



Title	Eye gaze and cerebral blood flow activation while watching social movies in children with autism spectrum disorder
Author(s)	吉田, 絢香
Citation	大阪大学, 2023, 博士論文
Version Type	VoR
URL	https://doi.org/10.18910/92007
rights	
Note	

The University of Osaka Institutional Knowledge Archive : OUKA

<https://ir.library.osaka-u.ac.jp/>

The University of Osaka

Eye gaze and cerebral blood flow activation while watching social movies
in children with autism spectrum disorder

(自閉スペクトラム症児における社会的相互作用の動画視聴時の視線と
脳血流量の変化)

大阪大学大学院
大阪大学・金沢大学・浜松医科大学・千葉大学・福井大学
連合小児発達学研究科
小児発達学専攻

吉 田 絢 香

2 0 2 3 年 2 月 博士学位論文

Eye gaze and cerebral blood flow activation while watching social movies in children with autism spectrum disorder

Ayaka Yoshida¹, Haruo Fujino^{1*}, Tomoka Yamamoto², Atsuko Ishii², Ikuko Mohri¹, Hiroko Okuno³

¹Department of Child Development, United Graduate School of Child Development, Osaka University, Suita, Osaka, Japan

²Molecular Research Center for Children's Mental Development, United Graduate School of Child Development, Osaka University, Suita, Osaka, Japan

³Graduate School of Nursing of Health and Human Science, Osaka Metropolitan University, Habikino, Osaka, Japan

*Correspondence:

Haruo Fujino

Department of Child Development, United Graduate School of Child Development, Osaka University, Yamadaoka 2-2, Suita 565-0871, Osaka, Japan

Email address: fjinoh@kokoro.med.osaka-u.ac.jp

Abstract

Children with autism spectrum disorder (ASD) have difficulties with social cognition compared to neurotypical children. Several studies have suggested that eye gaze abnormalities characterize social cognition deficits in children with ASD, and are related to specific differences in their brain activity. To examine the characteristics of perception of social situations, we compared eye gaze, cerebral blood flow, and the understanding of the social communication movies in Japanese children with and without ASD. The participants included 20 children with ASD, 18 children without ASD, and 16 adults without ASD. Their eye gaze and cerebral blood flow responses while watching the stimuli from four social communication situations movies were measured using an eye-tracker and functional near-infrared spectroscopy. We compared the differences in social cognitive abilities between children groups using Mann–Whitney's U tests. There were no significant differences between the two groups with respect to language tasks, gaze values, or changes in cerebral blood flow after Bonferroni correction. No statistically significant correlations were observed between the variables. Further research is required to characterize behavioral and cerebral activation towards social stimuli in children with ASD.

Keywords: autism spectrum disorder, near-infrared spectroscopy, eye movements, eye-tracking, communication, social interaction, natural scene

INTRODUCTION

Autism spectrum disorder (ASD) is characterized by qualitative impairment in interpersonal interactions [1]. Previous studies have shown that people with ASD have difficulty in interpreting intentions of people in complex social situations [2]. Difficulty in interpreting other people has been investigated in various experimental studies [3]. The impairment in interpretation of others' intentions may be related to difficulties in extracting essential information from their interactions, which suggest deficit in understanding of social cues (e.g., facial emotion, body action, and prosody) [4–7]. In addition to the evaluation of child behavior, recent studies have applied various devices, such as eye tracker and functional near-infrared spectroscopy, to detect more subtle neurophysiological differences between children with and without ASD.

Recently, cumulative evidence has suggested that abnormalities in eye gaze while viewing social stimuli are associated with impairment of social cognition in ASD [8–11]. People perceive and process verbal (e.g., verbal content) and nonverbal messages (e.g., facial expressions, physical signs, and tone of voice) during social interactions. These messages are important cues in inferring the emotional state of others, which are called social cues [12]. An option to investigate the process of social cognition is to analyze the behavior of individuals while watching movies involving social interactions. In dynamic social interactions, the situation changes continuously, whereas static stimuli (e.g., pictures) do not have such properties. Therefore, video stimuli may better detect the cognitive characteristics of people with ASD than static stimuli [12,13]. For example, Lönnqvist et al. [14] examined the association between eye gaze and context comprehension in adults with and without ASD using movies as they involve social communication. The stimulus movie had the following script: four women were chatting around a table. One woman offered the others sandwiches; however, she dropped the last sandwich while offering the fourth lady. This woman whose sandwich was dropped was briefly apologized to. While verbally she said, “It’s okay,” nonverbal messages

indicated that she did mind it. The study found that adults with ASD showed worse performance in understanding the situation of the stimulus movie, and their eye gaze on social cues in the stimulus and comprehension of the situation were positively correlated. [14]. Thus, understanding social communication may be influenced by gaze behaviors in individuals with ASD. Although children are often faced with situations involving communication that include both verbal and nonverbal messages, research on such social communicative situations in school-aged children is limited.

Functional near-infrared spectroscopy (fNIRS) is a non-invasive method for measuring oxy- and deoxy-hemoglobin (oxy-Hb and deoxy-Hb) levels in cerebral blood flow using near-infrared light. It is a useful instrument for examining brain activity during cognitive tasks in children [15–18]. A previous study in children with ASD reported differences in the response pattern of cerebral blood flow measured by fNIRS [19], although the findings are inconsistent [19–22].

While previous studies showed children with ASD show different patterns of eye gaze and brain activity while performing social cognition tasks compared to children without ASD, most of the studies did not investigate the characteristics using both eye-tracker and fNIRS. It would be worthwhile examining both patterns simultaneously and investigating the relationship between them. The aims of the present study was to investigate difference in eye gaze behavior and responses in cerebral blood flow, the association between verbal comprehension and eye gaze, and the association between eye gaze and cerebral blood flow while watching movies involving social interactions in children with and without ASD.

