The gaze characteristics in preterm children: The appropriate timing for an eye-tracking tool

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Original article

The gaze characteristics in preterm children: The appropriate timing for an eye-tracking tool

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Abstract

Background: An objective screening tool for autism spectrum disorder (ASD), also known as an eye-tracking tool, assesses the patient's abnormal gaze patterns and detects the risk of ASD. As this tool is generally used for children born at term, this study aimed to clarify the appropriate timing for using the tool for preterm children, factors that influence the timing, and evaluate their gaze characteristics using the Gazefinder®.

Method: In 90 preterm children, a total of 125 eye-tracking tasks were completed and analyzed in 3–6, 7–9, 10–12, 13–18, and 19–32 months of corrected age (CA). The Gazefinder® was used to compare the mean fixation time percentage (MFP) in each CA and evaluate the gaze patterns. Perinatal factors associated with low MFP were also analyzed.

Results: Only 50% of the children scored $\geq$70% MFP at 3–6 months of CA. The MFP increased significantly after 7 months of CA ($p = 0.0003$), reached 90% at 13–18 months, and 100% at 19–32 months of CA. Chronic lung disease (CLD) was a clinical factor associated with low MFP ($p = 0.036$). Preterm children gazed more at eyes but gazed at mouths when the mouth moved.

Conclusion: It is necessary for preterm children to begin using Gazefinder® atleast at $\geq$13 months of age, especially those complicated with CLD. Preterm children prefer gazing at social information just as typically developing children.

Keywords: Autism spectrum disorder; Eye-tracking; Face recognition; Gaze pattern; Preterm birth

1. Introduction

Advances in neonatal medicine are extremely conspicuous. Although worldwide birth rates are decreasing, preterm birth rates have increased to 10.6% in 2014 [1]. The incidence and severity of cerebral palsy in preterm children have decreased significantly, which could be attributed to a reduction in severe periventricular leukomalacia (PVL) and intraventricular hemorrhage (IVH) [2]. However, the prevalence of developmental disabilities in preterm children has not decreased [3]. Preterm birth is a possible predictor of neurodevelopmental and cognitive impairments during childhood [4]. In a *meta*-analysis using case-control studies that targeted 7000 children born between 1980 and 2009, those born at <28 weeks of gestation were estimated to have 13.9 points lower intelligence quotient than term-born controls [3]. Recent studies also revealed that prematurity and low birth weight are risk factors

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for developmental difficulties, such as autism spectrum disorder (ASD) and attention deficit hyperactivity disorder [5,6]. The prevalence of the diagnosis of ASD in children born at preterm (preterm children) is estimated to be 4–12 times higher than in those born at term (term children) [7,8].

Recently, an objective screening tool that uses the characteristic of impaired social communication in children with ASD has been developed to assess the child's abnormal gaze patterns and evaluate their risk for ASD. The deficit of eye contact and social communication are the hallmarks of ASD. Several previous studies have demonstrated that children and adolescents with ASD are more likely to prefer gazing at geometric patterns than human faces through the eye-tracking tools [3,9,10]. If the human face is shown to them, they prefer gazing more at the mouth than the eye [3,9,10]. Eye-tracking tools can be used in young children, possibly leading to the earlier identification of ASD.

Although several studies have used eye-tracking tools to investigate children with ASD, only a few have focused on preterm children [5,11]. Therefore, preterm children's unique pattern of social attention is still unknown. Moreover, the feasibility of using eye-tracking tools for preterm children in infancy and early childhood remains questionable because their development is slower than that of term children [3,4].

This study aimed to clarify the appropriate timing to start using eye-tracking tools for preterm children and identify the factors that influence this timing. We compared the mean fixation time percentage (MFP) of all sequences of the eye-tacking tool known as the Gazefinder® in each corrected age (CA). Furthermore, this study aimed to evaluate the characteristics of visual cognition in preterm children and discuss the differences compared to term children with or without ASD, as reported in previous studies [12–14].

2. Method

2.1. Participants

Ninety preterm children aged 3–32 months of CA who underwent periodic health checkups at Nihon University Itabashi Hospital in Tokyo between April 2021 and December 2022 were enrolled in this study. The 90 preterm children with gestational age at birth (28–35 weeks) completed eye-tracking tasks, and their gaze patterns were measured in 3–6, 7–9, 10–12, 13–18, and 19–32 months of CA. Twenty-nine children underwent the examination multiple times, and a total of 125 tasks were analyzed for their visual characteristics. Participants with the following conditions: serious brain damage, such as PVL and severe IVH, and those diagnosed with severe retinopathy of prematurity after vitrectomy were not included at the time of initial sampling.

2.2. Eye-tracking device

We used an eye-tracking device called Gazefinder® (JVC Kenwood, Hamamatsu, Japan) to measure the participants' line of sight and their fixation percentage on the screen. Gazefinder® also plots and evaluates the percentage of fixation allocated to specific objects on a video monitor. It is equipped with infrared light and cameras at the bottom of a 19-inch transistor monitor. The infrared light can detect the participant's eye position approximately 50 times per second [12–14].

2.3. Stimuli

The Gazefinder® consisted of six different patterns of short movie clips as stimuli, including four categories of social cues, which consisted of four different movie clips of human faces (I–IV) and two different movies of people and geometric figures (V–VI) (Fig. 1) [12–14].

The movie clips with human face consisted of an actress showing four different facial motions; (I) silent with eye blinking, (II) silent with still image, (III) silent with mouth opening and closing repeatedly, and (IV) the actress talking to the participant, saying "Hello, what is your name? Let's play together" in Japanese. The movie clips consisted of people and geometric patterns depicted in windows of the same size or a geometric pattern depicted in a small window in a movie of people (V–VI). In these six movie clips, there were two target areas, social and non-social areas. Social areas indicated social information needed for social communication, such as people's faces, especially the eyes of the human face (Area 1 in Fig. 2). On the other hand, non-social areas indicated information not needed for human social communication, such as geometric figures and mouth on faces (Area 2 in Fig. 2) [12–14].

2.4. The mean fixation time percentage of all sequences

We named the percentage of time that the participants were able to gaze at the screen during a series of video tasks played during the examination as the MFP. In several studies using Gazefinder®, the MFP was set at $\geq$70% as the cut-off value for which each participant gazed at the screen appropriately, and the task could be evaluated accurately [10,15,16]. In this study, the cut-off value of MFP was set at 70% to evaluate the differences in each month of CA.

