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The N270 in Facial S1-S2 Paradigm as a Biomarker for Children With Attention-Deficit/Hyperactivity Disorder

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ABSTRACT Children with attention-deficit/hyperactivity disorder (ADHD) might suffer from dysfunctions that affect their social interaction, however, this issue has been less investigated and the results were inconclusive, especially for face processing. Applying event-related potential technology, the current study used modified facial S1-S2 paradigm to investigate face recognition in children with ADHD and health control group. Twenty-nine ADHD children and twenty-nine health children were recruited. The results showed that central N270 was delayed under inconsistent condition than consistent condition for ADHD group and no significant difference was revealed between ADHD group and control group on amplitude and latency of N170, N270. N270 might be a sensitive neurophysiological marker for ADHD children.

INDEX TERMS Attention-deficit/hyperactivity disorder, N170, N270, event-related potential, S1-S2 paradigm, face processing.

I. INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is one of the top-ranking neurodevelopmental disorders with onset in childhood. The global prevalence of ADHD was estimated to be 5.29% in 2007 [1] and has rapidly increased to 7.2% in recent years [2]. China is no exception, according to two recent meta-analysis, the prevalence of ADHD among children and adolescents in China is about 6.3% [3], [4]. The core symptoms of ADHD are age-inappropriate inattention, hyperactivity and impulsiveness. While cognitive deficits in ADHD, such as sustained attention, inhibition control, and executive planning have been discussed extensively [5], [6], the social cognition in ADHD group was relatively less investigated and the findings were far from reaching consensus [7]–[9]. As the most common social stimuli we encounter, faces convey information that is essential for effective social communication. Abnormalities in facial and expression recognition in other psychiatric disorders (i.e. Autism Spectrum Disorders, Bipolar Disorder, Depression and Schizophrenia) have been well documented [10], however, face and emotion recognition deficit in ADHD has not always been reported. There are two reasons leading to this situation. The first one might be the scarce research specifically devoted to face recognition which led to this topic not fully be investigated. In fact, two recent reviews revealed that the majority of face memory and face recognition research in ADHD focused on hot aspects of face recognition (such as emotion recognition) while the recall for faces deserve much more attention [11], [12]. Secondly, most previous studies employed behavioral task to investigate the pattern of face recognition. However, the behavioral data might be not sensitive enough to detect the delicate processing of face recognition. With high temporal resolution, event-related potential technique would be a suitable tool to explore the processing of face recognition, especially for the neural mechanism underlying it. N170 and N270 are two components particularly relevant to face recognition.

The face-special N170 component has been widely used in the study of face processing. It is a negative component,

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TABLE 1. The characteristics of ADHD group and control group.

Characteristic	ADHD (N=29)	CONTROL (N=29)	*p*
Age(years), mean±SD	8.48±.35	8.22±.34	.602
Boys:Girls	23:6	18:11	.149
IQ, mean±SD	17.66±11.56	122.86±10.63	.070
ADHD subtype, n(%)			
Inattentive	17(59%)		
Inattentive	2(7%)		
Combined	10(34%)		

ADHD, attention-deficit hyperactivity disorder; HC, healthy control; IQ, intelligence quotient;

with peak amplitude appears around 170ms from facial stimulus onset, with reported that children have longer latencies than adults [13], [14], and it can reach the maximum negative peak value in the occipital temporal region of the brain. It is considered to indicate the structural encoding of faces [15]–[17]. The main neural generator of N170 lies in the fusiform gyrus [18], [19]. N170 may serves as a biomarker for facial recognition defects, which is a broad feature of multiple psychiatric/neurological disorders [10]. However, only few studies employed N170 to explore the face recognition in ADHD, which was either focused on facial emotion processing, or stimuli in upright and inverted orientations. The results of these studies were not consistent. Compared to control group, larger N170 amplitudes to faces were reported in children and adolescents with ADHD [20], while other study failed to find such differences [21]. In addition, N170 amplitudes to happy faces were smaller than angry faces in adults with ADHD [22]. No difference on peak latency was found between ADHD and control group [20], [21].

