



OPEN Inter-subject gamma oscillation synchronization as a biomarker of abnormal processing of social interaction in ADHD

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Children with attention-deficit hyperactivity disorder (ADHD) have difficulties in social interactions. Studying brain activity during social interactions is difficult with conventional artificial stimuli. This pioneering study examined the neural correlates of social perception in children with ADHD and matched controls using naturalistic stimuli. We presented 20 children with ADHD and 20 age-and-sex-matched controls with tailored movies featuring high- or low-level social interactions while recording electroencephalographic signals. Both groups exhibited synchronized gamma-band oscillations, but controls demonstrated greater inter-subject correlations. Additionally, the difference in inter-subject correlations between high- and low-interaction movies was significantly larger in controls compared to ADHD patients. Between 55 and 75 Hz comparing viewing high interaction movies with low interaction moves, controls had a significantly larger weighting in the right parietal lobe, while ADHD patients had a significantly smaller weighting in the left occipital lobe. These findings reveal distinct spatiotemporal neural signatures in social interaction processing among children with ADHD and controls using naturalistic stimuli. These neural markers offer potential for group differentiation and assessing intervention efficacy, advancing our understanding ADHD-related social interaction mechanisms.

Keywords Attention deficit-hyperactivity disorder, Naturalistic stimulus, Movie, Social interaction, EEG, Gamma oscillation

Attention-deficit hyperactivity disorder (ADHD) is characterized by symptoms of inattention or hyperactivity-impulsivity. This neurodevelopmental disorder becomes apparent before the age of 12¹. The early identification of ADHD in children allows for early intervention to overcome school dysfunction in late childhood and adolescence.

Currently, the diagnosis and classification of ADHD primarily depend on clinical observation of patients' behavior and diagnostic interviews¹. Several rating scales, such as the Swanson, Nolan, and Pelham rating scale version IV (SNAP-IV) are used to rate ADHD-related symptoms². However, subjective ratings by different observers, parents, and teachers may yield inconsistent results. SNAP-IV scores show high sensitivity but low specificity for clinical diagnoses. Therefore, these scores have been recommended as diagnostic screening tools for ADHD³. Neuropsychological tasks, such as the attention network test⁴ and continuous performance test⁵, which measure reaction time and accuracy, have been widely used to evaluate attentional control and information processing efficiency in individuals with ADHD. However, behavioral measurements of auditory and visual attention often require cooperation of participants in providing overt responses. Achieving this is difficult with children, particularly those with ADHD.

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Objective and clinically available tools for diagnosing ADHDs have been used for nearly a century. Electroencephalography (EEG) has been used in ADHD studies since 1938⁶. However, the feasibility of the clinical applications of EEG in psychiatry remains challenging⁷. For example, the theta-beta ratio, once conceptualized as a diagnostic tool for ADHD, was found to be unreliable for the diagnosis of ADHD⁸. Event-related potential (ERP), a time-locked EEG response, varies between individuals with ADHD and controls^{9,10}. A variety of ERP features, such as selective attention (P2, P3), response inhibition (N2, P3), involuntary attention switching (P3a), error detection (ERN, Pe), feedback processing (FRN), and attention reorienting for further evaluation (LDN), have been proposed as biomarkers of ADHD^{11,12}. However, the responses elicited by tasks and stimuli are highly variable across individuals, limiting the efficacy of ERP features in ADHD diagnosis⁷.