3. Procedure

The participants sat on their caregivers' laps and were placed approximately 60 cm from the computer

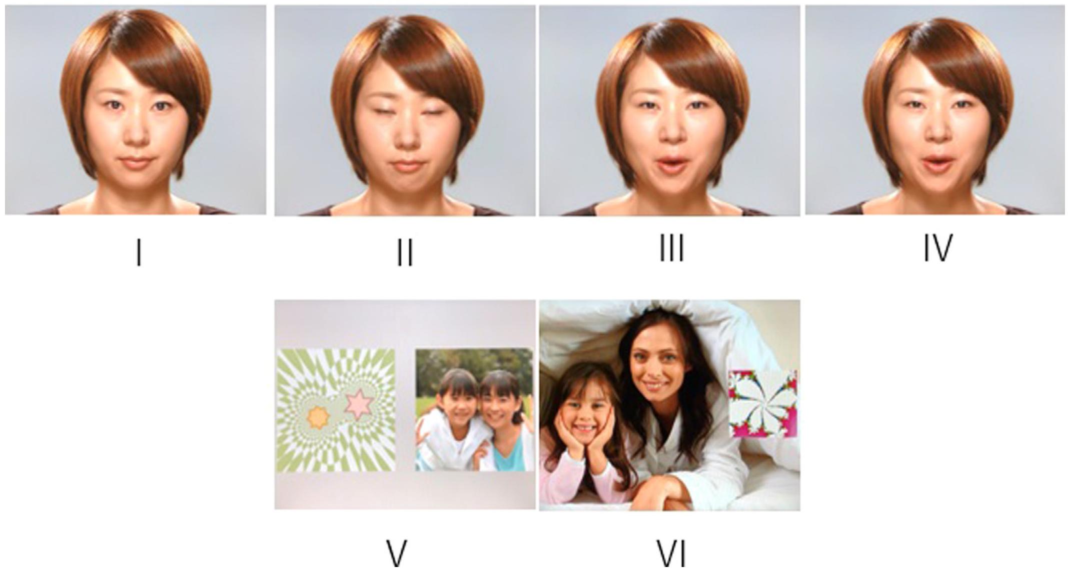

Fig. 1. **Gazefinder® movie samples.** (I) silent with eye blinking, (II) silent with still image, (III) silent with mouth opening and closing repeatedly, and (IV) the actress talking to the participant, saying "Hello, what is your name? Let us play together." (V) People and geometric patterns (same size); and (VI) People and geometric patterns (small window size). These pictures were from Gazefinder® (JVC Kenwood corporation Hamamatsu, Japan).

Fig. 2. **Six movies with social and non-social areas.** Area 1 with straight line indicates social information. Area 2 with stripe line indicates non-social information. A. Human face: Area 1 includes the eye region, and Area 2 includes the mouth region. B. People and geometric pattern (same size): Area 1 includes human face, and Area 2 includes geometric pattern. C. People and geometric pattern (small size): Area 1 includes human face, and Area 2 includes geometric pattern. These pictures were from Gazefinder® (JVC Kenwood corporation Hamamatsu, Japan).

monitor. To obtain the calibration information, the participants were first shown several patterns of animated animals that appeared on the screen. Then the infrared light and cameras in the Gazefinder® detected the participant' eye position and obtained calibration. Next, the experimental movie clips were shown for approximately 2 min. Only three people in the room detected the data: the participant, the caregiver, and the operator. The operator sat or stood behind the participants and caregivers to prevent distraction. Parents were asked not to speak to their children or direct their children to pay attention to the screen by pointing at it during the examination. The operator could check and know if the participants were appropriately gazing at the screen or not during the movie clips by a small red and green blinking light at the lower left corner of the screen. Green light indicated that the Gazefinder® detected the participants' line of sight correctly. Operators terminated and re-performed the examination from the beginning if the red light at the corner continued to blink and showed participants constantly gazing out of the screen for a long time [12–14].

3.1. Statistical analysis

We divided the tasks into five CA groups; 3–6, 7–9, 10–12, 13–18, and 18–32 months of CA and investigated the MFP. We also investigated the differences in the MFP allocated to each target area (social and non-social areas) between the five CA groups. The chi-square and Steel-Dwass tests were used to compare the total fixation percentages among these age groups. The Fischer's exact and the Mann – Whitney U tests were used to examine the clinical perinatal factors associated with low MFP. The significance level was set at $p < 0.05$. Statistical analysis was performed using the software Jmp14® (SAS Institute, Cary, NC, USA).

3.2. Ethics

All the legal guardians of the participants provided written informed consent. The study protocol was approved by the Ethics Committee of the Nihon University Itabashi Hospital Institutional Review Board (no. RK-210112) and conformed to the tenets of the Declaration of Helsinki.

4. Results

The background characteristics of the 90 participants and tasks are shown in Table 1. The mean gestational age was 31 weeks, and the mean birth weight was 1,542 g. A total of 125 tasks were analyzed because 29 children underwent multiple examinations. There were no statistically significant differences in perinatal factors, such as weeks of conception and birth weight, among the CA groups.

The percentage of participants with an MFP > 70% was compared according to the CA groups, indicating the point at which those preterm children reached sufficient development to be detected by Gazefinder® The percentage was 51% at 3–6 months of CA, which increased thereafter (90% at 13–18 months and 100% at 19–32 months of CA). The percentage of participants with MFP > 70% increased significantly as the CA increased ($p = 0.0003$, Table 2).

The lowest MFP was in the 36 months CA group, with a median of 70.3%, which increased as the CA increased. The highest MFP was observed in the 19–32 months CA group, with a median of 94.2%. The MFP in each CA group was compared accordingly, and the MFP in the 3–6 months CA group was significantly lower than that in the 19–32 months CA group ($p = 0.0272$ by Steel-Dwass multiple comparison test) (Fig. 3).

Table 1
Background characteristics of participants.

Participants	$n = 90$
Gestational age at birth (weeks), mean ± SD	31 ± 3.1
Birth weight (g), mean ± SD	1,542 ± 516
Sex: Male	34 (37%)
Tasks	$n = 125$
Number of tasks by corrected age group	
3–6 months	49 (49%)
7–9 months	28 (22%)
10–12 months	16 (13%)
13–18 months	19 (16%)
19–36 months	13 (10%)

SD, standard deviation.

The MFP was lower at 3–6 months of CA than that at other CA; therefore, 49 participants in this CA group were selected to examine perinatal factors and compared between those with > 70% and < 70% of MFP. None of the participants in the 3–6 months CA group performed multiple tasks. Chronic lung disease (CLD) was found to be a perinatal factor associated with low MFP ($p = 0.036$, Table 3).

The fixation percentages were allocated to the social and non-social target areas in each movie clip (I-VI) across all age groups to evaluate the specific gazing characteristics of preterm children. In the face tasks without mouth movement, (I) silent with eye blinking, and (II) silent with still images, all age groups gazed significantly longer at the eye region (Table 4a and b). In the face task with mouth movement, (III) silent with mouth opening and closing repeatedly, and (IV) the actress talking to participants, participants in the 7–9 months of CA and beyond gazed significantly longer at the mouth region. The rate of attention to the mouth increased as the CA increased, whereas the attention length to the eyes decreased (Table 4c and d). In the movie task (V-VI), consisting of people and geometric patterns, participants in the 7–9 months of CA and beyond gazed significantly longer at the human face than geometric patterns (Table 4e and f).

