



Title	Regular sleep habits in toddlers are associated with social development and brain coherence
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**Title: Regular sleep habits in toddlers are associated with social development and brain coherence**

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## Abstract

**Objective:** Although sleep habits are associated with the development of toddlers, factors affecting social development and brain function remain unclear. We aimed to elucidate the relationship between sleep habits and social development as well as brain coherence in toddlers.

## Methods:

We used the data set at 1.5-2 years old, in the longitudinal study-until 6 years old. We evaluated sleep parameters, such as average wake-up time, bedtime, nighttime sleep duration, total sleep duration, and the standard deviation (SD) of sleep habits. We also examined the development, including the social stimuli fixation percentage using GazeFinder<sup>®</sup> and electroencephalography (EEG) coherence between brain regions.

**Results:** Seventy-two children (37 boys and 35 girls) were included. The fixation percentage for the human face was negatively correlated with the SD of the total sleep duration, nighttime sleep duration, nap duration, and bedtime ( $r=-0.516, p=0.000$ ;  $r=-0.331, p=0.005$ ;  $r=-0.330, p=0.005$ ; and  $r=-0.324, p=0.005$ , respectively). The EEG analysis indicated that  $\alpha$ -band coherence in the right centro-parietal area was negatively correlated with the total sleep duration ( $r=-0.283, p=0.016$ ). The path diagram demonstrated a direct significant effect of sleep duration irregularity on development including social communication and fixation percentage for human faces. Additionally, total sleep duration exhibited a direct effect on  $\alpha$  cortical coherence in the right centro-parietal area.

**Conclusions:** In this study, we found an association between sleep irregularity and the development of social communication, preference for humans, and brain coherence in

54 toddlers. We suggest that regular sleep plays an important role in promoting the  
55 development of social communication.

56 **Keywords**

57 Irregular sleep, development, child, eye-tracking, coherence, electroencephalography

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## 1. Introduction

Sleep has a restorative effect on the brain and is thus essential for survival [1,2]. Furthermore, it plays a pivotal role in consolidating learning and memory by pruning excess synapses during sleep [2-5]. Consequently, sleep deprivation has been associated with detrimental effects on performance and language acquisition [6].

Worldwide birth cohort studies have demonstrated that short sleep duration, frequent awakening after sleep onset, and late bedtime in early childhood were associated with high scores for attention deficit hyperactivity disorder and lower language acquisition at 5–6 years old, along with depression, and psychotic symptoms in adolescence [7-11]. However, a previous systematic review demonstrated that the association between short night sleep duration, long sleep-onset latency, frequent night-waking, and less prosocial behavior remains controversial [12]. In addition, the duration of night sleep was positively related to the receptive vocabulary ability in children aged 36–60 months [13,14]; however, in another cross-sectional study of children aged 51–67 months, no significant association was reported [15]. In toddlers, while shorter nap duration and higher nighttime sleep ratios were reported to be associated with cognition, nighttime/total sleep duration and nighttime sleep midpoint were related to gross motor development [16].

In summary, the relationship between average sleep-related time and cognitive function or developmental profiles remains unclear.

Newborns show interest in human faces from birth [17]. Children with autism spectrum disorders (ASD) have been reported to prefer repetitive images (geometric patterns) rather than social images (such as humans) and pay less attention to the human eye than

86 children with typical development do [17-21]. Therefore, eye tracking is expected to be  
87 a biomarker for individuals with ASD, with gaze patterns being considered indicators of  
88 social development. Specifically, less fixation on the eyes is correlated with greater  
89 social disability [20]. Using an eye-tracking machine, infantile sleep problems were  
90 negatively associated with a later preference for human faces [22]; however, there have  
91 been only a few reports about the relationship between sleep habits and social attention  
92 using objective tools.

93 The brain networks associated with attention to social images involve the area of  
94 perceptual decoding and integration of social cues (face, gaze, action, and voice), which  
95 is related to the posterior superior temporal sulcus, adjacent lateral occipitotemporal  
96 cortex, fusiform gyrus, intraparietal sulcus, and premotor cortex [23-26]. These  
97 corresponded to central and parietal regions on electroencephalography (EEG). In a  
98 resting-state functional magnetic resonance imaging study, children with ASD had  
99 decreased functional connectivity in the action observational network, particularly in the  
100 lateral occipital cortex and fusiform gyrus [27].