Complex naturalistic stimuli consisting of rich audio and visual information have been used in neuroscience and research on psychiatric disorders to mitigate the challenge of reliably eliciting higher-order cognitive functions¹³. Such paradigms have successfully characterized social-cognitive impairments in individuals with autism spectrum disorder¹⁴. For example, while watching a movie, the brains of intellectually able autistic individuals do not synchronize with those of neurotypical participants¹⁴ and are idiosyncratically activated¹⁵. The advantage of using complex naturalistic stimuli is further exemplified by the robust activation of the default-mode network (DMN) during the perception of social interactions¹⁶. Impairments in distributed neural networks, including the DMN and cognitive control networks, have been observed in patients with ADHD¹⁷. Anti-correlations between the DMN and cognitive control network are either reduced or absent in patients with ADHD¹⁷. Looking at non-habitual interactions (e.g., a pedestrian patting a cyclist on the shoulder at a traffic light) activated the temporoparietal junction (TPJ), suggesting that the TPJ is intimately involved in the perception of a wide range of social cues and is specifically recruited during the perception of non-habitual social interactions¹⁸. Half of all children with ADHD suffer from impaired social functioning. This difficulty may be related to the patient's inattention, hindering their ability to learn social skills through observation and to notice social cues¹⁹. The brain activities underlying social interactions are difficult to study using conventional artificial stimuli, which are typically well-controlled, short, and isolated images or sounds that differ significantly from the actual life experiences of social interactions. Alternatively, complex naturalistic stimuli with rich and dynamic audio-visual contents are good tools for delineating realistic social interaction scenarios in daily life.

In this study, we used complex naturalistic stimuli to probe the neural correlates of social perception in children with ADHD. Specifically, two versions of tailored movies with the same scenes and crews but different high- or low-level social interactions were shown to the participants. EEG signals were continuously recorded during movie viewing. We examined how synchronized oscillatory brain responses occurred across individuals during movie viewing. The differences in synchronized oscillatory brain responses when viewing the two movie versions were used to sensitively isolate the neural activity underpinning social communication. These findings may guide training programs or medications to normalize the neural activity of individuals with ADHD toward healthy controls for improved social communication.

Methods

Participants and ADHD case identification

Twenty participants with ADHD were recruited from outpatient clinics at a tertiary medical center in northern Taiwan. They met the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria for the diagnosis of ADHD¹, and none had taken any ADHD medication before participating in the experiment (ADHD medication-naïve). The DSM-5 diagnostic criteria for ADHD requires at least six symptoms on either the inattention subscale (totally nine symptoms) or the hyperactivity-impulsivity subscale (totally nine symptoms), which presents in more than one setting (e.g., home and school) before the age of 12 years and that interferes with functioning or development¹. Those who only met the criteria for inattention were considered inattentive subtype, and those who only met the criteria for hyperactive/impulsive symptoms were considered hyperactive/impulsive subtype. Those who met both inattention and hyperactive/impulsive symptoms were considered combined subtype.

Twenty age- and-sex-matched controls were recruited from outpatient clinics. The diagnoses of control participants in the outpatient clinics included chronic headaches and dizziness without ADHD, tics, or epilepsy. At enrollment, doctors inquired actively about each participant's past history and school performance to rule out ADHD and intellectual disability in the control group. All children had normal or corrected-to-normal vision. None of the participants had any psychiatric or neurological disorders, and none were taking any medication. Children with autism spectrum disorder were excluded from the study. Baseline EEG data were collected from each participant to exclude epileptiform discharges.

Totally, twenty children with ADHD and 20 age- and-sex-matched controls were enrolled (Table 1). The male-to-female ratios were 1:1 in both groups. There were no significant differences in ages and sexes between the controls and children with ADHD. Their ages ranged from 6 to 14 years. Among the children with ADHD, 9 (45.0%) had inattentive subtypes, and 11 (55.0%) had combined subtypes. The DSM-5 criteria of our ADHD participants were higher in inattention domain than in hyperactivity/impulsivity domain. The parents and the teachers reported ADHD symptoms similarly.

Ethics approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study was approved by the Research Ethics Review Committee of Far Eastern Memorial Hospital, New Taipei City, Taiwan (FEMH No. 107146-F). Written informed consents were obtained from all participants and their parents before starting the experiment.

