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ORIGINAL ARTICLE

Preliminary observations on the associations between sensory processing abnormalities and event-related potentials in adults with autism spectrum disorder

Ryo Mizui MD[1] | Kazuhiko Yamamuro MD, PhD[1] | Kosuke Okazaki MD, PhD[2] | Mitsuhiro Uratani MD, PhD[1] | Natsuko Kashida MS[1] | Rio Ishida MS[1] | Manabu Makinodan MD, PhD[1]

[1]Department of Psychiatry, Nara Medical University School of Medicine, Kashihara, Japan

[2]Developmental Center for Child and Adult, Shigisan Hospital, Ikoma-Gun, Japan

Correspondence
Kazuhiko Yamamuro, MD, PhD, Department of Psychiatry, Nara Medical University School of Medicine, 840 Shijo-cho Kashihara, Nara 634-8522, Japan.
Email: muro@naramed-u.ac.jp

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Abstract

Aim: Autism spectrum disorder (ASD) is a neurodevelopmental disorder that is thought to involve a variety of neurophysiological characteristics. Event-related potentials (ERPs) reflect cognitive functions in the brain's cognitive processing. In this study, we investigated differences in P300 and N100 of ERPs between ASD and typically developing groups and focused on the relationship between the components of ERPs and measures of autistic traits and sensory processing characteristics.

Methods: ERPs were measured in 96 subjects in the ASD group and 62 subjects in the age- and sex-adjusted typically developing group. Correlations between each component and the scores of the Autism-Spectrum Quotient Japanese version (AQ-J) and the Adolescent and Adult Sensory Profile (AASP) were also evaluated.

Results: The ASD group showed a significant decrease in the amplitude of N100 at C3. Furthermore, a negative correlation was found between lower amplitude at C3 of N100 and low registered sensory scores in both groups.

Conclusion: Our findings imply that the N100 amplitude at C3 could be a potential indicator for examining the neurophysiological traits of ASD; however, these results should be interpreted with caution due to their preliminary nature. These tentative insights into sensory processing anomalies may be discernible in specific subsets of the ASD population, providing a foundation for future investigative pathways.

KEYWORDS
autism spectrum disorder, event-related potential, N100, sensory processing

INTRODUCTION

Autism spectrum disorder (ASD) is a neurological and developmental disorder that begins to appear shortly after birth and is associated with qualitative deficits in social interaction, communication, and imagination, as well as repetitive and habitual behaviors that can severely interfere with various aspects of family and social life depending on life stage. With a prevalence of approximately 2%, it is considered one of the most common disorders,[1] and understanding the neurophysiological basis of

ASD is important for elucidating the pathophysiology and developing treatments.

Event-related potentials (ERPs) are a type of evoked potential, which are transient, very weak electrical activities recorded during the process of various stimuli input from sensory receptors, such as the ears and eyes, reaching the cerebral cortex about an event. They are said to be an objective indicator of the early stages of information processing and cognitive functions, as they fluctuate reflecting cognitive functions in cognitive processes, such as anticipation, attention, perception, discrimination, and decision-making. They are also used in psychiatric disorders, such as ASD,[2,3] attention-deficit/hyperactivity disorder (ADHD),[4–7] schizophrenia,[8–10] and obsessive–compulsive disorder.[11,12] P300 is a rarely presented late positive waveform that occurs at a latency of approximately 300 ms after a target stimulus.[13] It is known to reflect executive and attentional functions, working memory, event classification, and attentional resource allocation.[14] It is known to reflect executive and attentional functions, working memory, event classification, and attentional resource allocation.[14] Previous studies have found that adult patients with ASD have a longer latency[3] and smaller amplitude[15] of P300 than controls. N100 refers to the negative peak that occurs approximately 100 ms after a sensory stimulus and is particularly well-known for auditory stimuli.[16] N100 reflects the response of the auditory nerve to the brainstem and auditory cortex phase after the presentation of auditory stimuli and the auditory cortex following the presentation of an auditory stimulus is thought to be related to attention, sensory selection, and early information processing. Previous studies have reported that the amplitude of N100 is reduced in childhood ASD.[17] Although sensory abnormalities are often observed and noted in ASD patients, the sensory specificity of ASD was first mentioned in the first report of autism by Kanner and is described as one of the behavioral characteristics observed in autistic children.[18] It has been mentioned frequently since then[19,20] and more than 80% of ASD children have been reported to show abnormal responses to sensory stimuli.[19] In the *Diagnostic and Statistical Manual of Mental Disorders* (fifth edition; DSM-5), the issue of sensory abnormalities in ASD received significant attention[21] and various studies have been conducted since the addition of a new item, sensory hypersensitivity and blunting, to the core symptom "Imaging Disorders with Repetitive and Addictive Behaviors." Problems with sensory abnormalities are found in a variety of senses, including sight, hearing, touch, smell, taste, and proprioception.[22] In particular, sensory abnormality problems in ASD have been reported to be associated not only with core symptoms but also with a variety of clinical features, including anxiety, attention problems, self-injury, problematic and maladaptive behaviors, and sleep disturbances,[23–25] making assessment and intervention important. Although there are several standardized rating scales for the assessment of sensory abnormality problems, objective assessment is difficult because of the highly subjective component and inevitable rater bias. In the DSM-5, if problems with sensory characteristics are missed, ASD may not be diagnosed, and from this perspective, objective assessment of sensory characteristics should be studied. ERP is attracting attention as a means of objectively assessing sensory characteristics.