METHODS

Participants

Participants were recruited between July 2017 and August 2018. Thirty children diagnosed with ASD by experienced pediatricians based on the Diagnostic and Statistical Manual of Mental Disorders criteria were recruited from the Department of Pediatrics of the Osaka University Hospital. Eighteen typically developing children aged 6–12 years were recruited through community advertisements, and 20 typically developed adults were recruited from the Osaka University using online advertisements (Table 1). Adult participants were included to provide information about the response to the tasks in line with a previous study [21]. Participants who satisfied the following criteria for the Autism-Spectrum Quotient (AQ) were included: a) $AQ \geq 25$ for children with ASD; b) $AQ < 25$ for children without ASD; and c) $AQ < 33$ for adults without ASD. Participants with an intelligence quotient (IQ) of less than 75, as assessed by the Wechsler Intelligence Scale for Children-Third and Fourth Edition or Wechsler Adult Intelligence Scale-Third Edition were excluded from the study. Written informed consent was obtained from the parents after the study's purpose and procedures were explained to them. This study was approved by the Research Ethics Review Committee of Osaka University Hospital (Ref: 14408) and conducted in accordance with the Declaration of Helsinki.

[Table 1]

Stimuli

Four video stimuli were prepared for this experiment : chatting scene (54 s), leaving out scene (30 s), stress-provoking scene (16 s), and class-disturbing scene (25 s). For the video of “chatting scene,” four children were sitting around a table and chatting, then a sandwich meant for a girl was dropped by another girl (Table 2).

[Table 2]

For the chatting scene, the content of the video stimulus was intended to replicate the social communication scene in the study by Lönngqvist et al. [14], but the performers were changed from adults to children in order to reduce the difference in age between the performers and the current participants. Three targets were prepared for the video similar to the previous study: Person 1, a person who felt negative emotions (a girl); Person 2, who evoked negative emotions in Person 1 (another girl); and Object, that interested the viewers (sandwich). The movie was divided into two parts: Period 1 was the time between 29.4 to 30.4 s from the start of Movie 1 (Person 2 dropped Person 1's sandwich) and Period 2 was the time between 30.4 to 40.0 s (Person 1 shows verbal and nonverbal messages in response to the event that occurred in Period 1).

Three other movies were prepared because the scene involving the four children might not be familiar to children. The scenes of these movies were developed to meet the following criteria: 1) Person 1 showed negative emotions, such as sadness or frustration through their facial expression and 2) the situation was an everyday situation for children in elementary school. Based on a pilot survey on 261 elementary school children (aged 7–11), three movies were selected that evoked negative emotions in 80% or more of the school children (leaving out the stress-provoking and class-disturbing scenes).

Three targets were prepared for the video similar to the one with the chatting scene: Person 1, a person who felt negative emotions; Person 2, who evoked the negative emotions in Person 1; and an Object that interested the viewers. The details of the stimuli are presented in Table 2.

Procedures

Participants were presented with the four video clips. Eye gaze and cerebral blood flow were measured using an eye tracker and fNIRS, during the experiment. Before viewing the movies, the participants were informed that they would be asked to answer questions about the video clips after watching each video clip. The experiment was conducted in a soundproof room, and the participants were seated in front of a monitor that presented the video stimuli. We asked the participants to maintain a stable posture, as far as possible, during the measurement to avoid artifacts. Four video clips were presented in random order. Each stimulus was preceded by at least a 30 s resting period (fixation) until the blood flow returned to baseline. The average total time of the experiment was approximately 15 min. The timeline of the experiment is shown in Appendix Figure A1.

Understanding of the situations

The verbal tasks were in the Japanese-translated version developed by Lönnqvist et al.[14], and included four questions on the comprehension of the internal state of the persons in the movies and a control question to check whether participants watched the movie. Participants who failed to answer the control question (for example, “What was the thing that fell?” for the chatting scene) were excluded from the analysis because they did not remember the movie's content. Similar questions were developed for the other three videos.

Responses for the verbal task were scored on a three-point scale (0–2) for each question based on the scoring criteria of the original study [14]. Two raters scored the responses. The inter-rater reliability of the two independent raters was estimated using intraclass correlation coefficients (ICC). The ICCs were sufficiently high for the current study (ICC = .78 for chatting scene; ICC = .87 for leaving out scene; ICC = .87 for stress-provoking scene; ICC = .68 for class-disturbing scene). The average rating scores were

used as verbal task scores. The total scores ranged from 0 to 8, with higher scores indicating a better understanding of the social interaction in the stimuli by the participant.

Measurement of eye gaze

A Tobii TX300 eye tracker (Tobii Technology K.K., Tokyo, Japan) and Tobii Studio 3.3 software (2014, Tobii Technology, Tokyo, Japan) were used to measure the eye gaze. Participants were seated such that their eye movements were measured 60 cm from the screen. The screen size was 1920 × 1080 pixels (23 inches) and the background of the monitor was black. The monitor's sound level was set to 50–60 dB constant level using a sound-level meter.

The sampling rate (binocular) for the noise measurement was 300 Hz. Calibration was performed before the experiments. The Stim Tracker (Cedrus, CA, USA) sensor connected to a Tobii TX300 eye tracker was used to synchronize event-related time.

Data processing

Participants with a gaze rate of less than 40% while watching the movies were excluded from the analysis. We used data from the period when the most relevant events occurred to understand the context (Table 2). The gaze values were calculated as described in a previous study [14]. The Euclidean distances between the center coordinate of each target (e.g., Person 1, Person 2, and the Object) and the gazing point were calculated. We then transformed the distances into gaze values. The transformation of gaze values was performed using a Gaussian distribution defined with a mean of 0 and a standard deviation of 50 (pixels). The probability value obtained based on the Gaussian distribution was defined as the gaze value. At zero distance ($X = 0$, the peak of the Gaussian distribution), the gaze value was transformed to be 1. As the distance increased, the gaze value of a target decreased according to the values based on the Gaussian distribution. When the distance between a participant's gaze point and a particular target

is small, the gaze value for that target is close to 1. Therefore, the gaze value is an index that quantifies the distance from a target [14].