5. Discussion

ASD is characterized by impairments in social reciprocity and communication and stereotyped repetitive behaviors, with onset during early childhood [17]. Early intervention that begins younger than 2 years of age is highly associated with an improved social prognosis [18,19]. However, because of the characteristic differences in ASD symptoms between preterm and term children [8], many preterm children with ASD do not meet the diagnostic criteria for ASD and are thus not diagnosed [20]. Eye-tracking tools may be useful for early diagnosis of ASD in preterm children. However, few studies have reported the gaze characteristics of preterm children [21]. According to a *meta*-analysis of eye-tracking studies in children at risk for ASD, the minimum age of patients was ≥2 years. The Gazefinder® does not require any special tools, such as goggles, to analyze the participant's gaze patterns; therefore, it was assumed that it could be used to assess the gaze patterns of children. Preterm children prefer to gaze at non-social information, such as the mouth of the human face and geometric patterns, similar to children with ASD [5]. Another study reported that preterm children preferred to gaze at non-social information at 7–9 months of CA, but gaze more at social information, such as faces and eyes, by 5 years of age [21]. However, the gaze characteristics of preterm children remain unclear. Since preterm children are more likely to have developmental

Table 2
The mean fixation time percentage in each corrected age group.

Age groups (corrected month)	3–6	7–9	10–12	13–18	19–32
Participants with ≥70% MFP /Total participants	25/49	18/28	11/16	17/19	13/13
(%)	51%	64%	69%	90%	100%
MFP increased as the CA increased ($p = 0.0003$)					

CA, corrected age; MFP, the mean fixation time percentage.

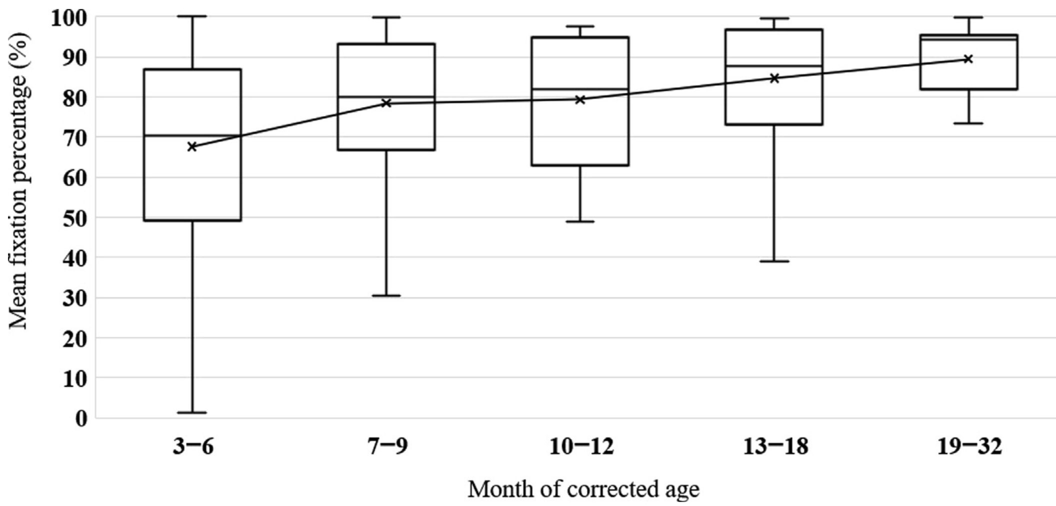

Fig. 3. The mean fixation percentages for the overall movie clip compared among the corrected age groups.

Table 3
Perinatal factors associated with the mean fixation time percentage.

	Total ($n = 49$)		p-value
	>70% $n = 25$ Number (%) orMedian (Min-Max)	<70% $n = 24$ Number (%) orMedian (Min-Max)	
Factors related to children			
Male	8 (32%)	12 (50%)	0.19
Gestational age at birth	33 (25–35)	31.5 (22–35)	0.23
Birthweight	1575 (578–2327)	1480 (578–2412)	0.50
SGA	17 (68%)	18 (75%)	0.59
RDS	11 (44%)	11 (45%)	0.89
IVH	2 (8%)	0 (0%)	0.16
PDA	0 (0%)	2 (8%)	0.14
ROP	0 (0%)	1 (4%)	0.30
Use of ventilator	12 (48%)	11 (54%)	0.88
PPHN	0 (0%)	1 (4%)	0.30
CLD	1 (4%)	6 (25%)	0.036
HOT	0 (0%)	3 (12%)	0.69
Apgar score (1 min)	8 (3–9)	7.5 (1–8)	0.12
Apgar score (5 min)	9 (6–9)	8.5 (3–9)	0.43
Factors related to the mother			
Age of mother (years)	32 (24–43)	33 (19–46)	0.52
First birth	13 (48%)	14 (58%)	0.65
Cesarean section	21 (84%)	19 (79%)	0.66
GDM	2 (8%)	1 (4%)	0.56
HDP	6 (24%)	4 (17%)	0.52
PROM	2 (8%)	4 (17%)	0.35
CAM	14 (56%)	17 (71%)	0.28

CAM, Chorioamnionitis; CLD, Chronic lung disease; GDM, Gestational diabetes mellitus; HDP, Hypertensive disorders of pregnancy; HOT, Home oxygen therapy; IVH, Intravenous hemorrhage; PDA, Patent ductus arteriosus; PPHN, Persistent pulmonary hypertension of the newborn; PROM, Premature rupture of membranes; RDS, Respiratory distress syndrome; ROP, Retinopathy of prematurity; SGA, Small for gestational age.

Table 4
Fixation percentages allocated to the social and non-social target areas in each movie clip (Movie I–VI) across all age groups.