The purpose of this study was to examine differences in P300 and N100 of the ERPs between an ASD group and a typically developing (TD) group and to focus on the relationship between the components of the ERP and sensory processing. Through these results, we hope to gain new insights into the characteristics and neurophysiological background of sensory processing in ASD.

METHODS

Participants

Ninety-six Japanese patients with ASD (68 males and 28 females, mean age = 28.92 ± 8.62 years) were recruited from the outpatient department of psychiatry at Nara Medical University (Table 1). ASD was accepted only if it was diagnosed according to the criteria and evaluated by an experienced psychiatrist.

All patients were diagnosed with ASD according to DSM-5[21] and the Japanese version of the Autism Diagnostic Observation Schedule, second edition (ADOS-2),[26] and autistic traits were also examined by the Autism Spectrum Quotient Japanese version (AQ-J).[27] The control group consisted of 62 age- and gender-matched healthy subjects (43 males, 19 females, mean age = 28.69 ± 5.95 years). They were recruited through local print advertisements (Table 1). In the control group, psychiatric diagnosis was made by standard clinical assessment, including psychiatric evaluation and a structured clinical

TABLE 1 Participant characteristics.

	Control *n* = 62		Patients with ASD *n* = 96			
	Mean	SD	Mean	SD	*t*-Value	*p*-Value
Sex (male/female)	43/19		68/28		NA	0.84
Age (years)	28.69	5.95	28.92	8.62	0.18	0.86
FIQ	108.56	8.91	103.03	14.68	2.67	<0.01
AQ-J (total)	17.73	7.06	35.01	13.37	9.37	<0.01

Note: The χ^2 test was used for testing group differences. Otherwise, *t*-tests were used.

Abbreviations: AQ-J, Autism-Spectrum Quotient Japanese version; ASD, autism spectrum disorder; FIQ, full-scale IQ; NA, not applicable; SD, standard deviation.

interview for DSM-5 Axis I Disorders Non-Patient Edition (SCID-NG). Control group participants did not have a history of psychiatric, neurological, or developmental disorders, and were asked to complete the Mini-International Neuropsychiatric Interview to exclude their current or past psychiatric history. Moreover, we evaluated them using the AQ-J, and a score <32 was used as the enrollment requirement. No psychiatric disorders were identified in the DSM-5. Exclusion criteria for both groups included any neurological disorder, head injury, serious medical condition, or history of substance abuse/dependence. The full-scale intelligence quotient (FIQ) of each participant was estimated using the Similarities and Symbol Search subsets of the Wechsler Adult Intelligence Scale Third Edition52, and those with FIQ scores below 70 were identified by a trained psychologist and excluded from the study. Finally, 96 ASD patients and 62 controls were enrolled in the study.

This study was approved by the Institutional Review Board of Nara Medical University, and written consent for participation was obtained from all participants.