The average of the gaze values in the time frame of interest of each participant were used in the analyses. Only the gaze value scores of Person 1, who showed negative emotions by their face, were used because understanding the facial and behavioral responses of Person 1 was the primary target of this study. For the chatting scene, the Object (sandwich) was also added to the analysis to compare the results with the findings of a previous study [14]. Data processing and transformation were performed using the image processing toolbox (MathWorks, Inc., Tokyo, Japan), statistics and machine learning toolbox (MATLAB 2017, MathWorks, Inc., Tokyo, Japan), and an automated analysis program (BRSystems Inc., Kanagawa, Japan).

Measurement of cerebral blood flow

The optical imaging brain function measurement system, Spectratech OEG-16 (Spectratech Inc., Tokyo, Japan), measured the temporal changes in the blood flow in the right and left prefrontal regions during the task. The device has a 16-channel probe. Two near-infrared light sources with different wavelengths (840 nm and 770 nm) were used to measure the cerebral blood flow dynamics in 650 ms units. The distance between the light-transmitting and receiving probes was 3 cm. The probe holder used was 469 mm x 60 mm in size and was mounted from the frontal to the temporal area so that the lowest probe was placed on the Fp1-Fp2 line according to the International 10-20 system, as in a previous study [21]. Calibration was performed before each participant was measured. Three indices were calculated to measure the cerebral blood flow: change in oxygenated hemoglobin concentration (oxy-Hb, mMmm), change in reduced hemoglobin concentration (deoxy-Hb, mMmm), and change in total hemoglobin concentration (total-Hb, mMmm).

Data Processing

To reduce the movement noise, the raw data from fNIRS were corrected as follows: a moving average filter with a window size of seven samples to reject artifacts emerging from the minor movement of participants was employed, which corresponded to the use of a 0.1 Hz low-pass filter by a fast Fourier transform. The mean value during 10 s intervals before the task started was corrected to zero to determine the baseline values. The data from the participants who showed the waveforms of oxy-Hb and deoxy-Hb that changed by more than 0.2 mMmm within 1 s or waved in the same phase in the experiment were excluded from the analysis because they were considered to be caused by body motion.

The median oxy-Hb value while watching the movies in each channel was calculated and used as the dependent variable. In this study, similar to a previous study, the regions of interest (ROIs) were set as the right inferior frontal gyrus (R-ROI; ch1, 2, 3, 4) and left inferior frontal gyrus (L-ROI; ch13, 14, 15, 16) [21]. The median change in the oxy-Hb concentration during the period of interest in each ROI was used as an index. The fNIRS data analysis was performed using MATLAB R2013a (MathWorks, Inc., Tokyo, Japan) with the Brain Analyzer software (BRSystems Inc., Kanagawa, Japan).

Statistical analysis

To focus on the differences in social cognitive difficulties between children with and without ASD, Mann–Whitney’s U tests was used to compare the groups for each measure. We did not include adult participants in the statistical comparisons because adults were only included to provide information about the study tasks. The dependent variables were the verbal task scores, gaze value scores, and fNIRS oxy-Hb values. Bonferroni correction was applied for multiple comparisons in verbal task, eye gaze, and fNIRS, dividing the significance threshold by the number of comparisons for each variable

(verbal task: 4, eye gaze: 7, fNIRS: 32). In addition, Kendall's rank correlation coefficients were calculated to examine the relationship between the performance in verbal tasks and gaze values, as well as the relationship between gaze values and fNIRS oxy-Hb values. For correlational analyses, we only examined data of the chatting scene, which was used in a previous study [14], to reduce the number of significance testing and false positives. Statistical analyses were performed using SPSS Statistics Ver. 26.0 (IBM, Armonk, USA). The significance level was set at $p < 0.05$.

RESULTS

The final number of participants included in the analyses was 20 children with ASD (aged 7–11 years, 18 boys), 18 children without ASD (aged 6–11 years, 6 boys), and 16 adults without ASD (aged 20–25 years, 7 men). The characteristics of the participants in each group are presented in Table 1.

Verbal task

The Mann–Whitney U test revealed no significant difference between the children with and without ASD (Figure 1).

[Figure 1]

Eye gaze

We have illustrated the time course of the gaze values for the chatting scene in Appendix Figure 2, showing the trajectory of gaze values during the target periods. Changes in gaze value were observed in response to the occurrence of the events in the movie (Period 1 and 2). However, the gaze values did not show significant differences between

the children with and without ASD, while watching the four movies, including the chatting scene ($p > 0.05$; Figure 2).

[Figure 2]

fNIRS

The response of oxy-Hb was higher in children with ASD compared to children without ASD in R-ROI (ch1; $Z = -2.01$, $p = .045$) in the leaving-out scene (Figure 3). Conversely, Oxy-Hb response was lower in children with ASD compared to that in children without ASD in ch15 (L-ROI, $Z = -2.01$, $p = .045$) in the stress-provoking scene and lower in ch2 (R-ROI, $Z = -2.16$, $p = .031$) and ch15 (L-ROI, $Z = -2.32$, $p = .021$) in the class-disturbing scene. However, these differences were not significant after applying the Bonferroni correction (significant threshold: 0.0016).

[Figure 3]

Correlation

The correlation coefficient between verbal comprehension and gaze value of children with ASD on Person 1 was 0.393 and did not reach a significant threshold ($p = 0.058$) (Table 3). No significant correlation was detected between gaze values and activation of oxy-Hb (Appendix Table A1).

[Table 3]

DISCUSSION

The present study investigated the differences in comprehension of social communication, eye gaze, and prefrontal cerebral blood flow responses while watching movie clips in children with and without ASD. We did not find significant differences in these indices between the two groups of children. Furthermore, the associations between the variables were not significant due to limited statistical power.

The results of the current study did not confirm that children with ASD had greater difficulty in understanding the social scenes of our video stimuli. A possible factor explaining the similar performances by children with and without ASD in the comprehension task could be due to the characteristics of the verbal tasks. The task difficulty or the child's immature linguistic ability may have caused the lack of group difference in the verbal task scores as even children without ASD were within the low range (median = 0.75 for the chatting scene). Such an interpretation may be supported by a distribution of adult participant's scores with little overlap with those of children (Figure 1). Additionally, the task may not have been sensitive enough to capture the difference in children since it was originally developed for adults [14].

