism vs. non-clinical $p = .755$; autism vs. schizophrenia $p = .173$; schizophrenia vs. non-clinical $p = .117$) or deviant trials (autism vs. non-clinical $p = .557$; autism vs. schizophrenia $p = .205$; schizophrenia vs. non-clinical $p = .117$) used in the analyses.

A mixed-effects analysis of variance (ANOVA) was run comparing electrode row (frontal, frontocentral, and central) and column (left, central, right) as within-subject variables, and group (autism, schizophrenia, and non-clinical) as the between-subject variable. Pairwise comparisons were used to tease apart significant main effects and were Bonferroni corrected.

Bayes Factors (BF) and Cohen's d effect sizes were also calculated to estimate the magnitude of significant comparisons, to help account for the small sample size in the schizophrenia group. BFs were calculated using Monte Carlo sampling over 50,000 iterations as part of the R packages "effectsize" and "BayesFactor". To assist with the interpretation of the BFs, they were inverted to provide estimates of the probability of the effect occurring under the alternative hypothesis (H1), with larger BFs reflecting a stronger probability that the effect is real. No additional interpretation or thresholds for the size of the effects were used.

Inter-Trial Coherence (ITC) and Event-Related Spectral Perturbation (ERSP) Analyses

To assess ITC and ERSP, epochs from − 250 to 330 ms around stimulus-onset were baseline corrected from − 150 to 50 ms. A wider pre-stimulus baseline window was used to ensure that ITC could be reliably calculated around the onset of the stimulus. Any epochs that contained signal ± 100 µV were automatically rejected from analysis. The power and phase at each frequency between 20 and 100 Hz at each time point was calculated using a Morlet wavelet at 3 cycles and a Hanning-tapered window. This resulted in 41 linearly spaced frequencies where ITC and ERSPs were calculated. Owing to the previous findings of group ITC differences at gamma frequencies, we kept the filtering open. ITC values were then normalized so that an ITC value of 1 was perfect coherence and 0 was no coherence. To compare groups, a random permutation analysis was used and only time points and frequencies where the group differences in ITC and ERSP values were significant ($p < .05$; FDR corrected for multiple comparisons) were highlighted. As the comparisons were conducted over time and frequency, the results are plotted in 2D graphs. To examine where the maximal group differences were over time and at what frequencies, uncorrected one-way ANOVAs were conducted on the ITC and ERSP values. The plots of the F- and p-values for each time point and frequency are shown in Supplementary Materials Figs. S4 and S5.

To assess any relationships between EEG results and demographic or neuropsychological scores, exploratory Spearman's correlations were conducted. Non-parametric correlations were run due to the heavy skew in demographic and in symptom data. To reduce the number of comparisons made, only EEG responses that showed significant group differences were assessed. Age, IQ (for autism and schizophrenia participants), and MATRICS sub-scores for the Brief Assessment of Cognition in Schizophrenia (BACS), processing speed, attention vigilance, working memory, verbal learning, visual learning, reasoning and problem solving, and social cognition (for autism and schizophrenia participants) were assessed.

Table 4 Cohen's d effect sizes for all group comparisons across all electrodes

Group Comparison	Cohen's *d*	
	MMN	TTV
Autism vs. Non-clinical	0.24	0.75
Schizophrenia vs. Non-clinical	0.60	0.62
Autism vs. Schizophrenia	0.77	0.08

Results

ERP Amplitudes

There were significant group differences in MMN amplitude ($F(2,57) = 4.27$, $p = .019$, BF = 2.4 times more likely under H_1; error = 5.91; Fig. 3), due to the schizophrenia group producing a smaller MMN than autism ($p < .001$), and non-clinical groups ($p < .001$; see Table 4 for Cohen's *d* effect sizes). MMN was smallest over the left hemisphere (main effect of hemisphere: $F(2,114) = 26.84$, $p < .001$), and largest in frontal electrodes (main effect of row: $F(2,114) = 21.83$, $p < .001$). The effect of group was largest in the Fz electrode ($F(8,228) = 2.93$, $p = .004$; BF = 6.929715e + 19 times more