Assessment of ASD symptoms

The Autism-Spectrum Quotient (AQ), created by Baron-Cohen et al. based on the autism spectrum hypothesis, is a standardized questionnaire designed to assess ASD tendencies and is widely used for ASD screening and research.[28] The Japanese version (the AQ-J) has been proven to have acceptable reliability and validity in screening young adults of normal intelligence with ASD, with the same cutoff points as the original AQ.[28–30] The AQ-J is a self-rated instrument that can measure the extent of ASD characteristics or its broad phenotype in adults with normal-range intelligence. The AQ consists of 50 items in total. The AQ can be used not only for clinical screening but also to measure individual differences in autistic tendencies in TD adults, which is beneficial for both diagnosis and research.[27]

Assessment of sensory characteristics

The Sensory Profile created by Dunn is a standardized measure of sensory processing tendencies that uses a conceptual model to assess patterns of sensory processing into four quadrants based on research with TD children.[31] The model assumes that a continuum of neurological thresholds and a continuum of behavioral responses and self-regulation interact with each other. A neurological threshold is the amount of stimulus required for a neuron or neuronal system to respond, with a high threshold at one end of this continuum and a low threshold at the other end. Behavioral response/self-regulation indicates how a person responds in response to that threshold, with passive responses to sensory stimuli at one end of this continuum and active responses to sensory stimuli at the other end. These two continua are assumed to intersect each other, and the pattern of sensory processing is described by four quadrants (low registration, sensation seeking, sensory sensitivity, and sensory avoidance) that are delimited by the continuum. The Sensory Profile applies to ages 3–10 years and is a peer-rated questionnaire, but a self-rated Adolescent/Adult Sensory Profile (AASP) applicable to ages 11–65 years has also been developed.[32] The Japanese version of the Adolescent/Adult Sensory Profile applies to ages 11–82 years.[33]

ERP measurements

The N100 and P300 were obtained by auditory oddball tasks, based on the evoked potential measurement guidelines, and NEC Multi Stim II (NEC) was used as the auditory stimulator. Based on the guidelines for measuring evoked potentials,[34] the auditory oddball task was used to induce the N100 and P300 components. N100 and P300 were analyzed between 200 ms before stimulation and 750 ms after stimulation. Frequent nontarget stimuli were presented as 1000-Hz bursts ($p = 0.8$) and infrequent targeted stimuli were presented as 2000-Hz tone bursts ($p = 0.2$). Both types of stimuli were presented with an intensity of 50 ms, 80 dB at 1.5 s intervals, and a rise/fall time of 10 ms. Both stimuli were randomly presented using headphones. All participants were instructed to keep their eyes open, listen carefully to the target stimuli, and press the response button as soon as they heard each target stimulus. The time for the auditory oddball task was 240 s. The sample rate was 1000 Hz.

Recording and analysis

ERP was recorded using an MEB2200 evoked potential measuring device (Nihon Kohden). Electroencephalograms (EEGs) were recorded at Fz, Cz, Pz, C3, and C4 positions on the scalp using disk electrodes. The impedance of all electrodes was set to ≤5 kΩ. The bilateral ear lobes were used as the reference electrode sites. An artifact-free response to the stimulus was added and averaged after excluding tests with EEG amplitude ≥100 μV. Trials with artifacts due to muscle activity and complex eye movements were excluded by initial visual examination of raw data by experienced scientific researchers. Finally, the data were corrected for eye movement artifacts.[35] Each study was performed only once to prevent participants from getting tired. For infrequent target stimuli associated with N100 and P300, the sum of 30 reactions was averaged. N100 was identified as a negative wave with a peak latency between 80 and 180 ms, and P300 was identified as a positive wave with a peak latency between 250 and 550 ms, and the average latency and amplitude of them were calculated.

Statistical analyses

We used PASW Statistics 18.0J for Windows (SPSS) for the statistical analyses. We conducted a statistical comparison of

participant characteristics for each group using two-tailed paired *t*-tests. We compared the latencies and amplitudes of N100 and P300 components, AQ-J scores, and AASP scores, between the control group and the ASD group using the Student's *t*-test. The significance level was set at $p < 0.05$. Spearman correlations were used to assess associations between AQ-J scores, AASP score, and the latencies and amplitudes of each component. Bonferroni correction was conducted to adjust the results of all analyses. Bonferroni-adjusted *p*-values are reported and *p*-values of 0.05 were considered statistically significant.