We found no significant difference in gaze values between children with and without ASD. Several studies have suggested that children with ASD show weaker preference for facial or social cues than those in the children without ASD [9] and have reported a wide variation in the gaze patterns of children with ASD [23–25], suggesting that the time for which the children with ASD gaze at faces is highly variable. In addition, the study did not detect differences in gaze patterns between children with ASD and typically developing children in age- and sex-matched comparisons. Therefore, to characterize the gaze behavior of children with ASD, we need to include other components of eye movement abnormalities or clinical variables. In addition, multiple measurements, stimuli, and analytic approaches may also be essential for evaluating children's gaze patterns[26]. The adults looked at Person 1's face when the target object

(sandwich) fell, while most children did not (Figure 2). Because the fall occurred during a short period (1 s), such a difference in gazing pattern may be explained by expectations or predictions about the situation. Such a prediction may be related to the higher gaze of adults in this short period. This difference may be related to differences in search strategies between developmental stages [27].

Contrary to our expectation, the oxy-Hb activation during watching movies did not show significant differences between the two groups of children. Four comparisons showed differences between children's groups ($p < 0.05$); however, these differences did not survive after applying the Bonferroni correction for multiple outcome comparisons. Although the findings of this study were limited by the small number of participants, the previous fNIRS studies have reported controversial findings on task-related oxy-Hb activation in the prefrontal cortex in Japanese children [19–22,28]. While one study reported a significant difference between the children with and without ASD [19], other studies [20–22,28] did not find any differences in the activation in the prefrontal regions in children. These inconsistencies may be due to the differences in task-evoked neural responses (e.g., watching and inhibitory control) in addition to the variability observed in children with ASD and nature of the stimuli used (e.g., eyes facial expressions, and social movies). Further, prefrontal cortex regions are related to social brain network and the measurement of functional connectivity may clarify the characteristics of the brain activity while watching social stimuli in children with ASD [29,30].

The correlation between understanding of the condition and eye gaze on Person 1 did not reach a significant threshold, although the strength of association was not small ($r = 0.393$). Therefore, limited statistical power affected the lack of significance. A previous study suggested that the activation of the cerebral blood flow was not associated with the eye gaze pattern, as observed through facial morphing detection tasks [22]. Because the studies that examined the association between gaze and activation in cerebral blood flow are limited, we

cannot reach a meaningful conclusion. Further investigations, including the temporal association between eye gaze and activation in the social brain network [13,31], would contribute to further understanding the neural mechanisms of atypical gaze behaviors in children with ASD.

Limitations

This study has several limitations. First, the sample size was small due to the exclusion criterion for gaze value (less than 40% of the measurements were valid); we excluded 35–50% of the participants across stimulus videos. Based on the similar criterion for fNIRS, we excluded 50–86% of the participants. In particular, the major cause of exclusion were the body movements in children with ASD. In addition to the increased sample size, developing methods to reduce noise from body movement are required. Second, differences in movies were not quantified in this study. The characteristics of the stimulus naturally affect gaze behavior and neural activation. Third, sex and age variability between groups may have affected the findings. Boys comprised 90% of all the children with ASD, while boys comprised 33% of the children without ASD. The difference in ratio of boys may have been a confounding factor for the findings of this study.

Conclusion

In the present study, we examined the eye gaze, cerebral blood flow, and degree of understanding of the context of social movie clips to investigate the characteristics of social cognitive difficulties in children with and without ASD. The results did not show significant group differences in children, which may have been affected by the limited statistical power and other confounding factors. Further investigations are required to detect gazing and neurophysiological characteristics of children with ASD.

Acknowledgments:

We would like to thank the people who assisted this research. We appreciate the participants of this study and the teachers and students of Sumiyoshi Elementary School in Kobe City, the Suminoe Children's Center in Kobe City, and Noda Elementary School in Sakai City.

Conflicts of Interest:

The authors declare no conflicts of interest associated with this study.

Funding

This work was supported by JSPS KAKENHI Grant Number JP15K11703.

Author contributions

Conceptualization: AY, HF, HO.; data curation: AY, TY, AI; formal analysis: AY, HF, TY, AI; funding acquisition: HO; investigation: AY, TY, IM; methodology: HO, TY; Project administration: HO and HF; resources: IM; supervision: HO, HF; visualization: AY, HF; writing – original draft: AY, HO, HF; writing – review & editing: AY, HO, HF, TY, AI, IM.

References

- 1 American Psychiatric Publishing. American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. 2013.
- 2 Carter AS, Davis NO, Klin A, et al. Social Development in Autism. Handbook of autism and pervasive developmental disorders: Diagnosis, development, neurobiology, and behavior, Vol. 1, 3rd ed., Hoboken, NJ, US: John Wiley & Sons Inc, 2005:312–334.
- 3 Deuel RK. Autism: a cognitive developmental riddle. *Pediatr Neurol* 2002;26:349–357.
- 4 Frith CD, Frith U. Mechanisms of social cognition. *Annu Rev Psychol* 2012;63:287–313.
- 5 Tomasello M, Carpenter M, Call J, et al. Understanding and sharing intentions: The origins of cultural cognition. *Behavioral and Brain Sciences* 2005;28:675–691.
- 6 Wheelwright S, Baron-Cohen S, Goldenfeld N, et al. Predicting Autism Spectrum Quotient (AQ) from the Systemizing Quotient-Revised (SQ-R) and Empathy Quotient (EQ). *Brain Res* 2006;1079:47–56.
- 7 Wang AT, Lee SS, Sigman M, et al. Neural basis of irony comprehension in children with autism: the role of prosody and context. *Brain* 2006;129:932–943.
- 8 Chita-Tegmark M. Social attention in ASD: A review and meta-analysis of eye-tracking studies. *Res Dev Disabil* 2016;48:79–93.
- 9 Ma X, Gu H, Zhao J. Atypical gaze patterns to facial feature areas in autism spectrum disorders reveal age and culture effects: A meta-analysis of eye-tracking studies. *Autism Research* 2021;14:2625–2639.
- 10 Babinet M-N, Cublier M, Demily C, et al. Eye Direction Detection and Perception as Premises of a Social Brain: A Narrative Review of Behavioral and Neural Data. *Cogn Affect Behav Neurosci* 2022;22:1–20.
- 11 Fujioka T, Tsuchiya KJ, Saito M, et al. Developmental changes in attention to social information from childhood to adolescence in autism spectrum disorders: A comparative study. *Mol Autism* 2020;11:24.
- 12 Speer LL, Cook AE, McMahon WM, et al. Face processing in children with autism: Effects of stimulus contents and type. *Autism* 2007;11:265–277.
- 13 Müller N, Baumeister S, Dziobek I, et al. Validation of the Movie for the Assessment of Social Cognition in Adolescents with ASD: Fixation Duration and Pupil Dilation as Predictors of Performance. *J Autism Dev Disord* 2016;46:2831–2844.
- 14 Lönnqvist L, Loukusa S, Hurtig T, et al. How young adults with autism spectrum disorder watch and interpret pragmatically complex scenes. *Quarterly Journal of Experimental Psychology* 2017;70:2331–2346.
- 15 Cuttler C, Spradlin A, McLaughlin RJ. A naturalistic examination of the perceived effects of cannabis on negative affect. *J Affect Disord* 2018;235:198–205.