101 This study aimed to investigate the relationship between sleep habits and development,  
102 especially social development, using an eye tracker and brain coherence EEG in  
103 toddlers.



## 2. Methods

### 2.1. Participants

Eighty-six young children, aged 1.5–2 years (range 18–25 months), were enrolled between March 2021 and January 2023 through web advertising and leaflet distribution around Osaka University. This study used the data set at the first time point in the longitudinal study, from toddlers until 6 years old. There has not been enough research on the relationship between sleep and brain functional development using objective tools such as EEG or eye tracking. Therefore, in this study, we evaluated the data set at the first time point as the cross-sectional exploratory study examining the sleep-related factors influencing brain functions. We will confirm its validity in a longitudinal follow-up study where improvement of these sleep-related indices may make a significant influence in brain functional development in the future study.

The inclusion criterion was healthy, full-term children aged 18–35 months. The exclusion criteria were as follows: 1) the children were suspected of being abused, 2) the caregiver could not cooperate with this study because of their mental disease, and 3) the children had received interventions for their mental and motor developmental problems.

This study was approved by the Institutional Review Board of Osaka University Hospital (20260-3) prior to the start of the study and conformed to the tenets of the Declaration of Helsinki. The parents of all children provided written informed consent before enrollment.

## **2.2.Sleep parameters**

Data for sleep parameters were collected for 8 consecutive days using the Nenne Navi app, as previously described [28]. Previous studies have demonstrated the app's sufficient usability and acceptability, and the reported data were sufficiently reliable in comparison with those obtained using actigraphy [28,29]. We obtained representative sleep parameters, such as average wake-up time, bedtime, nighttime sleep duration, total sleep duration, nap duration, and sleep onset latency. The mean sleep parameters in each child were averaged over 7 days. The standard deviations (SD) of these parameters for 7 days in each child were calculated and used as indices of sleep irregularity. We analyzed the children who have entered sleep factors on at least 3 consecutive weekdays and weekends.

## **2.3.Measure of Children's Development**

To assess global development, we used the Kinder Infant Development Scale (KIDS), which is a parent-rated questionnaire developed and validated in Japan [30], and the Bayley Scales of Infant and Toddler Development, Third Edition, Japanese version [31], which was used by psychologists to assess five domains: cognition, receptive communication, expressive communication, fine motor, and gross motor. To evaluate the ASD characteristics, the Japanese version of the Modified Checklist for Toddlers with Autism (M-CHAT) was administered [32]. The children who failed three or more items were suspected of having features of ASD.

## **2.4.Acquisition of eye-tracking data and EEG**

To evaluate the association between a lack of orientation toward humans and brain

connectivity during visual attention, we simultaneously measured eye tracking while watching a video monitor and recorded EEG.

The eye-tracking measurement was performed using Gazefinder<sup>®</sup> (JVC KENWOOD Co, Yokohama, Japan).

Children were placed on their caregivers' laps and fitted with a stretch cap (Waveguard; Eemagine Medical Imaging Solutions GmbH, Berlin, Germany) with 19 electrodes in a 10/20 system pattern (Figure 1a). The children watched a 19-inch monitor with 1280 × 1024 pixels, which was set approximately 60 cm away from them. Eye position was recorded at a sampling rate of 50 Hz. After calibration of the eye position was performed using a five-point method, a series of short movies lasting approximately 2 min were displayed to calculate the fixation time in the relevant area.

One of the presented images is shown in Figure 1b. The movie included several types of videos of a human face, biological motion, pointing objects, and human and geometric figures.

The percentage of fixation times for defined areas in each movie was automatically calculated. In the movies with human and geometric figures, the target areas were set as human or geometric figures, and the target areas were set as the eyes and mouth in a movie of a talking human. We analyzed only the fixation times with a whole viewpoint acquisition rate of 60% or higher. The mean percentage of fixation times in movies similar to those used in previous reports documenting ASD characteristics was analyzed [21,33].

Simultaneously, EEG, which is a noninvasive and readily available tool for toddlers, was recorded using the TruScan 32 system (DeyMed Diagnostic, Kudrnáčova, Czech

Republic) with a sampling rate of 1,000 Hz, and a CPz electrode was used as a system reference. The hardware filter setting was 0.1–100 Hz.