RESULTS

Demographic data

Demographic characteristics are presented in Table 1. The participant groups did not differ in terms of sex ($\chi^2 = 0.0394$, $df = 1$, $p = 0.84$) or age ($t = 0.178$, $df = 1$, $p = 0.859$). While they differed in terms of average FIQ ($t = 2.67$, $df = 15$, $p = 0.0085$).

Comparison of N100 and P300 component characteristics between patients with ASD and TD individuals

We show the individual average waveforms in Figure 1. We found that the grand average of N100 amplitude at C3 in patients with ASD was smaller than in TD individuals ($t = 2.79$, $df = 2.7$, $p < 0.05$). In contrast to the difference in N100 amplitude observed between the two groups, we found no significant differences in N100 latency and P300 amplitude, latency observed between the two groups. Although we have conducted to control the effect of FIQ on ERP components, we found that FIQ has no associations, as a covariate, with each ERP component (Tables 2 and 3).

Comparison of AQ-J scores between patients with ASD and TD individuals

We found that the scores on all AQ-J subscales were higher in patients with ASD than in TD groups. The total score of AQ-J in the

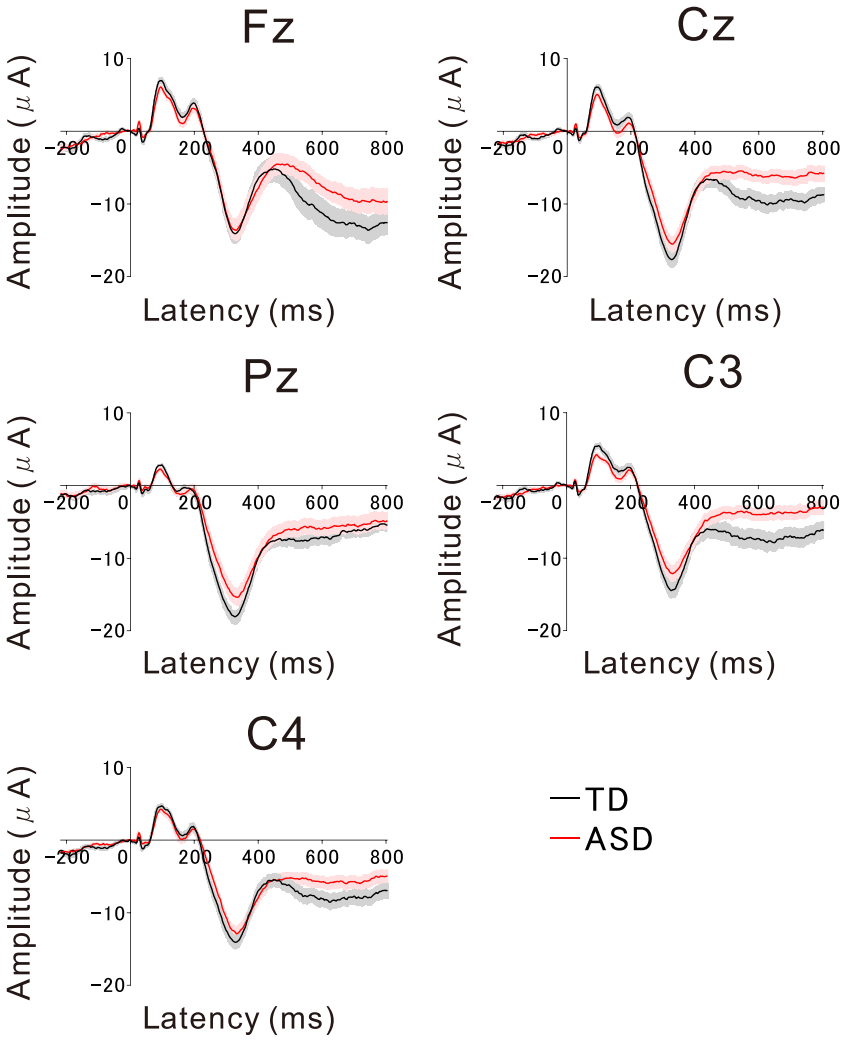

FIGURE 1 Grand mean waveforms of the N100 and P300 components from the autism spectrum disorder (ASD) group and the typically developing (TD) control group.

TABLE 2 Amplitudes and latencies of N100 components.