N270 is the second component which might be involved in face processing. In previous studies, when presenting a mismatch stimulus to the preceded stimulus to participants, a negative ERP component potential with peak latency of approximately 270ms (N270) was recorded [23], [24]. N270 was explored by S1-S2 paradigm and evoked by the mismatch between the presentation in working memory and the following perceptual input [25]. Cognitive basis of N270 is processing of working memory representation conflict [25]. It is reasonable to assume that the N270 is an electrophysiological marker of conflict processing during the simple working memory operations [24], [27]–[29]. Numerous researches indicate that N270 not simply can be elicited by uncomplicated perceptual features, such as color [27], or shape [30], [31], but also by complex stimuli, such as face [32]. N270 is not only sensitive to the conflict between physical properties but also reflects a stage that occurs between perception and recognition [28], [33], [34]. Faces represent highly informative non-linguistic visual stimuli, carrying numerous of social information, such as age, gender, race and inner feeling along with the person's identity [35]. Some studies have suggested that endogenous event-related potential (ERP) component N270 is an valuable and susceptible component used to reflect cognitive status of obstructive sleep apnea syndrome (OSAS), Parkinson's disease, major depression and transient ischemic attack (TIA) [31], [36]–[38]. However, whether N270 could be applied in ADHD remains unknown. Moreover, the conflict processing can be affected by attention and the amplitude of N270 can reflect conflict processing [39]. In general, these results suggest that N270 may be strongly relate to a variety of cognitive processes, including working memory and attention. N270 is suggested to generate in the dorsolateral prefrontal cortex and anterior cingulated cortex [40], [41]. Now that these areas are involved in the pathophysiology of ADHD as well [42], the study of N270 may provide a novel and effective method to determine the special cognitive processing deficits of ADHD.

In our present study, we used a facial S1-S2 paradigm, which could explore the facial processing and complex information conflict simultaneously. Participants' N170 and N270 were compared between ADHD group and control group. Considering the inconsistent findings on N170, We did not provide specific hypothesis on N170. However, as to N270, we predicted that N270 could be elicited by inconsistent face pairs as other mental disorders did. Specifically, inconsistent condition would elicit delayed and more negative N270 than consistent condition did. Moreover, N270 would be delayed and reduced in ADHD group than control group did.

II. METHODS

A. PARTICIPANTS

Fifty-eight children (29 with ADHD, 29 normal controls) participated in the study (see TABLE 1 for details).