Coherence analysis was performed using the EMSE Suit (Corthch Solutions, NC, USA). Artifacts were visually removed by experienced researchers (Y.I. and S.N.). EEG coherence between pairs of scalp locations can provide information on the intrahemispheric and interhemispheric networks. The frequency bands were divided into delta (1.96–3.92 Hz), theta (4.9–7.84 Hz), alpha (8.83–13.72 Hz), beta (14.7–24.5 Hz), and gamma (35.28–44.1 Hz). Coherence values were derived for each band.

## **2.5. Statistical analysis**

We conducted a correlation analysis of the variables after testing for normality. Spearman's rank correlation test in non-normal distribution or the Pearson correlation test in normal distribution was performed to evaluate the correlation between sleep habits and development, the percentage of fixation times for eyes and mouths in a face or preference for human and geometric figures, and EEG coherence. All the children were classified into group T with less than three failed M-CHAT items and group M with three or more failed items. The Mann–Whitney U test was used to detect the differences between these two groups to examine the effects of autistic features on communicative development and eye-tracking traits. Otherwise, children were classified into a group (group H) in which the father and mother are highly educated (university or graduate school graduates) and another group (group L) in which the father and mother are not highly educated. The comparison between sexes and, high and low parental education was performed using a Mann–Whitney U test or a t-test. Regarding family

income, children were classified into four groups. (1; 3,000,000–5,000,000 yen, 2; 5,000,000–7,000,000 yen, 3; 7,000,000–10,000,000 yen, 4; >10,000,000). The Kruskal-Wallis test was used for the analysis.

All analyses were performed using the Statistical Package for Social Sciences (SPSS), version 26.0 (SPSS Inc. Chicago, Illinois, United States).

Structural equation modeling (SEM) was used to elucidate the factors that are correlated with the development and coherence of toddlers based on the following hypothesis: We hypothesized that sleep habits, including average sleep duration, bedtime, awakening frequency after sleep onset, and the SD of these parameters influenced social and communication development and brain function. Moreover, we considered age, sex, parental education, and family income as potential confounding variables, performed correlation analysis, and added the factors correlated with the development and coherence. We ascertained that the models, consistent with the hypothesis, were either accepted or rejected. The goodness-of-fit index (GFI), adjusted goodness-of-fit index (AGFI), comparative fit index (CFI), and root mean square error of approximation (RMSEA) were used to evaluate the model fit. The SEM analysis was performed using AMOS version 29 (IBM Japan Ltd.).

### 3. Results

#### 3.1. Overall results of clinical characteristics

A total of 72 children (37 boys and 35 girls) were included in the analysis after excluding 14 children (Figure 2). Notably, all the children except three had sleep parameters for 7 days and the remaining three children had 6-days consecutive data.

The developmental quotient (DQ; mean  $\pm$  SD) of the KIDS in 72 children was 107  $\pm$  13 (Table 1). Eight children (11%) had three or more failed items of M-CHAT. The number of failed items was not associated with development on the Bayley Scales (data not shown). Moreover, there were no significant differences in cognition, receptive communication, expressive communication ability, or fixation percentage for humans between groups M and T ( $p=0.462$ ,  $p=0.107$ ,  $p=0.680$ , and  $p=0.936$ , respectively).

The number of group H in parental education or maternal education was 57 (79%) and 51 (71%), respectively. However, the number groups 1, 2, 3 and 4 in the family income were 11 (15%), 14 (19 %), 27 (38 %), and 17 (24%).

	Mean $\pm$ SD
Age (month)	22 $\pm$ 2
Sex (male/female)	37/35
<b>Bayley Scales of Infant and Toddler Development</b>	
Cognition	108 $\pm$ 15
Receptive communication	99 $\pm$ 24
Expressive communication	93 $\pm$ 24
Gross motor	99 $\pm$ 16
Fine motor	105 $\pm$ 12
<b>Kinder Infant Development Scale</b>	
Total developmental quotient	107 $\pm$ 13
<b>Sleep habits</b>	
Wake-up time (time, min)	7:13 $\pm$ 0:48