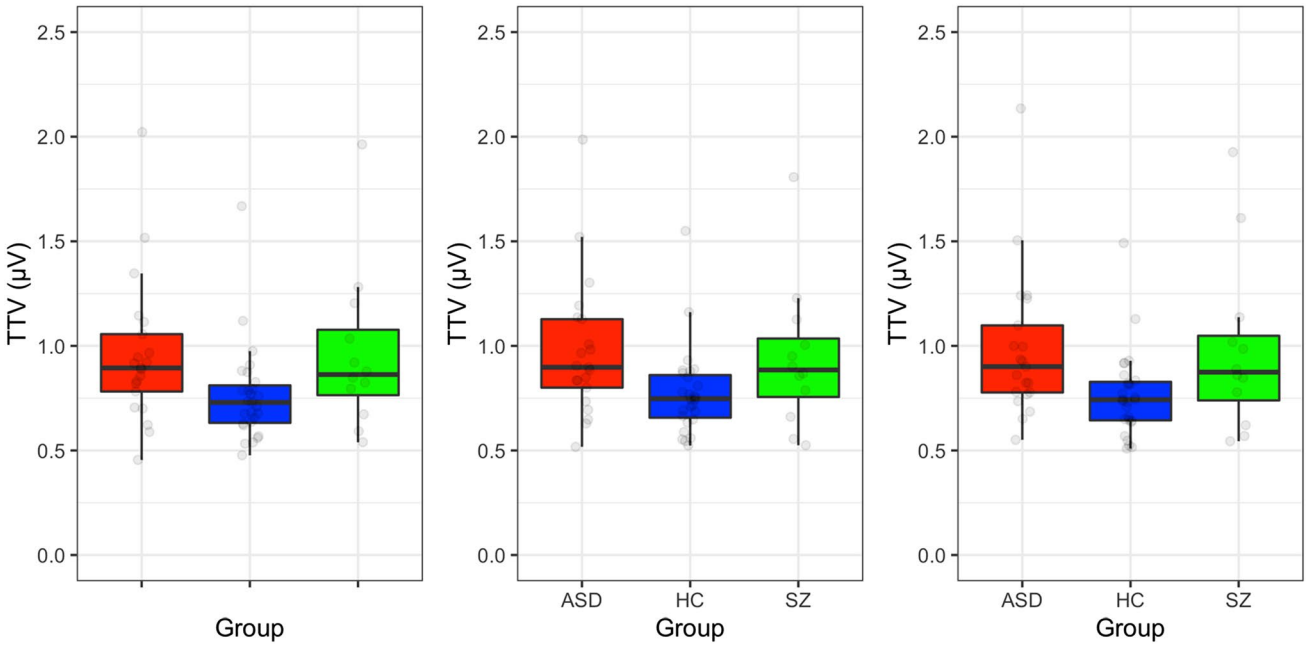

Fig. 4 TTV in the autism, non-clinical, and schizophrenia groups in electrodes Fz, FCz, and Cz

likely under H_1; error = 18.45). Deviant and standard waveforms are shown in Supplementary Materials (Figs. S2 and S3).

As the schizophrenia group were both older and had lower IQ compared to the autism and non-clinical groups, two follow-up analyses of covariance (ANCOVAs) were conducted. The first included age as a co-variate, but because IQ was not collected for the non-clinical group, only the autism and schizophrenia groups were compared for the second ANCOVA so that IQ could be used as a co-variate. The ANCOVA assessing the effect of age as a covariate showed that age was a significant co-variate ($F(24,1020) = 9.79$ $p < .001$) but that accounting for age only strengthened the group differences ($F(2,1020) = 32.34$, $p < .001$). Similarly, the ANCOVA assessing the effect of IQ on the differences between autism and schizophrenia groups showed that IQ was a significant covariate ($F(22,538) = 7.13$, $p < .001$) and strengthened the group differences ($F(1,538) = 118.34$, $p < .001$).

Trial-to-Trial Variability (TTV) in Amplitude

There was a significant main effect of group, where both autism and schizophrenia exhibited greater TTV than non-clinical individuals ($F(2,57) = 3.56$, $p = .035$, BF = 1.8 times more likely under H_1; error = 5.68; pairwise t-tests $p < .001$; see Table 4 for Cohen's *d* effect sizes), and TTV was greatest in the central electrodes ($F(2,114) = 8.50$, $p < .001$, BF = 3.8 times more likely under H_1; error = 1.97; pairwise t-tests $p < .001$). TTV for all three groups for the Fz, FCz, and Cz electrodes are shown in Fig. 4.