- 16 Mauri M, Crippa A, Bacchetta A, et al. The utility of NIRS technology for exploring emotional processing in children. *J Affect Disord* 2020;274:819–824.
- 17 Kruppa JA, Reindl V, Gerloff C, et al. Brain and motor synchrony in children and adolescents with ASD—a fNIRS hyperscanning study. *Soc Cogn Affect Neurosci* 2021;16:103–116.
- 18 Fukuda M, Uehara T, Ito M, et al. [Functional brain imaging in psychiatry using multi-channel near-infrared spectroscopy]. *Jpn J Clin Psychiatry*. 2001;30:937-951. (in Japanese)
- 19 Iwanaga R, Tanaka G, Nakane H, et al. Usefulness of near-infrared spectroscopy to detect brain dysfunction in children with autism spectrum disorder when inferring the mental state of others. *Psychiatry Clin Neurosci* 2013;67:203–209.
- 20 Ikeda T. Atypical neural modulation in the right prefrontal cortex during an inhibitory task with eye gaze in autism spectrum disorder as revealed by functional near-infrared spectroscopy. *Neurophotonics* 2018;5:1.
- 21 Kita Y, Gunji A, Inoue Y, et al. Self-face recognition in children with autism spectrum disorders: A near-infrared spectroscopy study. *Brain Dev* 2011;33:494–503.
- 22 Kita Y, Gunji A, Sakihara K, et al. Scanning strategies do not modulate face identification: eye-tracking and near-infrared spectroscopy study. *PLoS One* 2010;5:e11050–e11050.
- 23 Nakano T, Tanaka K, Endo Y, et al. Atypical gaze patterns in children and adults with autism spectrum disorders dissociated from developmental changes in gaze behaviour. *Proc Biol Sci* 2010;277:2935–2943.
- 24 Avni I, Meiri G, Bar-Sinai A, et al. Children with autism observe social interactions in an idiosyncratic manner. *Autism Research* 2020;13:935–946.
- 25 Zhao Z, Xing J, Zhang X, et al. Random and Short-Term Excessive Eye Movement in Children with Autism During Face-to-Face Conversation. *J Autism Dev Disord* 2022;52:3699–3710.
- 26 Tsuchiya KJ, Hakoshima S, Hara T, et al. Diagnosing Autism Spectrum Disorder Without Expertise: A Pilot Study of 5- to 17-Year-Old Individuals Using Gazefinder. *Front Neurol* 2021;11:603085.
- 27 Rider AT, Coutrot A, Pellicano E, Dakin SC, Mareschal I. Semantic content outweighs low-level saliency in determining children's and adults' fixation of movies. *J Exp Child Psychol* 2018;166:293-309.
- 28 Kikuchi M, Yoshimura Y, Shitamichi K, et al. Anterior Prefrontal Hemodynamic Connectivity in Conscious 3- to 7-Year-Old Children with Typical Development and Autism Spectrum Disorder. *PLoS One* 2013;8:e56087.
- 29 Leung RC, Pang EW, Brian JA, et al. Happy and Angry Faces Elicit Atypical Neural Activation in Children With Autism Spectrum Disorder. *Biol Psychiatry Cogn Neurosci Neuroimaging* 2019;4:1021–1030.

- 30 Arioli M, Cattaneo Z, Ricciardi E, et al. Overlapping and specific neural correlates for empathizing, affective mentalizing, and cognitive mentalizing: A coordinate-based meta-analytic study. *Hum Brain Mapp* 2021;42:4777–4804.
- 31 Senju A, Johnson MH. The eye contact effect: mechanisms and development. *Trends Cogn Sci* 2009;13:127–134.

Table 1. Characteristics of the participants

	Children with ASD (n = 20)		Children without ASD (n = 18)		Adults without ASD (n = 16)	
	Median	IQR	Median	IQR	Median	IQR
Age	9.9	1.5	8.8	4.0	21.5	1.8
IQ	90.0	28.3	106.5	19.5	114.0	9.5
AQ	33.5	7.5	15.5	7.3	19.0	6.5

ASD: autism spectrum disorder, IQR: interquartile range, IQ: intelligence quotient,
AQ: autism-spectrum quotient