	Control (n = 20)	ADHD (n = 20)	p value
Age (year)	9.14 ± 2.38	8.66 ± 1.85	0.479
Sex (male/female)	10/10	10/10	1.000
ADHD subtype			
IA		9 (45.0%)	
HI		0	
Combined		11 (55.0%)	
DSM			
IA (Parent)		5.06 ± 1.73	
IA (Teacher)		5.49 ± 2.02	
HI (Parent)		3.31 ± 2.78	
HI (Teacher)		2.79 ± 2.20	

Table 1. Demographic and ADHD characteristics. Sex is presented as the number of participants. ADHD subtype is presented as the number (percentage) of participants with ADHD. All other data are presented as mean ± standard deviation. *ADHD* attention deficit hyperactivity disorder, *DSM* Diagnostic and statistical manual of mental disorders, *HI* hyperactivity/impulsivity, *IA* inattention.

Stimuli

Two movie clips were professionally filmed with the same crew (four players) to show either high- or low-level verbal and non-verbal social interactions. The movie's theme was people playing basketball in an outdoor court, and the scenes in the two movie clips matched with each other. The duration of each film was 5 min 5 s. Sampled movie clips are available on GitHub (https://github.com/fahsuanlin/asociality_movies). Full-length high-resolution movies are available by contacting authors to arrange data transfer. Participants were instructed to view the movies. Each movie was played once for each participant. The order in which a low- or a high-level social interaction movie was first shown was randomized across participants. Figure 1 shows six representative snapshots from the two movies. Informed consents were acquired from actors and actresses in the films to allow for the publication of identifying information/images in an online open-access publication.

EEG data recording and analysis

EEG data (NicoletOne, Natus, Pleasanton, CA, USA) were sampled at 256 Hz using 21 channels. The topology of the EEG electrodes followed the international 10–20 system. The EEG was recorded continuously for each participant for the entire duration of the movie clip.

EEG signals were first re-referenced to the average of all channels. Dynamics of inter-subject correlated oscillations elicited by movie viewing were first derived by the correlated component analysis^{20,21}. Specifically, the dynamics of frequency-specific neural oscillation were extracted by applying the Morlet wavelet transform (central frequency 6–150 Hz in 4-Hz steps; 5 cycles) to EEG signals. At each frequency f , the pooled between-subject (for the subject pair between subject k and subject l) covariance $\mathbf{R}_b(f) = 1/(n(n-1)) \sum_k \sum_{l, l \neq k} \mathbf{R}_{kl}$ and the pooled within-subject (for subject k) covariance $\mathbf{R}_w(f) = 1/n \sum_k \mathbf{R}_{kk}$ was calculated. Here $\mathbf{R}_{kl}^f = \sum_t \left(\mathbf{x}_k^f(t) - \bar{\mathbf{x}}_k^f \right) \left(\mathbf{x}_l^f(t) - \bar{\mathbf{x}}_l^f \right)^T$. Here $\mathbf{x}_k^f(t)$ denotes the absolute value of the Morlet wavelet transformed EEG signal for participant k at time t and frequency f . $\bar{\mathbf{x}}_k^f$ is the average of $\mathbf{x}_k^f(t)$ over time. The dimension of $\mathbf{x}_k^f(t)$ was $n_{ch} \times n_{time}$, where n_{ch} denotes the number of EEG channels and n_{time} denotes the number of EEG samples over time. Accordingly, both $\mathbf{R}_b(f)$ and $\mathbf{R}_w(f)$ were of dimension $n_{ch} \times n_{ch}$. The component projection $\mathbf{v}(f)$ that maximizes the largest correlation between participants is the eigenvector of $\mathbf{R}_w(f)^{-1} \mathbf{R}_b(f)$ with the largest eigenvalue $\lambda_{max}(f)$ ^{20,21}. The inter-subject correlation (ISC) was calculated as $(ISC(f) = (\lambda_{max}(f) - 1)/(n - 1))$. $\mathbf{v}(f)$ and $ISC(f)$ were calculated separately for the ADHD and control participants and for each movie clip. The calculation was repeated for all individual frequency.



Figure 1. Representative snapshots of high (top row) and low (bottom row) level of social interaction from two movie clips shown to participants. The time stamp for each snapshot is indicated in the lower right corner of each image.

Statistical analysis

A paired t -test was used to compare age between the control and ADHD groups. Pearson's chi-squared test was used to compare sex between these two groups. EEG data was analyzed as mentioned above. These demographic data were analyzed using SPSS Statistics version 19.0 (IBM, Armonk, NY, USA). All tests on demographic data used were two-tailed and a p -value < 0.05 was considered statistically significant.