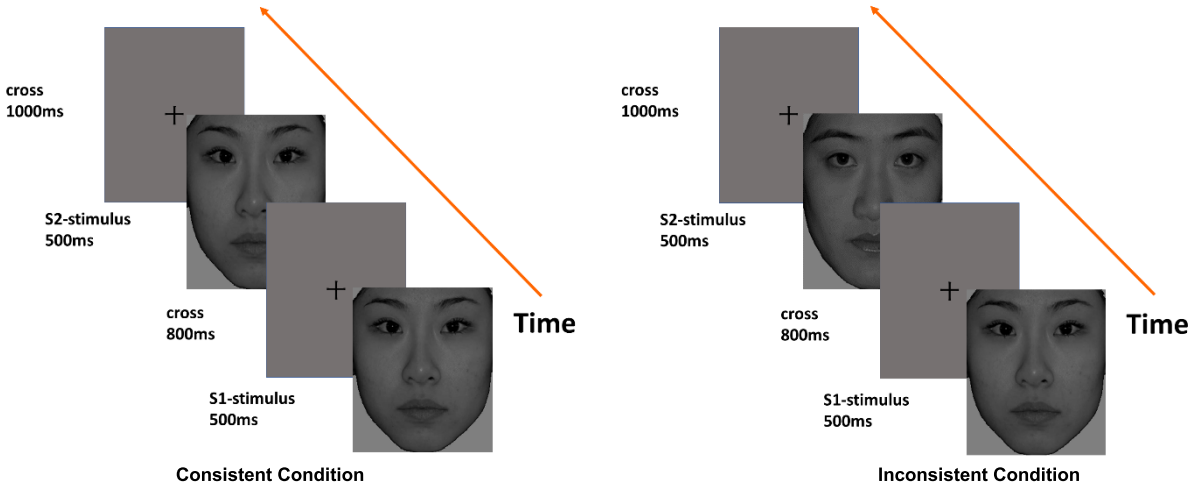

FIGURE 1. Example stimulus trains for the two conditions. A stimulus trial consists of unfamiliar grey-scale photographs of faces. The stimulus pairs included two series: (1) consistent condition: identical face picture S1 and S2; (2) inconsistent condition: different S1and S2.

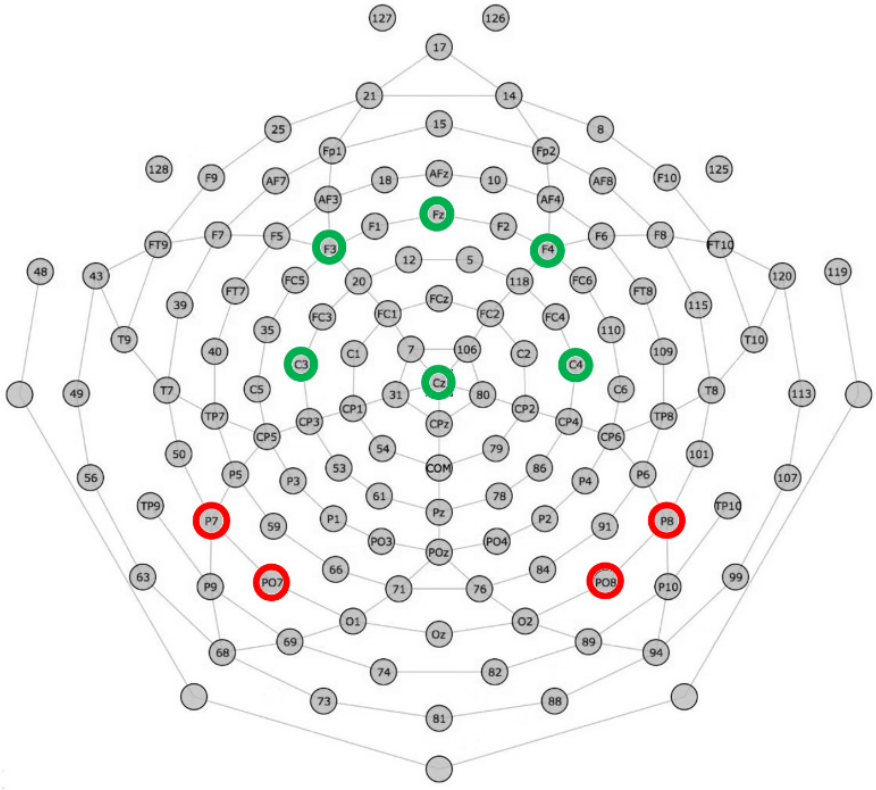

FIGURE 2. Location of electrodes used for analysis.

These two groups were matched on age, gender and IQ. Children with ADHD were recruited from Beijing Anding Hospital affiliated to Capital Medical University. The control group was recruited by advertisement. After the introduction of our study, written consent was provided by each participant and at least one guardian of each participating child. Participants received a small gift as appreciation of their participation. The project proposal was reviewed by the Ethics Committee of Beijing Anding Hospital.

All participants subsequently were interviewed with the Revised Schedule for Affective Disorders and Schizophrenia for School-Age Children: Present and Lifetime Version (K-SADS-PL) [43]. Parents completed SNAP-IV [44], and Conners' Parent Rating Scale (CPRS) [45] and Strengths and