MMN amplitude did not significantly correlate with IQ or any of the MATRICS scores, except for verbal learning improving with MMN amplitude in the schizophrenia group only ($r(10) = -0.63$, $p = .039$). However, age was positively correlated with MMN across all three groups ($r(62) = 0.34$, $p < .001$).

Similar to MMN amplitude, TTV did not significantly correlate with MATRICS scores. However, IQ was significantly correlated with TTV in the autism ($r(19) = -0.31$, $p < .001$) and schizophrenia groups ($r(10) = -0.41$, $p < .001$). Age did not significantly correlate with TTV across all three groups ($r(58) = -0.04$, $p = .323$; Fig. 5).

Inter-Trial Coherence (ITC) and Event-Related Spectral Perturbations (ERSPs)

When comparing ITC measures, there were no significant differences between autism, non-clinical, and schizophrenia groups for the entire epoch. Figure 6 shows the ITC values for each group and the group comparison p-values for each time point and frequency. Similarly, there were no differences between groups on ERSP measures either (Fig. 7). Uncorrected F- and p-values over time and frequency from the one-way ANOVA for the ITC comparison are plotted in Supplementary Materials Fig. S4 and for the ERSP comparison in Fig. S5. The maximal group differences appear around the MMN timing in gamma frequencies. To verify that the addition of the schizophrenia group was not obscuring any