The significance of $ISC(f)$ was evaluated by a permutation test, where the EEG time series from each channel was phase-scrambled before calculating the $ISC(f)$ 1000 times. The results from the unscrambled time series were considered significant if they exceeded the top 95% of the results from the scrambled data. We further compared the difference in $ISC(f)$ for viewing high- or low-level movie clips using a bootstrap test, where time series from participants within the same group (ADHD or control participants) were sampled with replacement 100 times. Two-sample t -tests were performed among the bootstrap samples at each frequency to quantify the significance of the differences. Within each group, we also assessed the significance of the $ISC(f)$ difference between watching high-level and low-level social interactions using samples from the permutation samples.

The topology $v(f)$ that contributed to the ISC metric $ISC(f)$ was statistically compared between the ADHD and control participants using a two-sample t -test. The potential inflation of the type-I error in all tests above across frequencies was controlled by taking the significance threshold at 5% of the false-discovery rate (FDR)²².

Results

We first examined $ISC(f)$ between 6 and 150 Hz. Significant inter-subject correlated oscillations were found in the gamma band between 55 and 80 Hz (FDR-corrected $p < 0.05$ in the permutation test) (Fig. 2A). Significant synchronized gamma band oscillations were observed in both the ADHD and control participant groups, regardless of whether they viewed either high- or low-level social interaction movies. We then compared the difference

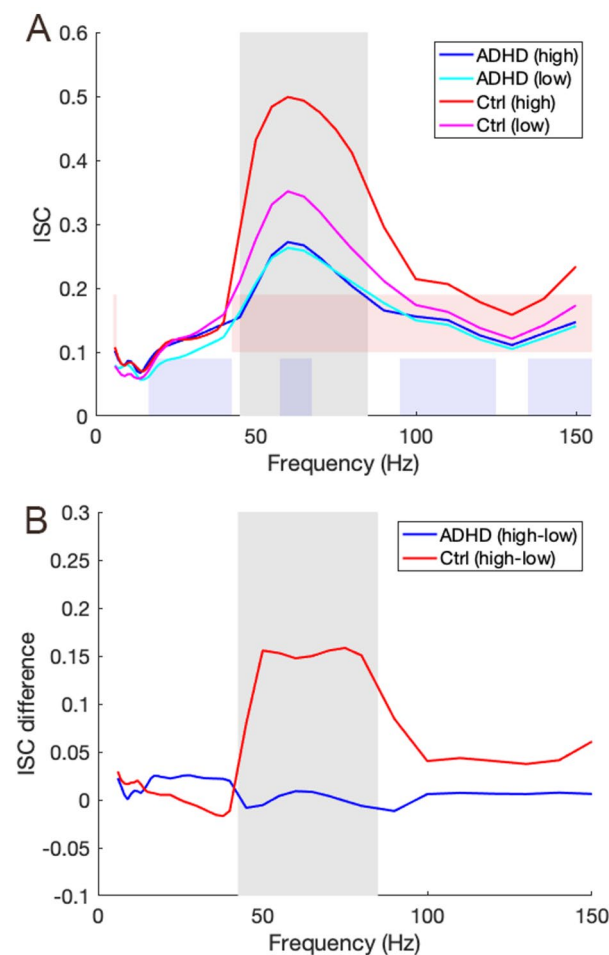


Figure 2. (A) Inter-subject correlation (ISC) increases between 55 and 80 Hz during movie viewing. The significance of ISC was evaluated by a permutation test. Frequencies with significant ISC are marked in gray. The comparison between viewing high- and low-level social interaction movie clips was evaluated using a bootstrap test. Significant difference in ISC between viewing both movies is marked in blue (participants with ADHD) and red (control participants). (B) The ISC difference in viewing high- vs. low-level social interaction movies was found significantly higher in control participants than ADHD individuals between 40 and 80 Hz. ADHD, attention-deficit/hyperactivity disorder.