Table 2. Details of each stimulus

Movie (Time)	Contents	Time period for analysis (sec)
Chatting scene (54 s)	Four children are sitting around a table, relaxing, and chatting. A girl (Person 2) hands out sandwiches (Object) to everyone by turn. When she presents the sandwich to the last girl (Person 1), she drops it (Period 1) and apologizes to Person 1. The girl (Person 1) replies, "Don't care about it". While the tone of her voice, posture, facial expression, and her stopping to talk in the latter half of the video while the other three continued to chat and laugh (Period 2) indicates that she was actually bothered by it and felt sad.	Period 1: 29.4–30.4 Period 2: 30.4–40.0
Leaving out scene (30 s)	Person 1 tries to talk to Person 2 about joining their group (Person 2 and other children), but Person 2 refuses Person 1's request, saying she will meet other friends. Person 1 has a regretful look and goes back to her seat in the classroom.	28.0–29.0
Stress- provoking scene (16 s)	Person 1 and Person 2 are wiping the window. While Person 1 is wiping the window carefully, Person 2 persistently complains the way Person 1 is wiping. Finally, Person 1 gives a disgusted look.	13.0–14.0
Class- disturbing scene (25 s)	During class, Person 1 is studying hard. Person 2 repeatedly disturbs Person 1 by talking to Person 1. Person 1 silently looks at Person 2 with a disgusted look, but Person 2 doesn't care and keeps talking to Person 1. Thereafter, Person 2 sticks out her tongue at Person 1, who does not respond, and goes back to her work.	11.0–12.0

Table 3. Correlation between verbal task scores and gaze scores in chatting scene (Kendall's rank correlation)

Event (Time)	Children with ASD (n = 15)		Children without ASD (n = 11)		Adults without ASD (n = 13)	
	τ	p	τ	p	τ	p
Period 1: Sandwich dropped (29.4– 30.4 s)	-0.109	0.598	0.141	0.57	-0.248	0.243
Period 2: Person 1's response (30.4–40.0 s)	0.393	0.058	-0.221	0.372	-0.248	0.243

ASD: autism spectrum disorder

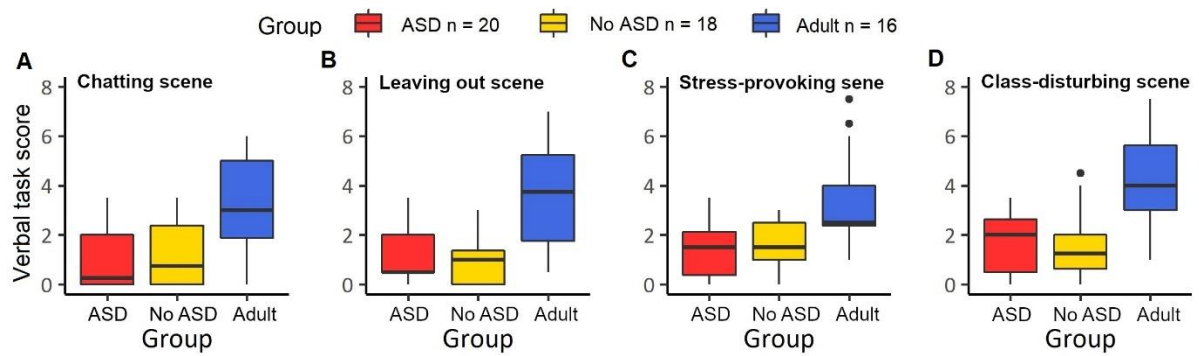


Figure 1 Boxplot of the verbal task score in each condition

The boxplots show an overlap in the performance of the verbal task in children with and without autism spectrum disorder. Adults score higher in these tasks.

ASD: Children with autism spectrum disorder, No ASD: Children without autism spectrum disorder, Adult: Adults without autism spectrum disorder

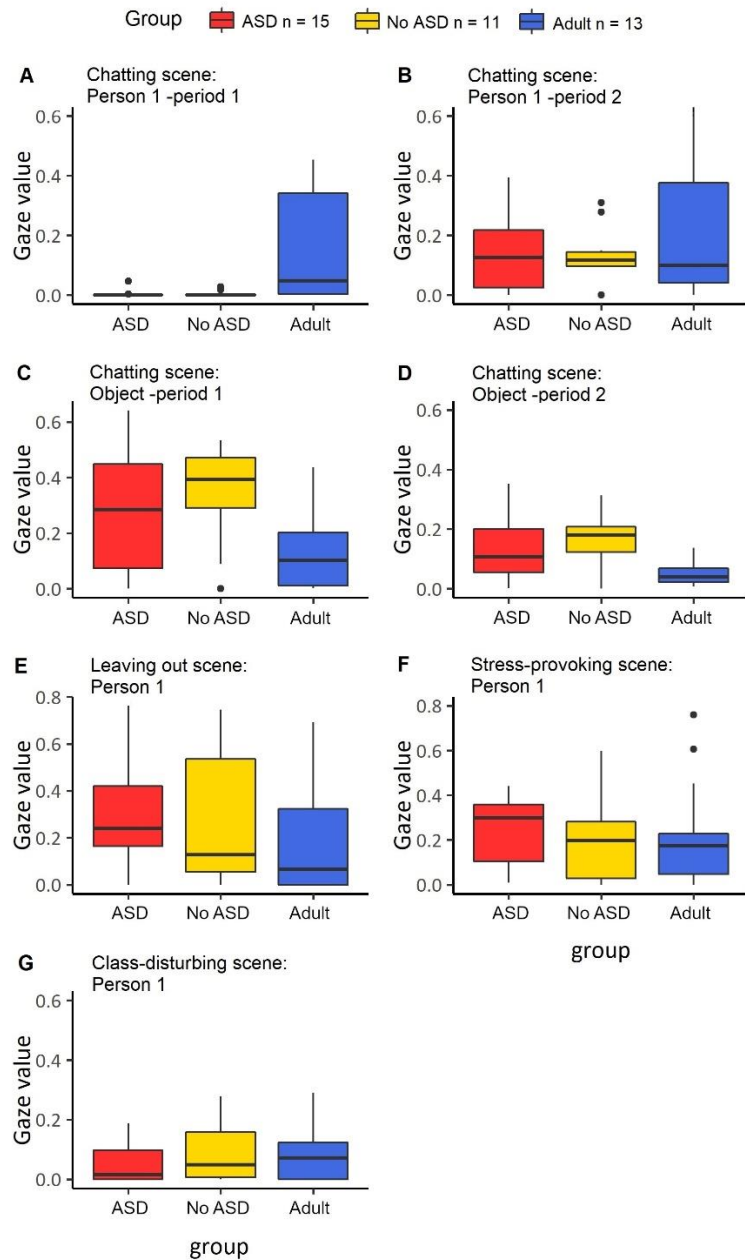


Figure 2 Boxplot of the gaze values in each condition

Each panel shows overlap of the performance in the gaze value in children with and without autism spectrum disorder (ASD). Panel A shows children did not look toward the target (Person 1) during the Chatting scene event. Other panels show overlap of the gaze values in children with and without ASD. Periods 1 and 2 refer to 29.4–30.4 s and 30.4–40.0 s periods of the chatting scene.