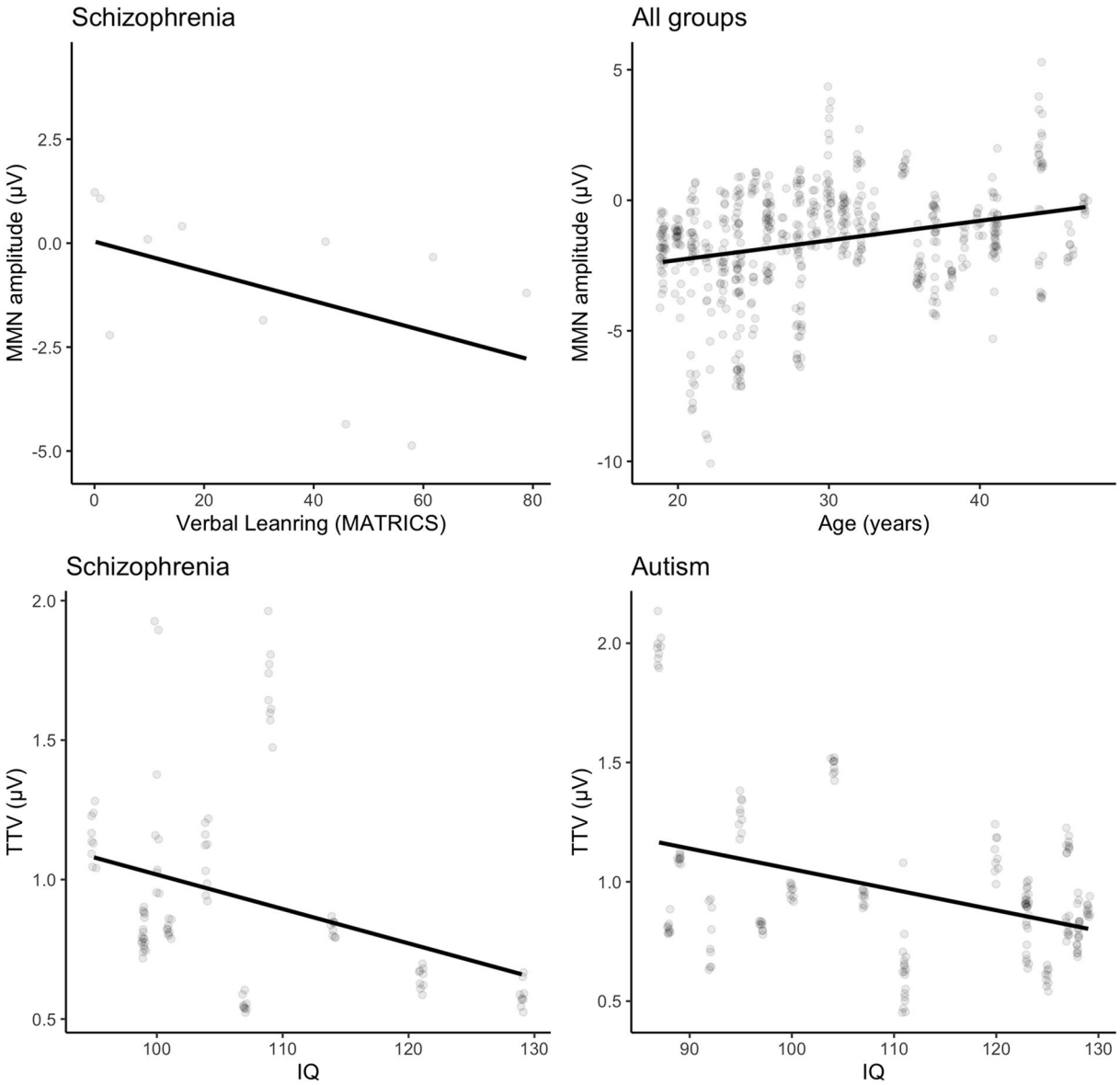

Fig. 5 Scatter graphs of the significant correlations. Top left: MMN amplitude increases with higher verbal learning scores in the schizophrenia group. Top right: MMN amplitude decreases with age across autism, non-clinical, and schizophrenia groups. Bottom: TTV decreasing with IQ in schizophrenia (left) and autism (right)

significant differences between the autism and non-clinical groups in ITC or in ERSPs, the analyses were rerun but only including autism and non-clinical participants. There was still no significant difference between the groups in their ITC (Supplementary Materials Figs. S6 and S7).

Discussion

Atypical sensory processing is characteristic of both autism and schizophrenia, although the exact manifestation of these irregularities differ between the two diagnoses. Here, we focused on auditory deviance detection in the EEG and compared ERP amplitude and timing across groups. The auditory MMN amplitude was significantly reduced in schizophrenia compared to autism and non-clinical participants, but both autism and schizophrenia groups showed greater trial-to-trial variability in their ERPs. However, when examining the timing in the ERPs, there were no significant differences between any pair of groups in inter-trial coherence (ITC) or event-related spectral perturbations (ERSPs). Together, these results suggest that there are differences in auditory deviance detection profiles between autism and schizophrenia, but that