	Control $n = 62$		Patients with ASD $n = 96$			
	Mean	SD	Mean	SD	*t*-Value	*p*-Value
N100 amplitude (uV)						
Fz	7.74	3.62	6.75	3.92	1.60	0.11
Cz	6.97	2.92	6.04	3.44	1.77	0.08
Pz	3.80	2.87	3.53	3.33	0.52	0.60
C3	6.51	3.12	5.15	2.89	2.79	<0.01
C4	5.61	2.81	5.32	3.01	0.62	0.54
N100 latency (ms)						
Fz	94.27	9.39	94.27	8.74	0.65	0.52
Cz	94.24	10.02	93.91	9.33	−0.37	0.83
Pz	92.87	11.39	93.50	9.58	−0.37	0.71
C3	94.94	10.49	93.55	9.55	0.86	0.39
C4	93.97	9.92	93.65	10.02	0.20	0.84

Note: The *t*-tests and Bonferroni corrected were used for testing group differences.

Abbreviations: ASD, autism spectrum disorder; SD, standard deviation.

TABLE 3 Amplitudes and latencies of P300 components.

	Control $n = 62$		Patients with ASD $n = 96$			
	Mean	SD	Mean	SD	*t*-Value	*p*-Value
P300 amplitude (uV)						
Fz	−15.32	10.92	−15.32	17.68	−0.01	0.99
Cz	−18.88	8.50	−16.90	8.50	−1.13	0.26
Pz	−19.76	7.03	−17.08	9.92	−1.85	0.07
C3	−16.03	8.64	−13.95	11.52	−1.21	0.23
C4	−15.62	7.25	−14.22	11.17	−0.87	0.39
P300 latency (ms)						
Fz	323.55	23.87	329.60	28.20	−1.40	0.16
Cz	323.90	24.09	329.22	28.33	−1.22	0.22
Pz	323.68	24.08	330.85	29.67	−1.60	0.11
C3	324.61	24.28	331.00	27.86	−1.48	0.14
C4	324.87	23.97	331.11	29.07	−1.41	0.16

Note: The *t*-tests and Bonferroni corrected were used for testing group differences.

Abbreviations: ASD, autism spectrum disorder; SD, standard deviation.

ASD group was higher than that in the TD group ($t = -9.37$, $df = 15$, $p < 0.05$). Further, patients with ASD had higher social skill scores compared with TD individuals ($t = -4.92$, $df = 15$, $p < 0.05$), and attention switching ($t = 10.63$, $df = 156$, $p < 0.05$) local details ($t = -4.60$, $df = 15$, $p < 0.05$) communication ($t = -10.54$, $df = 156$; $p < 0.05$), and imagination ($t = 6.23$, $df = 15$; $p < 0.05$) in the ASD group were higher than those in the control group (Table 4).

Comparison of AASP scores between patients with ASD and TD individuals

We found that the scores on several AASP subscales were higher in patients with ASD than in controls. Patients with ASD had higher low registration scores compared with TD individuals ($t = 9.68$, $df = 156$, $p < 0.05$), and sensory sensitivity ($t = 6.44$, $df = 156$, $p < 0.05$) and sensation avoiding ($t = 8.07$, $df = 156$, $p < 0.05$) in the ASD group were higher than those in the control group (Table 4).

Correlations between N100 amplitude and participant characteristics

We conducted a partial correlation analysis to investigate the relationship between N100 amplitude and AQ-J scores, AASP scores, controlling for FIQ as a covariate, because we aimed to elucidate the unique associations between ERP components and sensory hypersensitivity, independent of the influence of FIQ. In all participants, negative correlations were found between N100 amplitude at C3 and low registration scores of AASP ($\rho = -0.205$, $p < 0.05$) (Tables 5 and 6).

DISCUSSION

To the best of our knowledge, this study is the only study to examine the relationship between abnormal ERP and abnormal sensory processing in adult ASD patients.