SD of wake-up time (min)	29.9 ± 15.1
Bedtime (time, min)	20:53 ± 0:52
SD of bedtime (min)	30.3 ± 25.1
Sleep-onset latency (min)	32.7 ± 21.4
SD of sleep-onset latency (min)	18.8 ± 13.6
Total sleep duration (min)	691.1 ± 38.9
SD of total sleep duration (min)	50.4 ± 22.3
Nighttime sleep duration (min)	584.6 ± 43.3
SD of nighttime sleep duration (min)	45.0 ± 24.4
Number of awakenings after sleep onset (per night)	1.4 ± 1.3
Nap duration (min)	106.2 ± 33.2
SD of nap duration (min)	38.7 ± 19.3
Nap starting time (time, min)	13:13 ± 1:15
Nap ending time (time, min)	15:02 ± 1:20
<b>Gazefinder: Mean fixation percentages</b>	
Human (%)	0.578 ± 0.120
Geometric figure (%)	0.140 ± 0.111
Eyes in a talking human face (%)	0.229 ± 0.182
Mouth in a talking human face (%)	0.642 ± 0.233
<b>α-band coherence of the EEG</b>	
C3-C4	0.124 ± 0.070
C3-P3	0.328 ± 0.081
C4-P4	0.307 ± 0.081

227 Table 1. Characteristics and sleep habits of participants in this study

228 SD, Standard deviation; EEG, Electroencephalography

229

### 230 3.2. Development and sleep habits

231 The correlations between sleep habits and developmental and behavioral indices are  
232 shown in Table 2. The DQ of the cognitive domain was negatively correlated with the  
233 SD of bedtime ( $r=-0.242$ ,  $p=0.041$ ) and SD of nighttime sleep duration ( $r=-0.261$ ,  
234  $p=0.027$ ) (Figure 3a). Moreover, the DQ of the receptive communication domain was  
235 negatively correlated with the SD of bedtime ( $r=-0.397$ ,  $p=0.001$ ), SD of total sleep  
236 duration ( $r=-0.252$ ,  $p=0.032$ ), and SD of nighttime sleep duration ( $r=-0.245$ ,  $p=0.038$ ).

237 The DQ of the expressive communication domain correlated with the SD of bedtime  
238 ( $r=-0.317, p=0.007$ ) and nighttime sleep duration ( $r=-0.263, p=0.026$ ) (Figure 3b). The  
239 DQ of the gross motor domain was correlated with the SD of sleep-onset latency and  
240 SD of total sleep duration ( $r=-0.233, p=0.048$ ;  $r=-0.241, p=0.041$ ). However, fine motor  
241 development was not associated with any of these sleep habits.



	DQ					Human and geometric figure <sup>†</sup>		Talking human face <sup>†</sup>		Coherence of the EEG				
Sleep habits	Cog	RC	EC	Fine motor	Gross motor	Human face (%)	Geometric figure (%)	Eyes (%)	Mouth (%)	C3-P3 (α)	C4-P4 (α)	C3-C4 (α)	F3-F4 (θ)	Fp1-Fp2 (γ)
Wake-up time (time, min)	0.041	-0.083	0.103	0.138	-0.100	-0.052	-0.040	-0.011	0.151	0.152	-0.178	0.080	0.177	-0.082
SD of wake-up time (min)	-0.104	-0.191	-0.161	-0.112	0.158	-0.022	0.209	-0.038	0.050	0.216	0.064	0.147	0.107	<b>-0.247*</b>
Bedtime (time, min)	-0.092	-0.118	-0.016	0.065	-0.072	-0.105	0.001	-0.062	0.052	0.129	-0.059	0.124	0.205	-0.184
SD of bedtime (min)	<b>-0.242*</b>	<b>-0.397**</b>	<b>-0.317**</b>	0.004	-0.110	<b>-0.324**</b>	0.139	-0.190	<b>0.283*</b>	0.185	-0.113	0.043	<b>0.255*</b>	-0.168
Sleep-onset latency (min)	0.016	0.195	0.082	-0.008	-0.148	0.044	0.137	0.024	-0.042	-0.104	0.024	-0.093	0.155	-0.170
SD of sleep-onset latency (min)	-0.179	-0.019	0.023	-0.046	<b>-0.233*</b>	-0.183	0.211	-0.122	0.074	-0.027	0.042	-0.009	<b>0.338**</b>	-0.163
Total sleep duration (min)	-0.032	-0.107	-0.013	0.032	0.092	0.129	-0.212	0.130	0.037	0.019	<b>-0.283*</b>	-0.096	-0.073	<b>0.274*</b>
SD of total sleep duration (min)	0.038	<b>-0.252*</b>	-0.197	-0.010	<b>-0.241*</b>	<b>-0.516**</b>	<b>0.385**</b>	-0.133	0.111	<b>0.243*</b>	0.121	0.101	0.189	-0.200
Nighttime sleep duration (min)	0.084	-0.052	0.051	0.035	-0.018	0.132	-0.169	0.074	0.078	0.043	-0.144	-0.105	-0.149	<b>0.263*</b>
SD of nighttime sleep duration (min)	<b>-0.261*</b>	<b>-0.245*</b>	<b>-0.263*</b>	0.023	-0.073	<b>-0.331**</b>	0.199	<b>-0.270*</b>	0.231	0.080	-0.097	0.084	<b>0.337**</b>	<b>-0.295*</b>
Number of awakenings after sleep onset	-0.016	-0.059	-0.055	0.018	0.025	-0.030	-0.078	<b>-0.289*</b>	0.204	-0.123	-0.033	-0.095	0.040	0.036