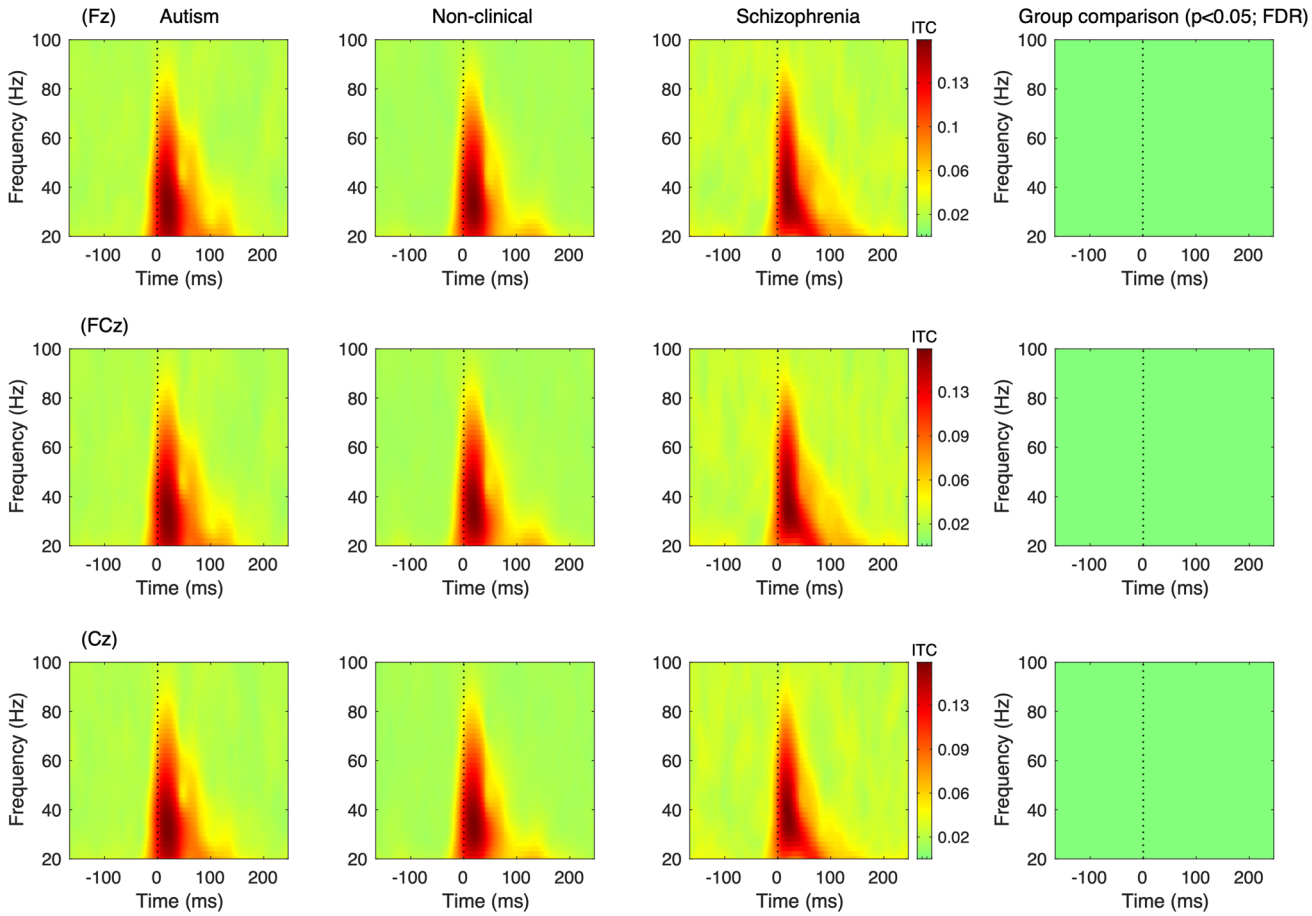

Fig. 6 ITC for autism, non-clinical, and schizophrenia groups in the Fz (top), FCz (middle), and Cz (bottom) electrodes. Group comparisons showed that there were no time points across the 41 linearly spaced frequencies (which make up the whole epoch) where there were significant differences between groups ($p > .05$, FDT corrected)

the differences are only evident in the amplitude of the responses and not in the timing per se.

These findings are consistent with previous reports of hypo-sensitive auditory processing in schizophrenia (Umbricht & Krjles, 2005) and greater TTV in auditory processing in autism (Dinstein et al., 2012; Haigh et al., 2014). Interestingly, a similar pattern of finding hypo-sensitive response amplitudes in schizophrenia compared to autism and non-clinical individuals was identified in the fMRI response in auditory cortices and were mirrored in the visual and somatosensory systems (Haigh et al., 2016). However, in the current study, the schizophrenia group exhibited significantly greater TTV in auditory ERPs compared to non-clinical individuals too (which was not identified in the auditory fMRI response). With regard to the ITC findings, a lack of significant differences between autism and non-clinical individuals in ITC measures have been reported previously (Butler et al., 2017), supporting the theory that the increased TTV in autism is due to variability in response amplitude and not in timing per se. Others have identified group differences but there are some discrepancies as to whether the ITC in autism is greater than (Yu et al., 2018) or less than (Yu et al., 2018; Milne et al., 2019) non-clinical groups, particularly in the theta range.

Surprisingly, there were no significant relationships between ERP responses and MATRICS sub scores, except for larger MMN amplitudes correlating with verbal learning scores in the schizophrenia group only. However, due to the number of correlations conducted, this did not survive multiple comparisons correction. MMN amplitude decreased with age which is typical (Laurens et al., 2020). Interestingly, TTV decreased with higher IQ in both the autism and schizophrenia groups. As we did not measure IQ in the non-clinical group, it is difficult to say whether this is a trend in the general population. However, it does suggest an intricate relationship between stability in the sensory systems and general intelligence.