ASD: Children with autism spectrum disorder, No ASD: Children without autism spectrum disorder, Adult: Adults without autism spectrum disorder

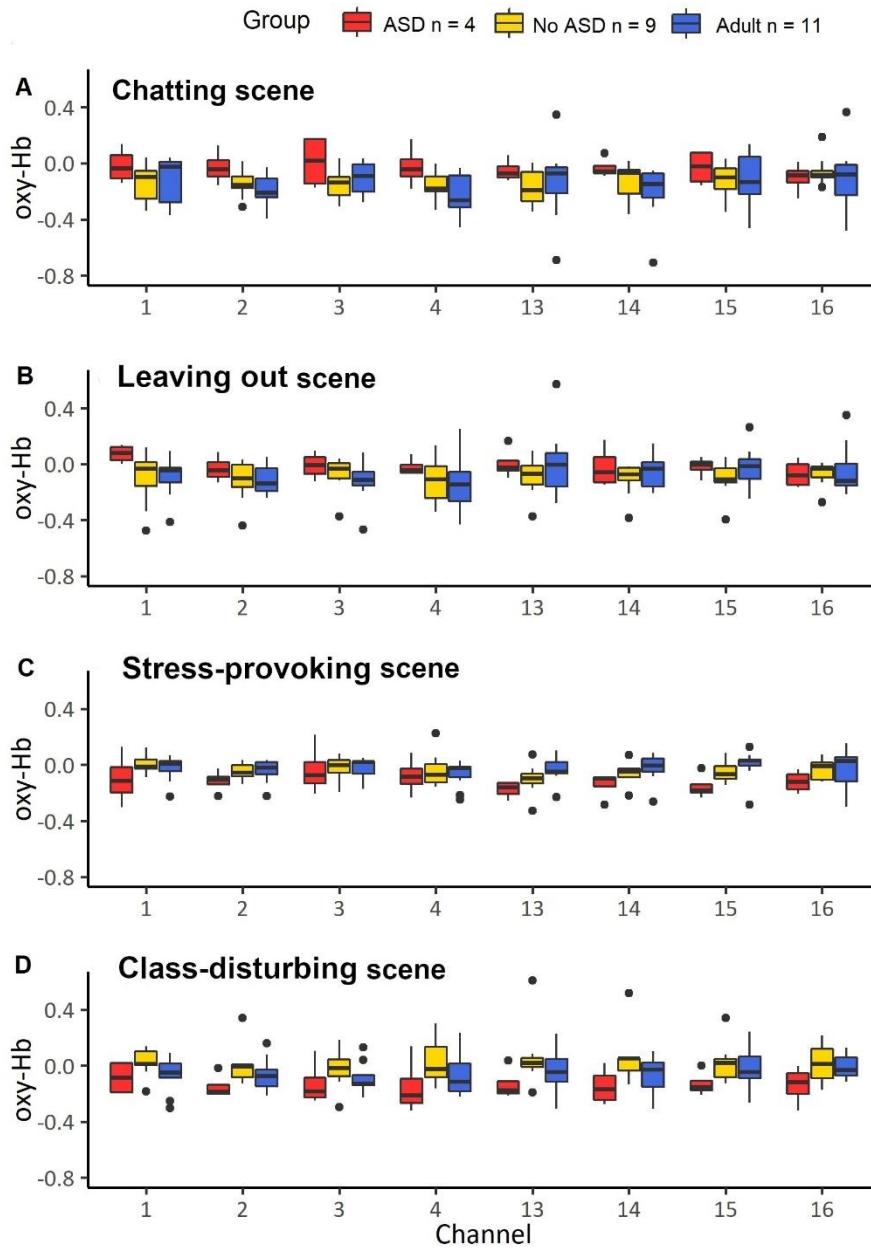


Figure 3 Boxplots of oxygenated hemoglobin (oxy-Hb) in each condition and channel.

Channels 1–4 were located on the right side and channels 13–16 on the left. The oxy-Hb response was higher in children with autism spectrum disorder (ASD) compared to that in children without ASD in ch1 ($Z = -2.01$, $p = .045$) in the leaving-out scene. Oxy-Hb response was lower in children with ASD compared to that in children without ASD in ch15 (L-ROI, $Z = -2.01$, $p = .045$) in the stress-provoking scene and lower in ch2 (R-ROI, $Z = -2.16$, $p = .031$) and ch15 (L-ROI, $Z = -2.32$, $p = .021$) in the class-disturbing scene. However, these

differences were not significant after applying the Bonferroni correction (significant threshold: 0.0016).