in $ISC(f)$ within the same group when viewing the two movies. Participants with ADHD showed a significant $ISC(f)$ between 55 and 80 Hz, whereas the control participants had a significant $ISC(f)$ above 40 Hz. Comparing between viewing high- and low-level social interaction movies, we found that the oscillation between 40 and 80 Hz were more synchronized in viewing high-level interaction movie than low-level interaction movie in control participants. In contrast, there was no clear ISC difference between 40 and 80 Hz in ADHD participants in viewing movies of different levels of social interaction (Fig. 2B). The ISC difference between viewing high- and low-level social interaction movies in control participants was significantly larger than that in ADHD patients (FDR-corrected $p < 0.05$ in the permutation test; Fig. 2B).

The scalp topologies of the EEG channels contributing to $ISC(f)$ averaged between 55 and 75 Hz were shown in Fig. 3. During viewing the high-level social interaction movie, both control participants and ADHD patients had relatively strong positive and negative v in the left occipitoparietal lobe and right posterior parietal lobe, respectively. In contrast, the topology of v for two groups showed different patterns during viewing the low-level social interaction movie. When viewing the low-level social interaction movie, the control participants had relatively positive v at the left occipital lobes, and negative v in the right parietal lobe, whereas the ADHD participants had strong negative v in the right frontal and posterior parietal lobe and positive v in the left occipital lobes. Comparing v between viewing the two movies, control participants had a significantly larger v in the right parietal lobe when viewing high-level interaction films than when viewing low-level interaction films. In contrast, the differences of v distribution between viewing two movies in the right parietal lobe was lacking in the participants with ADHD. The participants with ADHD showed relatively smaller v distributions in the left occipital region while viewing high-level interaction films than when viewing low-level interaction films.

Discussion

Our study demonstrated the feasibility of probing the neural substrates underpinning social perception in children with ADHD. Specifically, less synchronized activity across viewers in the gamma band (Fig. 2A) and topologies of EEG electrodes contributing to the synchronized brain dynamics between viewing low- and high-level social interaction films (Fig. 3) constituted the hallmarks of individuals with ADHD. The difference in the synchronized gamma oscillations between viewing high- and low-level social interaction movies in control participants was significantly larger than the difference in ADHD participants (Fig. 2B). Taken together, our results suggested the feasibility to distinguish between control and ADHD participants based on the difference in the gamma oscillation synchrony during viewing movies of high- and low-level social interaction movies.