Sensory responses that contain some variability over time are theorized to enable the system to be more robust when dealing with sensory environments that constantly change,

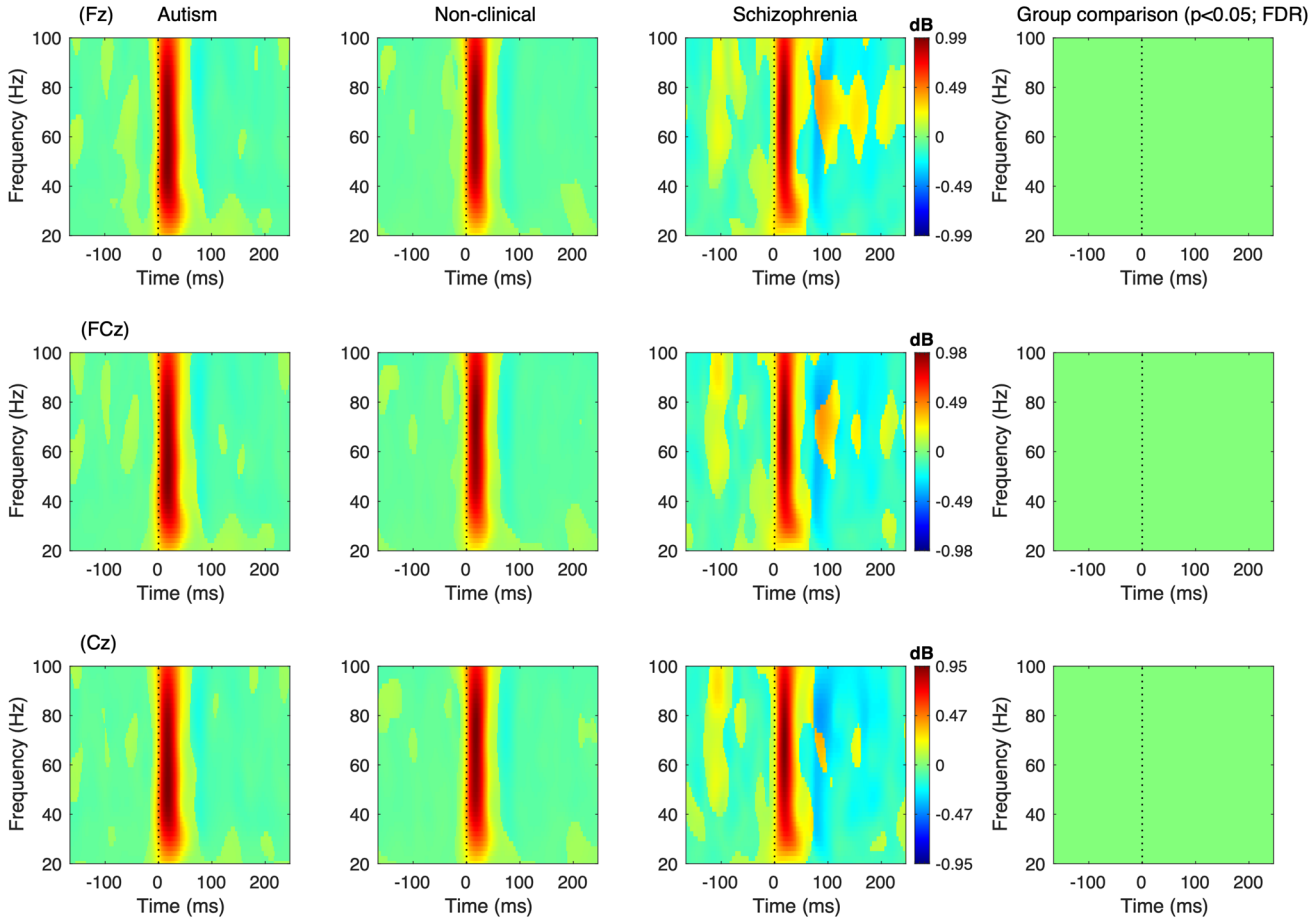

Fig. 7 ERSPs for autism, non-clinical, and schizophrenia groups in the Fz (top), FCz (middle), and Cz (bottom) electrodes. Group comparisons showed that there were no time points (of 41 points) across the whole epoch where there were significant differences between groups ($p > .05$, FDT corrected)