Nap duration (min)	-0.143	-0.060	-0.086	-0.006	0.115	-0.004	-0.062	0.115	-0.074	-0.031	-0.140	0.026	0.113	-0.010
SD of nap duration (min)	0.037	-0.232	-0.111	-0.175	-0.102	<b>-0.330**</b>	<b>0.354**</b>	-0.019	-0.003	0.208	0.135	0.048	<b>0.336**</b>	-0.082
Nap starting time (time, min)	-0.023	0.086	0.009	0.040	-0.051	-0.147	0.070	0.021	0.058	0.039	-0.007	-0.006	0.014	-0.163
Nap ending time (time, min)	-0.077	0.091	-0.009	-0.009	-0.019	-0.163	0.085	0.182	-0.068	0.017	-0.028	-0.003	0.047	-0.181

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Table 2. Correlation between sleep habits and developmental/behavioral indices

†; Mean fixation percentages measured using Gazefinder®. \*,  $p < 0.05$ ; \*\*,  $p < 0.01$ , Cog; Cognition, RC; Receptive communication; EC; Expressive, SD; Standard deviation.

### 3.3. Eye-tracking fixation time percentage and sleep habits

The average percentage of fixation was  $93.4 \pm 5.8\%$  in all series of movies. The fixation percentage for the human face was negatively correlated with the SD of the total sleep duration (Figure 3c), nighttime sleep duration, nap duration, and bedtime (Table 2;  $r = -0.516$ ,  $p < 0.001$ ;  $r = -0.331$ ,  $p = 0.005$ ;  $r = -0.330$ ,  $p = 0.005$ ; and  $r = -0.324$ ,  $p = 0.005$ , respectively). Only in group T and not in group M, the fixation percentage for the human face was negatively correlated with the SD of the total sleep duration ( $r = -0.530$ ,  $p < 0.001$ ) (Supplementary Figure 1).

The fixation percentage for geometric figures showed a positive correlation with the SD of total sleep duration and SD of nap duration ( $r = 0.385$ ,  $p = 0.001$ ; and  $r = 0.354$ ,  $p = 0.002$ , respectively) (Table 2). Children with a shorter SD of nighttime sleep duration and fewer awakenings tended to look at the eyes of a talking human for a longer time ( $r = 0.270$ ,  $p = 0.022$ ;  $r = -0.289$ ,  $p = 0.014$ , respectively). The averages of wake-up time, bedtime, sleep-onset latency, total sleep duration, nighttime sleep duration, and nap duration were not associated with any eye-tracking trait in human and geometric figures or talking human movies.

### 3.4. EEG coherence and sleep habits

The correlation between EEG coherence and sleep habits is presented in Table 2. The  $\alpha$ -band coherence in the left centro-parietal area (C3-P3) was correlated with the SD of

total sleep duration ( $r=0.243$ ,  $p=0.040$ ), while that in the right centro-parietal area (C4-P4) was negatively related with total sleep duration ( $r=-0.283$ ,  $p=0.016$ ) (Figure 3d). Moreover, there was a positive correlation between the fixation time percentage for geometry and  $\alpha$ -band coherence in the left and right centro-parietal areas ( $r=0.302$ ,  $p=0.010$ ;  $r=0.240$ ,  $p=0.042$ ) (Table 3, Figure 4-ab).