(a) Silent with eye blinking (Movie I)

Corrected Age (months)	Eye	Mouth	p-value
	Mean (%)	Mean (%)	
3–6	81.6	0.0	<0.0001
7–9	86.0	0.0	<0.0001
10–12	77.2	0.8	0.0174
13–18	88.4	0.0	<0.0001
19–32	76.0	1.2	<0.0001
Total	82.6	0.0	<0.0001

(b) Silent with still images (Movie II)

CorrectedAge (months)	Eye	Mouth	p-value
	Mean (%)	Mean (%)	
3–6	71.0	0.0	<0.0001
7–9	70.2	2.7	<0.0001
10–12	59.5	12.0	0.0061
13–18	83.5	0.0	<0.0001
19–32	50.0	18.5	0.0055
Total	82.6	0.0	<0.0001

(c) Silent with mouth moving (Movie III)

CorrectedAge (months)	Eye	Mouth	p-value
	Mean (%)	Mean (%)	
3–6	41.6	4.8	0.0006
7–9	23.8	39.4	0.367
10–12	18.8	48.8	0.0038
13–18	11.2	63.2	0.0003
19–32	11.6	69.2	<0.0001
Total	23.6	41.0	0.0099

(d) Talking to participants (Movie IV)

CorrectedAge (months)	Eye	Mouth	p-value
	Mean (%)	Mean (%)	
3–6	35.4	12.0	0.0023
7–9	30.6	51.4	0.0327
10–12	11.7	57.7	0.0070
13–18	20.0	54.3	0.0072
19–32	19.5	54.3	0.0428
Total	27.5	50.0	0.0211

(e) People and geometric patterns of the same size (Movie V

CorrectedAge (months)	People	Geometric patterns	p-value
	Mean (%)	Mean (%)	
3–6	23.9	26.9	0.2252
7–9	41.9	16.3	<0.0001
10–12	32.3	16.2	0.0873
13–18	56.2	9.3	<0.0001
19–32	55.6	7.2	<0.0001
Total	37.3	15.5	<0.0001

(f) People and geometric patterns of different sizes (Movie VI)

CorrectedAge (months)	People	Geometric patterns	p-value
	Mean (%)	Mean (%)	
3–6	34.5	11.3	<0.0001
7–9	55.3	18.5	<0.0001
10–12	60.7	11.8	0.0256
13–18	57.3	11.1	<0.0001
19–32	50.5	16.5	0.001
Total	46.9	13.0	<0.0001

delay in their early life period, when is actually the ideal time for them to start inspecting with Gazefinder in the first place? According to the developer of Gazefinder®, it is safely useable in children aged 2–7 years. Several studies using Gazefinder® for children with ASD were conducted around the 2-year-old age group. According to a previous report that examined the appropriate timing for the use of Gazefinder® for term children, use from 4 months of age was feasible [14]. Several studies comparing preterm and full-term children have a minimal sample age of 6–7 months; however, no report examined the appropriate time to start using Gazefinder® for preterm children [5,21].

Therefore, in this study, we investigated the appropriate timing to start using the Gazefinder® for preterm children. Previous research demonstrated the feasibility of using Gazefinder® on children from 4 to 11 months of age, which indicated that the Gazefinder® was applicable to term children starting at 4 months of age [14]. Moreover, this previous research demonstrated that term children had >80% of MFP at 4–5 months of age, which continued until 11 months of age [14]. In the present study, when we defined ≥70% MFP as a criterion for the participants to properly analyze their gaze patterns, our results showed that preterm children started catching up to ≥70% MFP after 7 months of CA. The percentage increased with age, with more than 90% of preterm children at 13 months and 100% at 18 months of CA and thereafter being able to maintain their MFP at ≥70%. This finding indicates that participants in the 3–6 months CA group were not sufficiently developed for their gazing data to be collected accurately by the Gazefinder®. For this reason, we considered that 18 months of CA or at least 13 months of CA was the minimum appropriate age to analyze gaze patterns accurately using the Gazefinder® in preterm children.

We found that the MFP at 3–6 months of CA was lower than that in other CA groups in this study. We analyzed the perinatal factors that influence preterm children to have lower MFP. We expected that the lower MFP would be due to factors that directly affect brain and visual development, such as gestational age at birth, birth weight, presence of IVH, Apgar scores, and retinopathy of prematurity that needed treatment. Contrary to our expectations, we found that CLD was the only factor that was significantly associated with lower MFP in preterm children. CLD in preterm children is usually defined as those with long-term respiratory problems whose oxygen demands remain beyond the 36-week CA. CLD is one of the common lung diseases in preterm children with low birth weight. Prolonged oxygen requirement and acidosis are risk factors for developmental delays [22]. According to a previous study, preterm children with respiratory disorders who had prolonged hypoxemia and acidosis showed delays in motor and mental measures on the Bayley developmental assessment at a CA of 6 months but not at 2 years of age [23]. Another study also demonstrated that preterm children with CLD but without IVH or PVL did not have developmental delays on either the mental or motor scales of the Bayley developmental assessment when they were 2 years of age [24]. These findings indicate that preterm children with CLD are likely to have developmental delays at a younger age but catch up as they grow. Similarly, they take a longer time than term children to reach an MFP of $\geq$70%. It is especially important in preterm children with CLD complications to use the Gazefinder® carefully when they are younger than 13 months of CA. Furthermore, we compared the fixation percentages allocated to the target areas of social and non-social information in each movie clip in preterm children in different CA groups. Several previous studies have demonstrated that children with ASD are more likely to prefer looking at geometric patterns than at human faces through the use of eye-tracking tools [3,9,10]. Since preterm children have a higher prevalence of ASD than those with typical development, we expected that preterm children would also prefer non-social information, such as geometric patterns and the mouth of the human face. Fukushima et al. reported that typically developed full-term children showed a higher percentage of gazing at eyes than at mouth only when the mouth is not moving, even at 4–7 months of age [14]. Dean et al. found that preterm children had a lower social preference at 7–9 months of age compared with term children but caught up by 5 years of age [21]. In our study, contrary to our expectations, preterm children tended to gaze at social information, even at 3–7 months of age, just as well as typically developed term children. Moreover, preterm children gazed more at the mouth only when the actress moved her mouth and talked, which is consistent with previous findings that moving mouth attracted young children with or without ASD [14,16]. Chen et al. reported that preterm ASD children had worse non-verbal social interactions, such as direct gaze and social smiles, but they tended to have better peer relationships than term ASD children [8]. They have a strong interest in their surroundings and a high level of social reciprocity, which suggest that they are a unique subgroup of ASD. These preterm ASD children's unique qualities might explain why our participants are more attracted by social information, just like full-term typical development children.

6. Limitations

First, the cohort size was small. In particular, a small number of participants had medical factors associated with low MFP. Moreover, we did not compare preterm participants with full-term children in the task-specific comparisons because this study was conducted at a university hospital where a few term children with typical development were followed up. Thus, it is unclear how the gazing rate of preterm children differs from that of full-term children.

7. Conclusions

The MFP in preterm children is low at a younger age, and the feasibility of using the Gazefinder® is poor in children younger than 13 months of CA. Therefore, it is necessary for preterm children to begin using Gazefinder® at least at $\geq$13 months of CA, especially those with CLD complications. Preterm children prefer gazing at social information just as typically developing children. Further research with a larger sample size needs to be conducted on the characteristics of visual cognition in preterm children compared to term children. In addition, the utility of the Gazefinder® for the early diagnosis of preterm children with ASD needs to be investigated further.

Author contributions

All authors meet the ICMJE authorship criteria. SY, WI, NN, KD, and IM contributed to the conception of this study. SY, WI, NN, AO, EM, and KD were responsible for the clinical data analysis. SY, WI, NN, and IM performed the statistical analysis. SY, WI, and IM drafted the initial manuscript. All authors reviewed the manuscript draft and revised it critically on intellectual content. All authors approved the final version of the manuscript to be published.