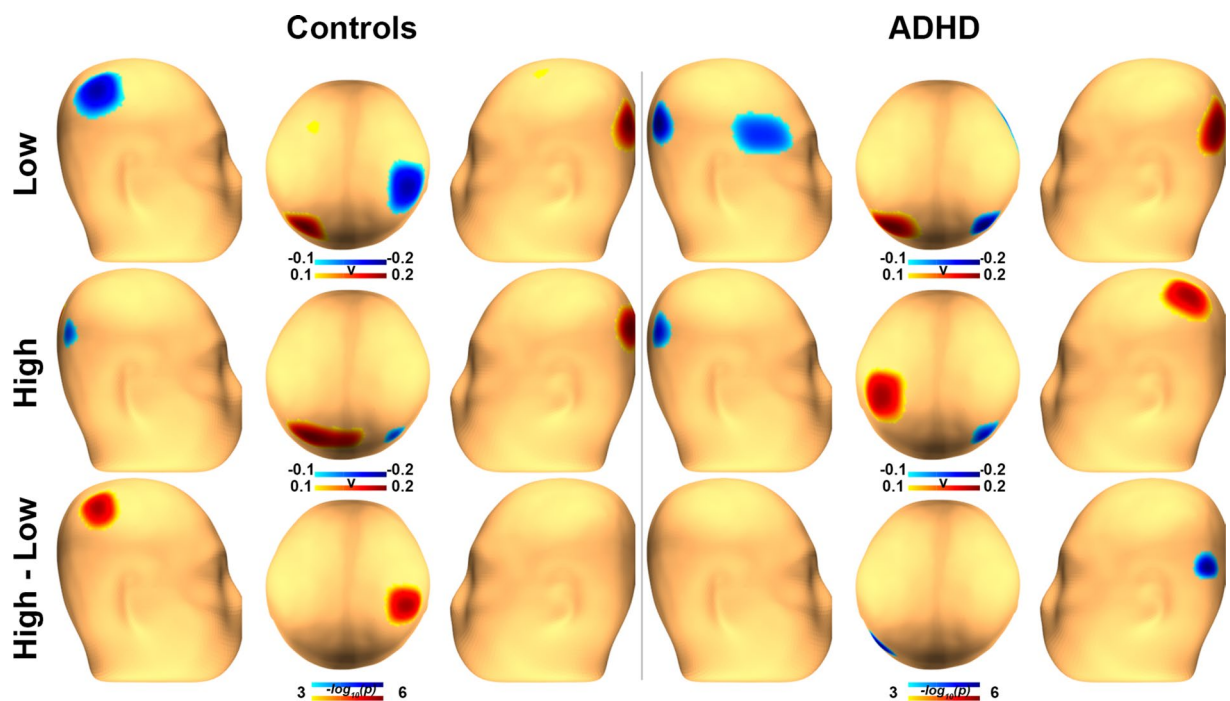


Figure 3. Topologies of electroencephalographic channels contributing to inter-subject correlation between 55 and 75 Hz. Data from controls and patients with ADHD are shown in the three columns on the left and right, respectively. Top: low-level social interaction movie clip. Middle: high-level social interaction movie clip. Bottom: difference between high- and low-level social interaction movies. Colors in the top and middle panels denote v . Colors in the bottom panel denote the negative 10-based logarithm of the p-values after the false discovery rate correction for the inflation of multiple comparisons. The polarities of values were determined by the sign of the effects. ADHD, attention-deficit/hyperactivity disorder.

Our experimental design only asked individuals to watch movie clips during EEG collection without engaging in any explicit task. In this experimental design, participants had high compliance, and experimenters could easily study high-level cognitive functions by manipulating the content shown.

Furthermore, our study revealed significant ISCs in the gamma band during movie viewing (Fig. 2A). Gamma activity in EEG has been associated with numerous cognitive functions, including memory processes, attention, object representation, feature binding, and motor function²³. Enhanced gamma-band oscillations in children with ADHD during the auditory target detection paradigm have been implicated in impaired motor inhibition²⁴. This augmentation of the gamma band response was noted only when the stimuli were presented to the right ear. During a visual memory paradigm, ADHD children showed larger gamma oscillation in the parieto-occipital area than healthy controls²³. These findings suggested that neuronal excitation with enhanced gamma oscillations occurs in children with ADHD. Our study showed that reduced inter-subject synchronized gamma band dynamics mostly contributed to neuronal activity in right parietal lobe, especially during viewing low-level social interaction movie (Figs. 2 and 3). Taken together, these studies reveal potential biomarkers of impaired neurotransmission in ADHD²³.

Traditional EEG and ERP studies in patients with ADHD have used artificial visual or auditory stimuli that do not mimic real-world experiences. The naturalistic stimuli used in this study helped to elucidate the neural basis of selective attention in conditions that resemble real life¹³. Naturalistic stimuli have also been used in studies of human memory, attention, language, emotions, and social cognition¹³. In addition to attention deficit, patients with ADHD may also have comorbidities including mood disorders, intellectual disabilities, and communication disorders²⁵. Manipulating the content of movies makes it possible to investigate multiple deficits in ADHD. For example, by analyzing the ISC of EEG signals while viewing short film clips, synchrony reflects attention- and emotion-modulated cortical processing²⁶. Children in the control group showed greater ISCs than children with ADHD when viewing both high- and low-level social interaction movies. A higher ISC of EEG activity predicts greater voluntary sustained attention to a movie²⁷. Therefore, lower ISCs in children with ADHD are compatible with the manifestations of attention deficits found in previous studies^{13,25,26}.