	Human and geometric figures		Talking human face	
	Human figure (%)	Geometric figure (%)	Eyes (%)	Mouth (%)
<b><math>\alpha</math>-band coherence of EEG</b>				
C3-C4	0.089	0.215	0.089	0.044
C3-P3	-0.108	.302**	0.211	-0.125
C4-P4	-0.034	.240*	0.005	-0.111

Table 3 Correlation between eye tracking results and centro-parietal coherence indices

\*:  $p < 0.05$ , \*\*:  $p < 0.01$

### 3.5. Directional association between sleep habits and development

As each sleep parameter may be associated with the others, we created a path diagram to examine which sleep habits influenced social and communication development and brain function most strongly. Age was neither correlated with the DQ, nor (Supplementary Table) with the percentage of fixation times for preference for human and geometric figures or coherence. Regarding the sex, the Fp1-Fp2 coherence and DQ of expressive communication were significantly higher in girls than in boys ( $p=0.012$ ,  $p=0.031$ ). There was no relationship between the DQ, the percentage of fixation times and coherence and parental education and family income (Supplementary Table). Therefore, we created a suitable model according to the results of the correlational

analysis. The previous model of the relationship among sleep habits, development, and frontal and centro-parietal coherence proposed that irregular sleep habits influence the connection of different brain regions and development. This model demonstrated that the direct effect of nighttime sleep duration irregularity on development, consisting of receptive/expressive communication, cognition, and fixation time for humans, was statistically significant. Moreover, we identified the direct effect of total sleep duration on  $\alpha$  cortical coherence in the C4-P4 area while watching the movies, irregular nighttime sleep duration on  $\gamma$  coherence at Fp1-Fp2, and irregular nap duration on  $\theta$  coherence at F3-F4 (GFI=0.890, AGFI=0.828, CFI=0.946, and RMSEA=0.050; Figure 5). There was no significant direct link between development and brain coherence. However, sex was associated with expressive communication. Another model was created based on the hypothesis that sex was associated with Fp1-Fp2 coherence and DQ of expressive communication (GFI=0.887, AGFI=0.827, CFI=0.966, and RMSEA=0.037). In the model, the SD of nighttime sleep duration on Fp1-Fp2 coherence tends to be significant ( $p=0.055$ ), and sex on DQ of expressive communication was not significant. Therefore, the former of these two models was judged to be a fit when considering suitability.

#### **4. Discussion**

This is the first study to demonstrate that nighttime sleep duration irregularity in toddlers is associated with the development of cognition and social communication. In addition, we found a correlation between total sleep duration, irregularities in night sleep/nap duration, and coherence in the centro-parietal and frontal regions.

#### **4.1. Sleep habits and child early development**

Since the average bedtime and nighttime sleep duration for Japanese children at less than 3 years old were  $21:11 \pm 1:04$  and  $565.2 \pm 65.4$  min, respectively [34], the sleep habits in this study were representative of the population in Japan.

Our study revealed no significant correlations between the developmental profiles and any average values of sleep parameters. The discrepancies in our results compared to those of these previous studies may be attributed to the age group included in our study, which is younger than that in previous studies. Alternatively, many previous longitudinal reports have evaluated language and behavioral difficulties, including inattention, at a later stage [7,9,11,35]; however, our study is a cross-sectional one where the present developmental profile may reflect the preceding sleep habits of toddlers and brain function. Notably, no previous study has evaluated the relationship between the sleep habits of toddlers and functional evaluation using EEG and eye-tracking.

Recently, the association between irregular bedtime and aggression or inattention in children aged 2–5 years [36] and that between irregular wake time and poor cognitive development in preterm toddlers [37] were demonstrated. Moreover, in a longitudinal study of children aged 3–7 years, irregular bedtimes led to problematic behavior, which improved with consistent bedtimes [38]. Our study added to the evidence that the irregularity of sleep habits, but not their average time, may have a larger impact on the development of toddlers.

#### **4.2. Sleep habits, visual preference for human and geometric images, and brain coherence**

It may be argued that sleep irregularity, a feature of ASD, led to decreased attention to the faces in this study. However, although 11% of children had M-CHAT scores of more than 3, M-CHAT scores at baseline were not related to sleep habits or development. In addition, as described, only in group T and not in group M, the fixation percentage for the human face was negatively correlated with the SD of the total sleep duration ( $r = -0.530$ ,  $p < 0.001$ ). This correlation might indicate that the correlation of non-preference for humans with irregular sleep duration was not a direct result of the autistic traits among children. Whereas the M-CHAT score at this young age does not precisely predict later ASD diagnosis, this result may indicate that irregular sleep habits distort social development towards autism even in children without inborn ASD traits.