The present study revealed that the amplitude at C3 of N100 was significantly lower in the ASD group. Baruth et al. reported a reduction in the amplitude of the N100 in individuals with ASD, which is consistent with our findings.[36] N100 reflects the response of the auditory nerve to the brainstem and auditory cortex phase after auditory stimulus presentation and is thought to be related to attention, sensory selection, and early information processing.[16] This suggests that auditory processing abnormalities in ASD are at least in part due to result of atypicality that occurs relatively early in the cognitive process from the auditory nerve to the brainstem and auditory cortex. In addition, the superior temporal gyrus is thought to be one of the main regions of N100, and magnetic resonance imaging studies in other modalities have reported a low density of gray matter near the superior temporal gyrus in ASD patients, which is associated with language impairment, confirming this result.[37,38] The superior temporal gyrus is thought to be involved in face recognition, speech processing, and processing of social information, suggesting that impaired superior temporal gyrus function may affect ASD symptoms.[39] Taken together, the N100 amplitude may reflect some kinds of sensory abnormality, such as abnormal auditory processing related

TABLE 4 Participants score of AASP, AQ-J.

	Control $n = 62$		Patients with ASD $n = 96$			
	Mean	SD	Mean	SD	*t*-Value	*p*-Value
AASP						
Low registration	25.21	6.54	39.41	10.28	9.68	<0.01
Sensation seeking	37.73	7.83	35.49	8.12	1.71	0.09
Sensory sensitivity	31.55	7.63	98.04	12.43	6.44	<0.01
Sensation avoiding	31.05	8.12	43.92	10.72	8.07	<0.01
AQ-J						
Total	17.73	7.06	35.01	13.37	9.37	<0.01
Social skill	4.19	2.83	9.40	8.00	4.92	<0.01
Attention switching	3.84	2.01	7.29	1.98	10.63	<0.01
Local details	3.77	2.18	5.43	2.23	4.60	<0.01
Communication	2.58	2.13	6.57	2.44	10.54	<0.01
Imagination	3.34	2.03	6.57	2.21	6.23	<0.01

Note: The *t*-tests and Bonferroni corrected were used for testing group differences.

Abbreviations: AASP, Adolescent/Adult Sensory Profile; AQ-J, Autism-Spectrum Quotient Japanese version; ASD, autism spectrum disorder; NA, not applicable; SD, standard deviation.

TABLE 5 Correlations between the N100 components and AASP scores.

	N100 amplitude					N100 latency				
	Fz	Cz	Pz	C3	C4	Fz	Cz	Pz	C3	C4
AASP										
Low registration	−0.193	−0.198	0.090	−0.218*	−0.137	−0.084	−0.006	−0.023	−0.029	−0.069
Sensation seeking	0.180	0.079	0.050	0.114	0.051	0.002	0.051	0.044	0.013	0.037
Sensory sensitivity	−0.051	−0.131	−0.031	−0.116	−0.052	−0.052	−0.008	−0.027	−0.043	−0.032
Sensation avoiding	−0.020	−0.095	−0.040	−0.072	−0.010	−0.104	−0.057	−0.085	−0.102	−0.096

Note: Pearson's correlations were performed for all participants.

Abbreviation: AASP, Adolescent/Adult Sensory Profile.

*$p < 0.05$.

TABLE 6 Correlations between the N100 components and AQ-J scores.

	N100 amplitude					N100 latency				
	Fz	Cz	Pz	C3	C4	Fz	Cz	Pz	C3	C4
AQ-J										
Social skill	0.075	0.093	0.187	0.063	0.120	0.038	0.059	0.042	0.082	0.063
Attention switching	−0.086	−0.152	−0.105	−0.198	−0.072	−0.015	0.022	−0.023	0.012	−0.012
Local details	0.020	−0.034	−0.031	−0.085	0.019	−0.091	−0.061	−0.052	−0.069	−0.088
Communication	−0.108	−0.170	−0.093	−0.205	−0.108	−0.068	−0.020	−0.051	−0.048	−0.022
Imagination	0.077	0.070	0.056	−0.040	0.052	−0.081	−0.022	−0.046	−0.058	−0.015

Note: Pearson's correlations were performed for all participants.

Abbreviation: AQ-J, Autism-Spectrum Quotient Japanese version.

to the superior temporal gyrus, suggesting an association with ASD symptoms, including language impairment related to the superior temporal gyrus.