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Data statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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論文の内容の要約

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論文題名：The gaze characteristics in preterm children: The appropriate timing for an eye-tracking tool

（早産児の視線パターン：早産児に対する視線解析装置の適切な使用開始時期）

1. 緒言

近年の新生児医療の進歩に伴い、早産児の出生率は 10.6%に増加しているが [1]、早産児に多い脳性麻痺や脳室周囲白質軟化症（Periventricular leukomalacia, PVL）や脳室内出血（Intraventricular hemorrhage, IVH）の発生率は減少している [2]。しかし、早産児の発達障害の有病率は減少していない[3]。早産自体が自閉症スペクトラム障害（Autism spectrum disorder, ASD）の危険因子とされており [4-6]、早産児の ASD 有病率は正期産児の 4-12 倍高いと報告されている [7-8]。しかし、ASD の診断には客観的検査がなく、一般的に診断は難しいとされる。そのため近年、客観的なスクリーニング検査として、ASD 児の特徴である社会的コミュニケーションの障害を利用した視線解析装置が開発されている。視線解析装置では、ASD 児は人の顔や目などの社会的コミュニケーションに必要な情報よりも非社会的情報である幾何学模様や目ではなく口をより注視する傾向がある [3, 9, 10]。視線解析装置を使用する事で、ASD の早期発見につながる可能性がある。ASD の診断は保育園など集団生活をし始める 3 歳以降の診断が多く、２歳以下での診断は困難だが、 2 歳以下の早期療育の開始は社会的予後の改善に繋がるとされており、早期診断の意義は大きいことが分かる [18]。

視線解析装置を用いた研究はいくつかあるが、その多くは ASD 児と定型発達児を比較したものであり、対象年齢も学童期から思春期を比較したものが多く、最小年齢でも 2 歳以上となっていた [3]。更に ASD の有病率が高いとされる早産児を対象にした研究は少なく [5, 11]、早産児特有の視覚認知の特徴はあまり分かっていない。

本研究は、早産児に対する Gazefinder®の適切な使用開始時期を明らかにし、その時期に影響を与える要因を見つける事を目的の一つとした。さらに、早産児の視覚認知の特徴を Gazefinder®で評価し、先行研究 [12-14] で指摘されている早産児の注視パターンとの違いについて検討した。

2. 対象と方法

2.1 対象

2021 年 4 月から 2022 年 12 月に日本大学医学部附属板橋病院（東京都板橋区）のフォローアップ外来を受診した、修正月齢 3-32 か月の早産児（在胎週数 28-35 週）を対象とした。修正月齢とは実際に出生してからの月齢ではなく、出産予定日（在胎週数

40 週 0 日）を生後 0 日として考えた月齢である。それぞれ修正 3-6 か月、7-9 か月、10-12 か月、 13-18 か月、19-32 か月の時点での視線パターンを解析した。PVL や重症 IVH のような重篤な脳障害や硝子体手術後に重症未熟児網膜症と診断されていた児は、初回サンプリングの時点で本研究対象から除外した。

2.2 視線解析装置

本研究では Gazefinder®と呼ばれる視線解析装置（JVC ケンウッド、浜松、日本）を用いて、被験者の視線を測定した。Gazefinder®は、被験者の角膜に反射した赤外線を 2 つのカメラで検知し、被験者の視線を追跡する。Gazefinder®は 19 インチのモニターとその下に設置された 2 つのカメラ、赤外線照射用の近赤外線 LED から構成されており、被験者の眼位を 1 秒間に約 50 回検出する事ができる。ビデオモニター上に映し出される特定の動画に対し、被験者がどの部分をどの程度注視しているか評価する事ができる[12-14]。

2.3 刺激

Gazefinder®は、6 種類の短い動画を刺激とし、4 種類の人の顔の動画（I-IV）と 2 種類の人と幾何学模様の動画（V-VI）から構成されている（図 1）[12-14]。

人の顔の動画は、4 つの異なる女性の顔の動きを見せる物で、(I)無言かつ瞬きをする動画、（II）無言かつ無表情の動画、（III）無言で口の開閉する動画、（IV）被験者に「こんにちは、お名前は？一緒に遊ぼうよ」と日本語で話しかける動画となっている。人物と幾何学模様の動画は、（V）左右同じ大きさの画角に人物の顔の動画と幾何学模様の動画が並んでいるもの、（VI）大きい画角の人物の動画に小さい小窓に幾何学模様が写されたもので構成されている。これら 6 つの動画には、社会的領域と非社会的領域の 2 つの対象領域があり、社会的領域は、人の顔やその中でも特に目など、社会的コミュニケーションに必要な情報を示している（図 2 の領域 1)。一方、非社会的領域とは、幾何学模様など人間の社会的コミュニケーションに不要な情報や口などの目と比較して社会的コミュニケーションをとる際に重要視されないものを（図 2 の領域 2)、非社会的コミュニケーションとして情報を示している[12-14]。

2.4 Mean Fixation Percentage

Mean Fixation Percentage（MFP）とは、検査中に約 2 分間流れる動画タスク中に、被験者の視線がモニター画面上にあった時間の割合の事であり、被験者の各動画タスクにおけるターゲット領域への注視率を計る際に、正確に画面を注視できていたかの評価指標となる。Gazefinder®を用いた研究では、MFP のカットオフ値を 70%以上とすることで、被験者が適切に画面を注視し、各動画の課題を正確に評価できるとしている[10, 15, 16]。

本研究でも、MFP のカットオフ値を 70%に設定し、各修正月齢群に MFP を 70%以上に保てている被験者の割合を求め、その違いについて評価した。また、MFP が 70%以下の被験者が多かった修正月齢 3-6 か月群に対して、被験者 49 人を MFP が

70%以上と 70%未満に分け、13 個の新生児因子[性別、修正月齢、出生体重、体格、呼吸窮迫症候群、脳室内出血、動脈管開存症、未熟児網膜症、人工呼吸器使用、遷延性肺高血圧症、新生児慢性肺疾患（Chronic lung disease, CLD）、高濃度酸素療法、Apgar スコア 1 分値、 Apgar スコア 5 分値]および 6 個の母体因子（母体年齢、出産回数、妊娠糖尿病、妊娠高血圧症候群、前期破水、絨毛膜羊膜炎）との関連について比較検討した。

3. 手順

実際の検査の手順は、被験者が保護者の膝の上に座り、Gazefinder®のモニターから約 60cm 離れた場所で画面を見ながら行った。キャリブレーション情報を得るために、被験者はまずモニター上に映し出されるアニメーションの動物を見て、Gazefinder®の赤外線 LED ライトとカメラが被験者の視線位置を検出し、キャリブレーションを行った。次に、実際の検査用の動画が約 2 分間上映され、被験者の視線の位置から、各検査動画の社会性領域と非社会性領域の注視率を割り出した。検査は、被験者、保護者、研究者の 3 人だけで行い、研究者は被験者の気が散らない様に、被験者と保護者の後ろに立って観察した。また、保護者が検査中に被験者に話しかける事や指さしをして画面に注目するよう促すことはしないように指示した。