Different types of social interactions shown in movies activate distinct cerebral cortices. For example, watching non-habitual interactions activates the temporoparietal junctions, whereas watching habitual interactions activates the hippocampus and lateral occipital cortex¹³. Different levels of social interactions trigger different levels of neural synchrony. For example, gamma-band neural synchrony in the temporal-parietal area was found for interactions between couples but not for strangers²⁸. Naturalistic functional magnetic resonance imaging mapping of audiovisual movie clips revealed the superior temporal sulcus as a hub for the distributed brain network for social perception²⁹. Our movie clips involved nonnarrative and non-habitual social interactions. The high-level social interaction version activated the left parietal area in both the control participants and children with ADHD as shown in a previous study¹³. Interestingly, the right parietal lobe activation shown in the control participants during watching a low-level social interaction movie was reduced in children with ADHD. This spatio-spectral signature suggests a differential neuronal mechanism supporting the cognitive processing of social interactions between children with ADHD and controls. Social functioning difficulties, such as peer relationship difficulties, in children with ADHD have been previously reported^{30,31}. Our study provides evidence of the abnormal processing of social interactions in children with ADHD.

Strengths and limitations

The strengths of the present case-control study include the use of naturalistic stimuli and the provision of evidence regarding the abnormal processing of social interactions in children with ADHD. However, there were also some limitations. Firstly, none of the children with ADHD in our study exhibited the hyperactivity-impulsivity subtype. Therefore, it remains to be determined whether children with the hyperactivity-impulsivity subtype also exhibit this abnormal processing of social interaction, or if this abnormality is specific to children with attention deficit, requiring further investigation. Secondly, we did not enroll patients with autistic spectrum disorder for comparison purposes. Consequently, it is unclear whether this abnormal processing of social interaction is specific to ADHD or could be generalized to all disorders characterized by social interaction difficulties. This question necessitates further investigation. Thirdly, we did not conduct an analysis of the relationships between the EEG measures we obtained and the clinical symptom scales in children with ADHD. Quantitative EEG measures that reflect clinical severity are anticipated to be valuable in clinical practice and warrant exploration in the future.

The signal processing in this study only included re-referencing and wavelet transform to extract frequency-specific oscillatory power envelopes. ADHD patients typically have more prominent muscular artifacts on EEG than control participants. Thus, suppressing muscular artifacts on EEG, such as using Independent Component Analysis and automatic component classification³², may improve results. However, it has been suggested that current practices of muscular artifact suppression did not bring obvious advantages³³. In this study, we believe that an individual's muscular effect has a relatively minor effect³² because our analysis focused on synchronized brain activities across individuals. The muscular effect is unlikely to be correlated between participants. We also considered the difference in the muscular noise as an intrinsic part of the EEG signal difference between groups. Answering how muscular noise specifically affects the evaluation of brain oscillation synchrony requires further development of signal processing methods to reliably and specifically isolate such contamination from neurophysiological signatures.

Implications for practice

In addition to the well-known symptoms of attention deficit, hyperactivity, and impulsivity, this study has demonstrated that children with ADHD also exhibit impaired processing of social interactions. Therefore, it is crucial to incorporate awareness of social difficulties into the comprehensive care of children with ADHD. Furthermore,

the use of EEG studies employing naturalistic simulations, such as movie clips, can be particularly engaging for children, especially those who struggle with attention deficits.

Conclusions

To the best of our knowledge, this study represents the first attempt to utilize naturalistic stimuli in investigating the neural processing of social interactions among children with ADHD. Our findings offer compelling evidence of abnormal social interaction processing in this population. This neural signature has the potential to serve as a valuable neural biomarker for distinguishing between healthy individuals and those with ADHD, facilitating the evaluation of the efficacy of training programs or medications in managing the disorder, particularly regarding enhancing social communication skills.

Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Author contributions

MTY recruited patients, collected data and wrote the initial draft of the paper; HJL executed EEG data analysis; KJW assisted data analysis and interpretation; HCF and KSL supervised study execution; JSL collected EEG data; FHL contributed the main idea, designed the study, and revised the paper. All authors reviewed the manuscript.

Competing interests

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Additional information

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