and ensure that small changes in pitch or volume do not grossly disturb the perception of the whole scene (Stein et al., 2005; Faisal et al., 2008; Dinstein et al., 2015; Ermentrout et al., 2016). For example, our visual system responds optimally to the statistical regularities of the natural environment (Attneave, 1954; Barlow, 1961; Field, 1987; Atick 1992; Field, 1994; Olshausen & Field, 1996, 1997), and adapts to the statistical regularities in the sensory environment during development (Schmitt et al., 2014; Dan et al., 1996). When these statistics are violated, the visual system over-responds (Wilkins et al., 1984; Fernandez & Wilkins, 2008; Juricevic et al., 2010; Penacchio et al., 2021; Huang et al., 2003; Coutts et al., 2012). This would explain why the non-clinical individuals also show some TTV, although to a lesser extent than the autism and schizophrenia individuals. Having too much (or too little) variability in the system might be equally detrimental resulting in a chaotic or overly rigid percept.

The greater TTV in auditory processing in autism and in schizophrenia compared to non-clinical individuals suggests that their auditory perception may be unstable. This is based on the assumption that the small amount of variability in auditory responses in non-clinical individuals is not detrimental to their sensory processing. Having reduced stability in their sensory environment may result in the subjective reports of being over-whelmed by sensory stimuli, which in turn may encourage some of the social withdrawal symptoms that are characteristic of both autism and schizophrenia (DSM-V, 2013; Eack et al., 2013). Currently, it is unknown whether highly variable sensory processing in autism and schizophrenia is detrimental to later cognition, and, if so, how much is too much? Identifying methods to reduce the sensory variability would be one approach to examining whether improving the fidelity of the signal impacts later processing and behavioral performance. There is some evidence to suggest that focusing on sensory training causes improvements in cognitive functioning in schizophrenia, such as verbal learning and memory (Fisher et al., 2009, 2010), processing speed (Fisher et al., 2010), and executive and prefrontal functioning

(Dale et al., 2016; for summaries see Vinogradov et al., 2012; Adcock et al., 2009).

A potential mechanism for the increased TTV in autism and schizophrenia is an imbalance in excitatory and inhibitory neurotransmitters. Dopamine dysfunction, for example, has been linked to greater neural noise (Backman et al., 2006; MacDonald et al., 2009, 2012; Li et al., 2001; Lindenberger et al., 2011), and atypical dopaminergic regulation has been linked to sensory irregularities in both autism (Hamilton et al., 2013; Nguyen et al., 2014) and schizophrenia (for a review, see Eyles et al., 2012). Imbalances in neurotransmitters have also been linked to hyper- and hypo-sensory sensitivity too. For example, greater excitation from excess transmitters such as glutamate and/or reduced inhibitory GABAergic activity have both been identified in autism and can contribute to the hyper-sensitivity in sensory processing (Wood et al., 2021; glutamate/glutamine: He et al., 2021; GABA: Umesawa et a., 2020). On the other hand, reduced excitation is theorized to contribute to the hypo-sensitivity in schizophrenia (glutamate: Kantrowitz 2019; GABA: Hoshino et al., 2020). Therefore, while similar mechanisms may be impacted in autism and schizophrenia, the exact manifestation of the perturbed mechanism differs between the diagnoses. Gamma-band power elicited in the auditory steady-state response has been linked to the excitation/inhibition mechanisms (for a review, see Tada et al., 2019) and so a future investigation into group differences in gamma power may identify a mechanism to target for intervention. This possible difference in the perturbed mechanism across the two diagnoses underscores the critical need to explore similarities and differences in sensory profiles between autism and schizophrenia. This is particularly important as these conditions overlap in many behavioral, cognitive, and genetic domains which can obscure the identification of the underlying neurobiology. Further exploration earlier in development would identify the use of these sensory characteristics in being a biomarker for identifying or discriminating between diagnoses, particularly given the behavioral and neuropsychological overlap in autism and schizophrenia profiles (Eack et al., 2013).