3.1 統計分析

被験者は修正 3-6 か月、7-9 か月、10-12 か月、13-18 か月、18-32 か月の 5 つのグループに分け、MFP と各対象領域（社会的領域と非社会的領域）の注視率の違いについて調べた。これらの修正月齢群間の MFP の比較にはカイ二乗検定と Steel-Dwass 検定を使用した。低 MFP に関連する周産期臨床因子の検討には、Fischer の正確検定と MannWhitney の U 検定を用いた。そして、各対象領域の注視率の比較は Steel-Dwass 検定で行った。有意水準は $p<0.05$ とし、統計解析はソフトウェア Jmp14®（SAS Institute, Cary,
NC, USA）を用いて行った。

3.2 倫理

本研究プロトコルは、日本大学板橋病院施設審査委員会倫理委員会（RK-210112-1 号）の承認を得ており、ヘルシンキ宣言の信条に準拠している。そして、本研究は被験者の保護者全員から書面によるインフォームド・コンセントを得て検査を行った。

4. 結果

被験者 90 人の特徴を表 1 に示す。90 人中、29 人の被験者が複数の検査を受けたため（23 人が検査を 2 回ずつ受け、6 人は 3 回ずつ検査を受けた）延べ 125 人分の検査結果
について視覚的特徴を解析した。平均在胎週数は 31 週、平均出生体重は 1,542g であり、在胎週数や出生体重など周産期因子は、各修正月齢群間で統計的な有意差は認められなかった。

MFP が 70%以上であった被験者の割合を各修正月齢群別に比較したところ、修正月齢 3-6 か月群では 51%であったが、修正月齢の増加に伴い MFP が 70%以上の被

験者の割合は有意に増加した（修正 13-18 か月で 90%、修正 19-32 か月で 100%）（p＝0.0003、表 2）。

MFP が最も低かったのは修正 3-6 か月群（中央値 70.3%）であったが、月齢の増加に伴い MFP は増加し、MFP が最も高かったのは 19-32 か月群（中央値は 94.2%）であった。各修正月齢群の MFP を比較した所、修正 3-6 か月群の MFP は修正 19-32 か月群より有意に低かった（Steel-Dwass 多重比較検定で p=0.0272）（図 3）。

次に修正 3-6 か月群の低い MFP に影響する周産期因子について検討するため、修正 3-6 か月群の被験者 49 人を MFP が 70%以上と 70%未満に分けて比較した。その結果、CLD において有意差を認め、低 MFP との関連があることが判明した（p=0.036、表 3）。

早産児特有の注視特性を評価するため、各検査用動画（I-VI）において、全月齢群にわたって社会的・非社会的標的領域への注視率を評価した所、口を動かさない顔動画、 (I)、(II)ではどの月齢群も有意に眼球領域を長く注視していた（表 4a、b）。口を動かす顔動画、(III)、(IV)では、修正 7-9 か月以降の被験者は口領域を有意に長く注視した。口への注意の割合は月齢が上がるにつれて増加し、目への注視率は減少した（表 4c、d）。人物と幾何学模様からなる動画課題（V-VI）では、修正 7-9 か月以降の被験者は、幾何学模様よりも人物の顔を有意に長く注視した（表 4e～f）。

5. 考察

ASD は、社会的コミュニケーションおよび相互関係における持続的障害と限定された反復的な行動、興味、活動の様式を特徴とし、それらの特性が幼児期より出現しているものとされる [17]。現在 ASD の有効的な治療法は無いが、2 歳未満での早期介入は、社会的予後の改善が期待できる [16,18]。しかし、ASD の症状には早産児と正期産児でその特徴が異なり [8]、早産で生まれた ASD 児の多くは診断基準を満たさず、診断に至らない事も多い [20]。視線解析装置は、そんな早産の ASD 児に対しても早期診断に有用な可能性がある。正期産の ASD 児を対象にした視線解析装置のメタアナリシスでは、被験者の対象年齢の最低年齢は 2 歳であったが [3]、早産児は発達が遅れるため、彼らに対して Gazefinder®を適切に使用開始できる年齢がいつなのかは不明である。正期産児への Gazefinder®の適切な使用開始時期について過去の研究では、生後 4 か月の時点ですでに MFP は 80%以上になると示されており [14] 適切に検査が行える事が示されている。早産児と正期産児の ASD を比較したいくつかの研究では、最小の対象月齢は 6-7 か月（早産児の場合は修正月齢）としている物が多い [5, 21]。しかし、早産児に対する Gazefinder®の使用開始の適切な時期を検討した報告は現時点ではない。

そこで本研究では、早産児に対する Gazefinder®の使用開始時期について検討した。本研究では被験者の視線パターンを適切に分析するために、MFP70%以上を基準として定義したところ、早産児は修正 7 か月以降に MFP が 70%以上に追いつき始める

という結果が得られた。その割合は月齢とともに増加し、修正 13 か月で 90%以上、18 か月以降では 100%が MFP を 70%以上に維持した。つまり、修正 3-6 か月の被験者は、
Gazefinder®で視線を正確に解析できる程十分な発達をしていなかった事が推察できた。そのため、早産児の視線パターンを正確に分析するには、少なくとも修正 18 か月以降が適切だと考えられた。
次に、修正 3-6 か月時のグループは MFP が低く、何がその低さに影響しているか、いくつかの周産期因子について分析した。MFP が低いのは、在胎週数、出生体重、IVH の有無、アプガースコアなど、脳や視覚の発達に直接影響する因子を予想していたが、予想に反して CLD のみが早産児の MFP 低下に有意に関連する周産期因子であった。早産児における CLD は、酸素需要が生後 36 週を超えても持続する長期的な呼吸器障害であり、長期にわたる酸素投与や呼吸性アシドーシスが発達遅滞の危険因子と言われている [22]。低酸素血症とアシドーシスが長期化した呼吸器疾患のある早産児は、修正 6 か月時の
Bayley 発達評価で遅れが見られたが、2 歳時点では見られなかったという報告がある [23]。
また、IVH や PVL を伴わない CLD の早産児でも、2 歳時の Bayley 発達評価で発達の遅れは認められなかった [24]。つまり、CLD を有する早産児は、低年齢では発達の遅れが見られるが、成長とともに回復する可能性が高いと示された。そのため、早産児の場合 MFP が 70%以上になるには、正期産児よりも長い時間を要すると考えられ、CLD を合併している早産児の場合に Gazefinder®を使用する際は、発達評価に注意が必要であると考えられた。