ASD: Children with autism spectrum disorder, No ASD: Children without ASD, Adult: Adults without ASD

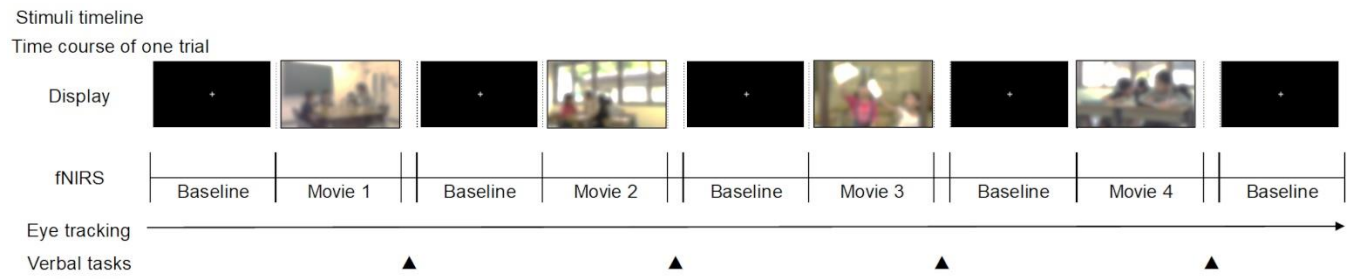
Appendix

Appendix Table A1. Correlation coefficients between gaze values and oxygenated-hemoglobin values in chatting scene for each group (Kendall's rank correlation)

Event (Time)	Channel (fNIRS)	Children with ASD (n = 5)		Children without ASD (n = 8)		Adults without ASD (n = 11)	
		τ	p	τ	p	τ	p
Period 1: Sandwich dropped (29.4–30.4 s)	1	0.20	0.62	0.07	0.81	0.13	0.59
	2	-0.20	0.62	-0.14	0.62	0.06	0.82
	3	0.00	1.00	0.21	0.46	0.24	0.31
	4	0.00	1.00	0.07	0.81	0.13	0.59
	13	-0.60	0.14	0.07	0.81	-0.02	0.94
	14	-0.40	0.33	0.07	0.81	0.13	0.59
	15	0.00	1.00	-0.07	0.81	0.13	0.59
	16	-0.40	0.33	0.29	0.32	0.06	0.82
Period 2: Person 1's response (30.4–40.0 s)	1	0.40	0.33	-0.07	0.81	0.31	0.19
	2	0.40	0.33	-0.14	0.62	0.16	0.48
	3	0.60	0.14	-0.21	0.46	0.35	0.14
	4	0.60	0.14	-0.21	0.46	0.09	0.70
	13	0.00	1.00	-0.07	0.81	0.09	0.70
	14	0.20	0.62	-0.21	0.46	0.24	0.31
	15	0.60	0.14	0.07	0.81	0.24	0.31
	16	0.60	0.14	0.00	1.00	0.24	0.31

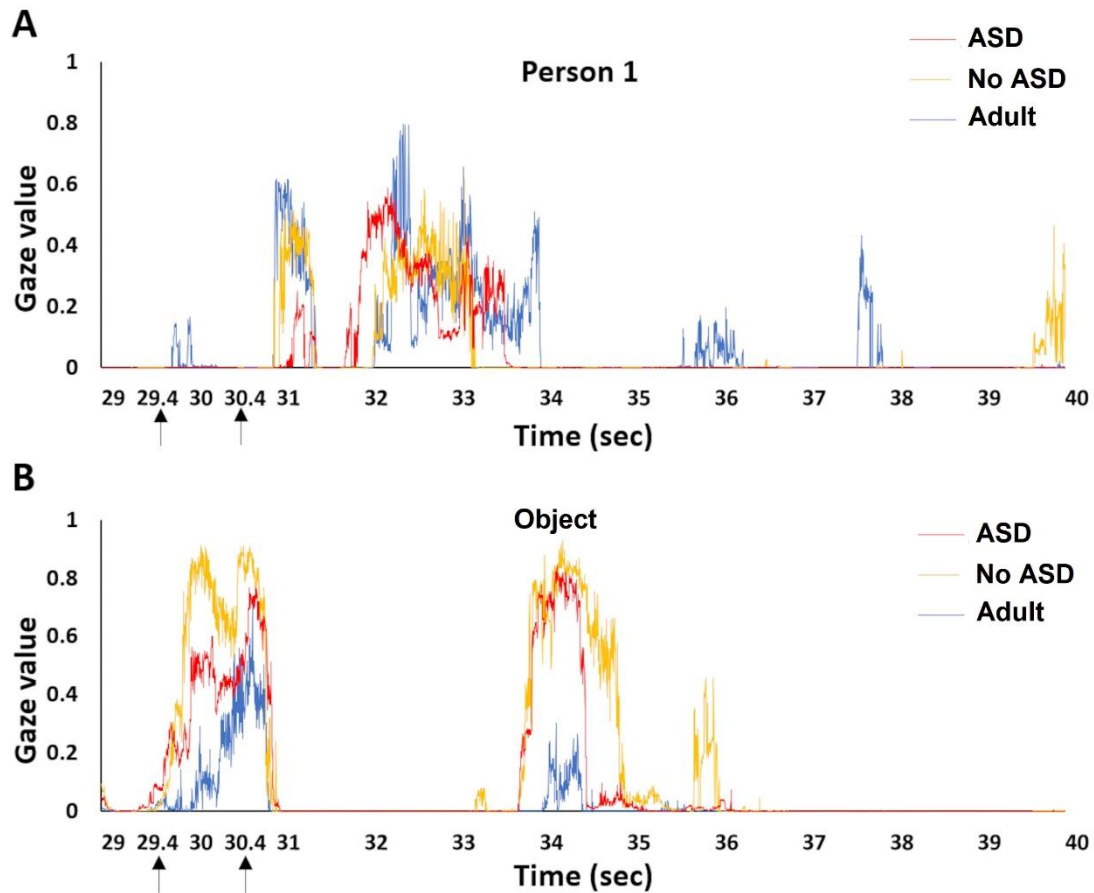
ASD: autism spectrum disorder; fNIRS: near-infrared spectroscopy

Participants who satisfied the data processing criteria for eye-tracking and fNIRS data for the chatting scene were included.



Appendix Figure A1. Timeline of the experiment

The images are blurred versions of the original movies.



Appendix Figure A2. Time course of the gaze values in chatting scene for each group

The vertical axis shows the gaze value, and the horizontal axis shows the time course.

Panels A and B show the median gaze value of Person 1 and the sandwich, respectively, as a function of participant groups. The black arrows indicate the beginning time point of Period 1 (sandwich dropped) and Period 2 (Person 1's response).

ASD: Children with ASD (red line); No ASD: Children without ASD (yellow line); Adult: Adults without ASD (blue line)