There are several limitations in the current study. The first is that the sample size in the schizophrenia group is relatively small, particularly compared to the autism and non-clincial groups. While the effect sizes and Bayes Factors suggest that the smaller MMN and greater TTV in schizophrenia are robust and large enough to be detected with a small sample size, this may have negatively impacted the ITC and ERSP measures. A verification of how timing variability is impacted in schizophrenia compared to autism is warranted. The second is that we do not have IQ scores for the non-clinical group, which limits the ability to claim that there is no evidence of IQ causing the group differences in auditory MMN and TTV measures. This is particularly concerning considering the correlation between TTV and IQ: individuals with autism or schizophrenia with higher IQ tended to exhibit reduced TTV. It may be the case that the non-clinical group had higher overall IQ, and this could be driving the TTV differences. However, the autism group does have a higher average IQ than the schizophrenia group and yet both autism and schizophrenia groups show greater TTV than the non-clinical group. In addition, the autism group had particularly high IQs making it unlikely that the non-clinical group would have had even higher IQs. Finally, IQ did not correlate with MMN amplitude and so there is no evidence that IQ can explain the group differences in MMN. Closer assessment of how IQ is or is not related to auditory processing will help identify the impacts on symptomatology. Third, many of the schizophrenia (nine) and autism (seventeen) participants were on a range of medications and we were unable to account for the effect of medications on auditory responses. Even for medications that are designed to treat the same symptom, for example, antipsychotics to treat psychosis, it is difficult to generalize over the different types of medication (e.g., clozapine compared to risperidone). To complicate things further, only two of our eight schizophrenia participants were on antipsychotics alone. The rest were on additional medications to deal with the side effects of the antipsychotics. While estimated chlorpromazine equivalents have been reported for antipsychotics (Andreasen et al., 2010; Gardner et al., 2010), this cannot be done for other types of medications such as antidepressants or antianxiety medications. For the current study, we only requested that participants describe the type of medication they were on and what it was for, and so cannot attempt to account for estimated chlorpromazine dosage. Fourth, we assumed that the ERPs of auditory processing reflect behavioral sensitivity, which is not the case (Ward, 2019). Our behavioral measures of pitch discrimination and prosody identification (see Supplementary Materials) did not identify any differences in performance between autism, schizophrenia, and non-clinical groups, except for slower reaction times in the autism and schizophrenia groups compared to the non-clinical group. While these tasks were conducted on a subset of individuals and so there may be some limitation of statistical power, it is possible that the tasks were not sufficient to detect subtle group-level differences in behavioral measures of pitch sensitivity.

In summary, adults with schizophrenia produced a smaller MMN and adults with autism produced larger MMNs to changes in pitch compared to non-clinical adults. However, both schizophrenia and autism groups produced greater trial-to-trial variability in the amplitude of their ERPs. In the timing domain, there were no significant group differences in ERSPs or ITCs suggesting that the differences in sensitivity were in the amplitude and not temporal domain. Continued efforts to identify the similarities and differences in

sensory perturbations in autism and schizophrenia will help improve differentiation of the conditions ensuring correct diagnoses and treatment. Future exploration on how auditory sensitivity impacts the different symptom profiles in autism and schizophrenia individually and across diagnoses will identify if auditory sensitivity is a prime target for treatment intervention.

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Author Contributions SMH acquired the funding and was the lead on the project, designed the study, analyzed the data, interpreted the results, and wrote the paper. LVK analyzed the data and assisted in writing the paper. PB helped design the project and collected the data. SME assisted with funding acquisition, participant recruitment and experimental design. DIL assisted with funding acquisition and the experimental design. DFS assisted with funding acquisition, experimental design, data analysis, and interpretation. MB was the mentor on this project and assisted with all levels of the study.

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Data Availability Data are available through the Open Science Framework (https://osf.io/pnvay/) and MATLAB scripts for stimulus presentation and data analysis are on GitHub (SarahMHaigh/AuditoryInAutism).

Declarations

Conflict of interest The authors have no conflicts of interest to declare.

Ethical Approval Protocols were approved by the Institutional Review Board at Carnegie Mellon University and were conducted in accordance with the Declaration of Helsinki.

Informed Consent All participants gave their informed written consent.

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