最後に、早産児における視線のパターンを計測し、社会的情報と非社会的情報の注視率を比較した。先行研究では、正期産の ASD 児は人の顔よりも幾何学模様を好んで見
る傾向があるとされ [3, 9, 10]、早産児は定型発達児に比べて ASD の有病率が高いことから、早産児も幾何模様や口などの非社会的情報を好んで注視すると予想された。福島らは、定型発達の正期産児では、生後 4-7 か月でも、口が動いていない時のみ、口よりも目を注視する割合が高いと示し [14]、Dean らは、早産児は修正 7-9 か月の時点で正期産児に比べて社会的情報を注視する割合は低かったが、5 歳の時点では早産児も正期産児と同程度に社会的情報を注視する割合が増加すると報告している [21]。しかし、本研究では予想に反して、修正 3-7 か月の早産児でも、定型発達児と同様に社会的情報をより注視した。
Chen らによると、早産児の ASD 児は視線を合わせる事や人に微笑むなどの非言語的コミュニケーションは苦手だが、正期産の ASD 児よりも良好な交友関係が築くと分かっている [8]。一般的に早産児は ASD の有病率が高い事は知られているが、そうした早産児特有の ASD 特性が、本研究結果にも影響を与えた可能性が考えられる。そのため、今後は Gazefinder®による正期産児との注視パターンの比較や早産児の ASD の有無を踏まえたうえでの研究を継続していく必要がある。

6. 研究の限界

本研究では、初回サンプリングの時点で PVL や重症 IVH のような重篤な脳障害や硝子体手術後に重症未熟児網膜症と診断されていた児は、研究対象から除外したため、除外した症例数やその割合は定かではない。サンプリングの際に被験者の視機能を評価できておらず、視機能が低い事による MFP やターゲット領域への注視率への影響が考慮できていない。また、本研究では被験者の ASD の診断は行っておらず、対象早産児における ASD 有病率が彼らの MFP やターゲット領域の注視率に影響を与えた可能性がある。

その他、コホートサイズが小さく、特に低 MFP に関連する医学的要因の検索においてはサンプル数の小ささから、CLD 以外の要因に有意差を認められなかった可能性がある。更に、本研究は大学病院で実施されたため、定型発達児の被験者を集めることが難しく、早産児と正期産児を比較する事ができなかった。したがって、早産児の注視率が正期産児とどのように異なるかは不明である。また、現段階で本研究の早産児が ASD や ADHD の特性を認めるか確認する事ができないため、彼らの ASD 特性、ADHD 特性が本研究の結果にどの程度影響しているかは不明である。

7. 結論

早産児の MFP は低月齢では低く、大部分の児で検査が実施できるのは修正 13 か月以降だが、修正 19 か月以降であればほぼ全ての児に対し Gazefinder®で正しく視線を解析できると言える。また、特に CLD を合併していた早産児の場合は、Gazefinder®を使用する際に、発達評価に注意することが望ましい。また、早産児は、定型発達児と同様に社会的情報をより注視すると分かった。今後は、早産児と正期産児の視覚認知の特徴について比較することで、早産児の注視パターンを更に明らかにし、早産の ASD 児に対して Gazefinder®が早期診断に有効か、更に調査していく予定である。

表 1.被験者背景

被験者　（人）	n = 90
在胎週数, (週)平均 ± SD	31 ± 3.1
出生時体重（g）,平均 ± SD	1,542 ± 516
性別　男児　（人）	34 (37%)
被験者（重複含む）（回）	n = 125
修正月齢別　結果　（回）	
3−6 か月	49 (49%)
7−9 か月	28 (22%)
10−12 か月	16 (13%)
13−18 か月	19 (16%)
19−36 か月	13 (10%)

SD, 標準偏差

表 2. 修正月齢別 MFP

修正月齢（か月）	3−6	7−9	10−12	13−18	19−32
MFP≥70％以上 / 各月齢別合計（回数）	25 / 49	18 / 28	11 / 16	17 / 19	13 / 13
(%)	51%	64%	69%	90%	100%
月齢増加に伴い MFP も統計学的有意に増加	(p = 0.0003)				

MFP, 総注視率

表 3. MFP に影響する周産期因子

	Total (n=49)		
	>70%　n=25	<70%　n=24	
	人数: 中央値 (%)（最小値-最大値）	人数: 中央値 (%)（最小値-最大値）	p-value
周産期因子			
男児	8 (32%)	12 (50%)	0.19
修正月齢	33 (25−35)	31.5 (22−35)	0.23
出生体重	1575 (578−2327)	1480 (578−2412)	0.50
SGA	17 (68%)	18 (75%)	0.59
呼吸窮迫症候群	11 (44%)	11 (45%)	0.89
脳室内出血	2 (8%)	0 (0%)	0.16
動脈管開存症	0 (0%)	2 (8%)	0.14
未熟児網膜症	0 (0%)	1 (4%)	0.30
呼吸器使用	12 (48%)	11 (54%)	0.88
遷延性肺高血圧	0 (0%)	1 (4%)	0.30
新生児慢性肺疾患	1 (4%)	6 (25%)	0.036
高濃度酸素療法	0 (0%)	3 (12%)	0.69
Apgar スコア　1 分	8 (3−9)	7.5 (1−8)	0.12
Apgar スコア　5 分	9 (6−9)	8.5 (3−9)	0.43
母体因子			
母体年齢 (歳)	32 (24−43)	33 (19−46)	0.52
初産婦	13 (48%)	14 (58%)	0.65
経産婦	21 (84%)	19 (79%)	0.66
妊娠糖尿病	2 (8%)	1 (4%)	0.56
妊娠高血圧	6 (24%)	4 (17%)	0.52
前期破水	2 (8%)	4 (17%)	0.35
絨毛膜用膜症	14 (56%)	17 (71%)	0.28

SGA: Small-for-gestational age（在胎週数に比して、出生体重が 10%ile 未満の児）

表 4. 各動画（I～VI）の、修正月齢別ターゲット領域への注視率

(a)無言かつ瞬き　(動画 I)

修正月齢 (か月)	目 平均注視率 (%)	口 平均注視率 (%)	p-value
3−6	81.6	0.0	<0.0001
7−9	86.0	0.0	<0.0001
10−12	77.2	0.8	0.0174
13−18	88.4	0.0	<0.0001
19−32	76.0	1.2	<0.0001
全月齢	82.6	0.0	<0.0001

(b) 無言かつ無表情　(動画 II)

修正月齢 (か月)	目 平均注視率 (%)	口 平均注視率 (%)	p-value
3−6	71.0	0.0	<0.0001
7−9	70.2	2.7	<0.0001
10−12	59.5	12.0	0.0061
13−18	83.5	0.0	<0.0001
19−32	50.0	18.5	0.0055
全月齢	82.6	0.0	<0.0001