In many reports, individuals with ASD have shown differences in coherence based on EEG, because of the age differences, the types of presented tasks, and conditions (e.g., eyes open or eyes closed) [39-42]. A previous systematic review using EEG and magnetoencephalography demonstrated under-connectivity between long-distance regions, including the interhemispheric and interlobar distances, in the lower frequencies (delta to beta bands) in ASD. However, local (short-distance) underconnectivity at lower frequency ranges or overconnectivity at lower and higher frequencies have also been reported in ASD. These inconsistent results indicate that local connectivity remains controversial [43].

Direct gaze elicits a gamma burst over the right prefrontal area in 4-month-old infants [44]. Increased or decreased coherence in the frontal area is associated with later ASD symptoms and diagnosis [45,46]. The decreased gamma coherence with increased theta coherence in the frontal region in this study might be associated with later symptoms of ASD. The centro-parietal area is associated with visual attention and the execution of

actions when observing other people's actions [47]. This area plays an important role in higher brain functions, such as execution and social behavior.

Irregular sleep directly affects the circadian rhythm, which interacts with a homeostatic process [48]. In a study assessing motor skill and visual skill tasks, correlations were observed between improvements in daytime performance and a higher percentage of slow wave sleep (SWS) in the first quarter of the night, as well as stage 2 rapid eye movement (REM) and non-REM (NREM) sleep in the last quarter of the night [6].

Therefore, maintaining regular sleep-wake rhythms is crucial, as they influence the pattern of the sleep stage. On the other hand, under normal conditions, synaptic strength increases during wakefulness and decreases during sleep [49]. This downscaling of synaptic strength is beneficial for learning and memory consolidation. Notably, SWS and REM sleep are thought to contribute to the consolidation of complex memory [6].

Irregular sleep might thus affect the downscaling of synaptic strength and gamma oscillation emerging from the coordinated interaction of excitation and inhibition, which might be reflected in EEG coherence. Our results suggest a concerning implication: sleep irregularity during early childhood disrupts brain coherence, potentially impairing social development or possibly reinforcing existing impairments. In this study, we performed SEM by dividing the data based on sex, which is considered a covariate. However, the number of cases was small; therefore, we were unable to analyze it. Thus, considering the suitability of SEM, we thought that a model that did not include sex would be better. Given that previous studies have indicated significant long-term effects of sleep habits on developmental outcomes, it is imperative to conduct a longitudinal cohort study to track the children from this study and validate our findings.



### **4.3. Strengths and limitations**

In this study, we analyzed children's development as evaluated by a psychologist and objective tools, such as eye-tracking devices and EEG. However, this study has some limitations. First, this study analyzed data from the first time point in the longitudinal study, from toddlers until 6 years old with a relatively small sample size. Therefore, to mitigate this limitation, we used the Bayley Scales of Infant and Toddler Development and the report of sleep habits over consecutive 8 days to estimate the SD. Although EEGs and eye-tracking measurements can be challenging in many uncooperative toddlers, we provided the results based on exact and objective data with only a small number of dropouts. Second, the sleep habits were exclusively based on the parental reports. However, the used app requiring daily inputs made the recall bias insignificant. Third, in this study, the number of children with three or more failed items of the M-CHAT was small; therefore, we could not completely deny the association between sleep habits and social development with eye tracking in children with innate ASD.

## 5. Conclusion

The development of social communication may be associated with sleep irregularity in toddlers. Regular sleep plays an important role in promoting socio-communicational development, which is the basis of well-being. In the future, we should confirm the association between sleep habits, development, and brain connectivity in a longitudinal study to determine whether improvement in sleep habits could facilitate social communication skills in each child.

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## Author contributions

Drs. Iwatani and Taniike had full access to all of the data in this study and take responsibility for the integrity of the data and accuracy of the data analysis.

Study concept and design: Iwatani, Kagitani-Shimono, Yoshizaki, Yamamoto, and Taniike

Acquisition, analysis, or interpretation of data: Iwatani, Ono, Yoshizaki, Yamamoto, and Kagitani-Shimono

Drafting of the manuscript: Iwatani and Taniike

Critical review of the manuscript for important intellectual content: Iwatani, Mohri, and Taniike.

Statistical analysis: Iwatani and Ono

Supervision: Taniike, Mohri, Kagitani-Shimono, and Yamamoto

Declaration of interests

No disclosures were reported.

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