On the other hand, no significant differences were found in the latency of the N100 or P300 component. Several previous studies of ASD patients have found inconsistent ERP abnormalities. For the P300 component, some studies have reported a shortened latency,[40] while others suggest prolonged latency.[3,41] Furthermore, the amplitude of P300 is similarly inconsistent, with some studies reporting a decrease in amplitude,[42–44] and others indicating an increase.[17,41,45,46] In the present study, ASD patients showed a trend-level amplitude decrease in the P300 component ($p = 0.07$). The possible reason for this inconsistent finding is that the decrease in P300 amplitude may be just at the threshold of detection using this ERP paradigm, and thus the finding of statistical significance may be highly dependent on the subject group evaluated. For the N100 component, the scientific consensus remains varied. Some studies show an increased amplitude,[3,47] while others suggest a decrease.[17,36,48] Latency findings for the N100 are also inconsistent, with certain studies indicating prolonged latency[36] and others reporting a shortened latency.[45,48]

The variability observed in these previous research outcomes about ERPs of ASD can be attributed to several factors, including differences in research methodologies, assessment tools, and sampling of participants.[49] However, our study distinguishes itself by utilizing the ADOS-2, a diagnostic tool known for its high reliability and validity in the context of ASD.[50,51] This use of ADOS-2 increases the reliability of our findings and positions our study as having distinct value, setting our study apart from many others in the field. Accordingly, our study offers nuanced perspectives on the previously inconsistent findings pertaining to ERP alterations in ASD, specifically with respect to the N100 and P300 components. However, the relatively modest effect sizes observed in our data call for a cautious interpretation of these insights. Subsequent research is warranted to delineate the extent of these ERP changes using a larger sample size and more targeted sensory modalities more precisely. Furthermore, a negative correlation was found across participants between amplitudes of N100 at C3 and low registration scores of AASP. This suggests that abnormalities in sensory processing may affect not only ASD but also the TD group. Since the distribution of severity scores for autistic symptoms and autistic behavioral characteristics is continuous with no discontinuity points in the general population,[52,53] it has been considered that there may be continuity between ASD and normal participants in sensory processing as well as ASD characteristics.[54] The results of the present study support that hypothesis and suggest that N100 may be useful as an indicator of their sensory processing characteristics. On the other hand, this study found no significant correlation between the N100 component and each score of AQ-J subitems. This suggests that N100 and AQ-J may be assessing different aspects of ASD symptoms.

The main limitation of the present study is the presence of a mismatch between task stimuli and AASP. Specifically, the task stimulus in our experiments was an auditory oddball task, but the AASP was used as a tool that also assessed nonauditory stimulus modalities. Therefore, it is possible that a direct correspondence between the task stimuli and AASP has not been established. In the future, a more auditory-specific sensory assessment tool may reveal more direct and specific associations.

Integrated evaluation with other neurophysiological measures is needed to generalize the results of this study.

Furthermore, another limitation of this study is the inclusion of individuals with ASD who also have comorbid psychiatric disorders, which may confound the specificity of findings to ASD alone. Additionally, the presence of psychotropic medication use among some participants in the disorder group could not be controlled for, possibly influencing the neurophysiological measures observed.

CONCLUSION

The study observed a modest reduction in the N100 amplitude at C3 in adults with ASD when compared to healthy controls. Additionally, there was a mild negative correlation between the diminished N100 amplitude and the low registration score of the AASP, suggesting a tentative link between sensory processing traits and ERP variability. It is anticipated that future research will explore this association with greater specificity by employing sensory modality-specific assessment tools.

AUTHOR CONTRIBUTION

Ryo Mizui: Conceptualization; methodology; investigation; data curation; formal analysis; writing—original draft; writing—review & editing. **Kazuhiko Yamamuro**: Conceptualization; methodology; writing—review & editing. **Kosuke Okazaki**: Conceptualization; methodology; investigation. **Mitsuhiro Uratani**: Investigation. **Natsuko Kashida**: Investigation; data curation; formal analysis. **Rio Ishida**: Investigation; data curation; formal analysis. **Manabu Makinodan**: Conceptualization; methodology; supervision. All authors have read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data are available from the corresponding author upon request.

ETHICS APPROVAL STATEMENT

This study was approved by the Institutional Review Board of Nara Medical University, and written consent for participation was obtained from all participants.

PATIENT CONSENT STATEMENT

All study participants provided written informed consent according to the approved study.

CLINICAL TRIAL REGISTRATION

This study was not conducted as a clinical trial, therefore this section is not applicable.

ORCID

Ryo Mizui http://orcid.org/0009-0008-9836-2128
Kazuhiko Yamamuro http://orcid.org/0000-0002-4362-3262

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