(c) 無言で口の開閉 (動画 III)

修正月齢 (か月)	目 平均注視率 (%)	口 平均注視率 (%)	p-value
3−6	41.6	4.8	0.0006
7−9	23.8	39.4	0.367
10−12	18.8	48.8	0.0038
13−18	11.2	63.2	0.0003
19−32	11.6	69.2	<0.0001
全月齢	23.6	41.0	0.0099

(d) 日本語で話しかける (動画 IV)

修正月齢 (か月)	目 平均注視率 (%)	口 平均注視率 (%)	p-value
3−6	35.4	12.0	0.0023
7−9	30.6	51.4	0.0327
10−12	11.7	57.7	0.0070
13−18	20.0	54.3	0.0072
19−32	19.5	54.3	0.0428
全月齢	27.5	50.0	0.0211

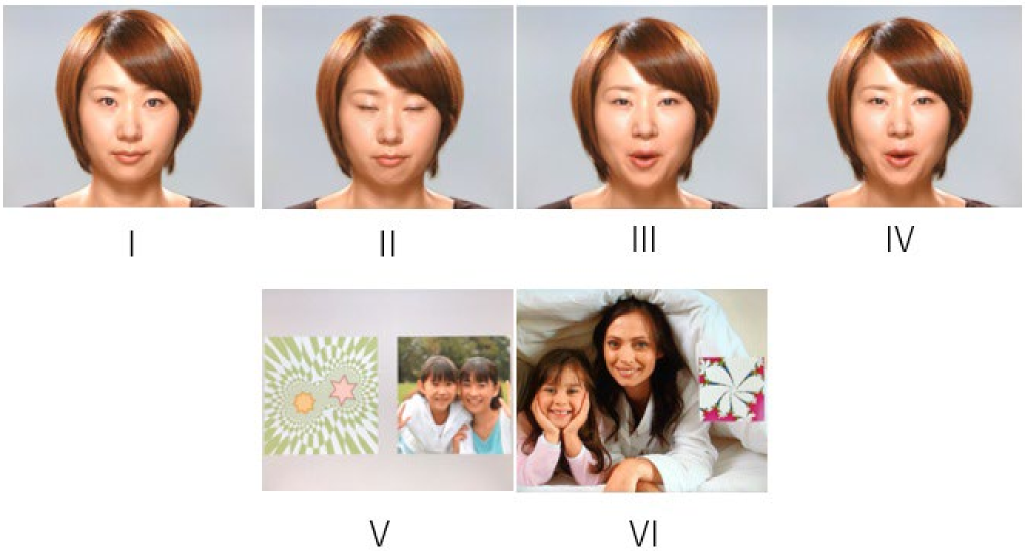
(e)　人物と幾何学模様（大きさの画角）(動画 V)

修正月齢 (か月)	人の顔 平均注視率　(%)	幾何学模様 平均注視率　(%)	p-value
3−6	23.9	26.9	0.2252
7−9	41.9	16.3	<0.0001
10−12	32.3	16.2	0.0873
13−18	56.2	9.3	<0.0001
19−32	55.6	7.2	<0.0001
全月齢	37.3	15.5	<0.0001

(f) 人物と幾何学模様（小窓）(動画 VI)

修正月齢 (か月)	人の顔 平均注視率 (%)	幾何学模様 平均注視率(%)	p-value
3−6	34.5	11.3	<0.0001
7−9	55.3	18.5	<0.0001
10−12	60.7	11.8	0.0256
13−18	57.3	11.1	<0.0001
19−32	50.5	16.5	0.001
全月齢	46.9	13.0	<0.0001

図 1. Gazefinder®動画サンプル



（I）無言かつ瞬きをする動画、(II) 無言かつ無表情の動画、(III) 無言だが口の開閉を繰り返す動画、(IV) 被験者に「こんにちは、お名前は？一緒に遊びましょう」、（V）左右に同じ大きさの画角に数名の人物が見つめている動画と幾何学模様の動画が並んでいるもの（VI）大きい画角の人物の動画に小さい小窓に幾何学模様が写されたものである。

図 2. 社会的領域と非社会的領域を持つ 6 つの動画

直線で囲まれたエリア 1 は社会的情報を示す。

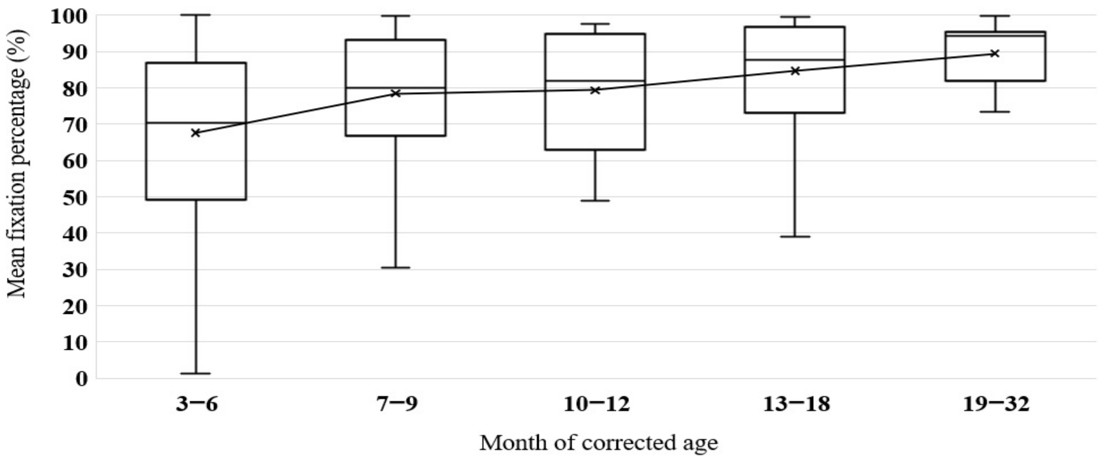
縞模様のエリア 2 は非社会的情報を示す。

A. 人間の顔： エリア 1 には目の領域、エリア 2 には口の領域が含まれる。

B. 人物と幾何学模様（同じ大きさ）： エリア 1 は人の顔、エリア 2 は幾何学模様。

C. 人物と幾何学模様（小サイズ）： エリア 1 は人の顔、エリア 2 は幾何学模様。

図 3 修正月齢別に MFP を比較したもの



総注視率（The mean fixation time percentage of all sequences）を MFP として、70%とカットオフ値として、各修正月齢別に被験者の MFP を比較した。MFP が最も低かったのは修正 3-6 か月群（中央値 70.3%）であったが、月齢の増加に伴い MFP は増加し、MFP が最も高かったのは 19-32 か月群（中央値は 94.2%）であった。各修正月齢群の MFP を比較した所、修正 3-6 か月群の MFP は修正 19-32 か月群より有意に低かった（Steel-Dwass 多重比較検定で p=0.0272）。

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