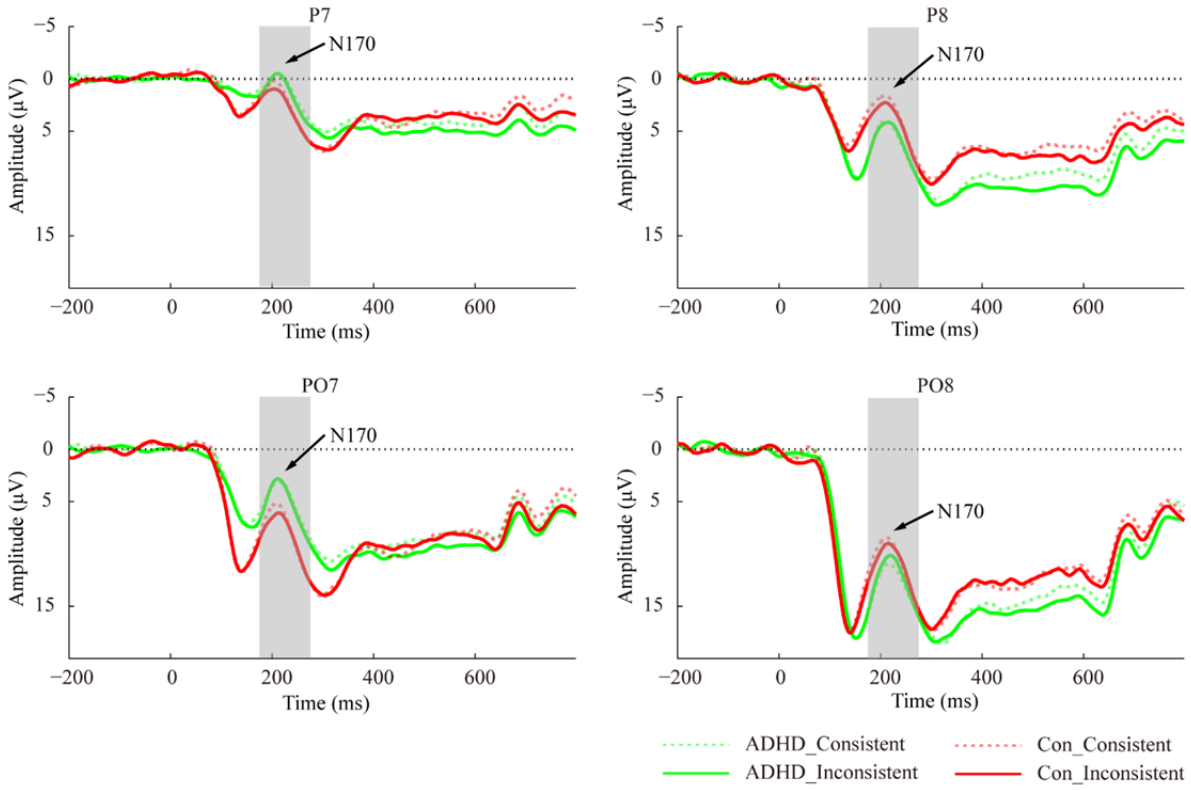

FIGURE 3. The grand-average ERPs of N170 at P7, P8, PO7 and PO8 (175–225 ms).

Difficulties Questionnaire about their children [46]. Consensus best-estimate diagnoses were made according to DSM-5 criteria by two clinically experienced child psychiatrists using all sources of useful information, including parent-report rating scales and all available clinical records. All participants were evaluated with a short form of the Wechsler Intelligence Scale for Children, Fourth Edition [47]. No participant was taking medication before our measurements were taken. Participants were excluded if they had a history of intellectual disability, head injury with loss of consciousness, or a chronic neurological disorder. Patients were excluded if they had a lifetime diagnosis of schizophrenia, other psychotic disorder, bipolar disorder, substance-related disorder, conduct disorder, obsessive-compulsive disorder, or anorexia nervosa. Additional exclusion criteria for control participants were having a history of a psychiatric diagnosis, severe somatic diseases and a positive family history of psychosis.

B. PROCEDURE

The modified S1-S2 paradigm [23] was used in the current study. The formal visual stimuli were 120 pairs of face photographs (half female and half male, not shown in practice phase) which were chosen from the Chinese Facial Affective Picture System [48]. The first and the second stimulus appeared 500 ms in sequence, with an onset interstimulus interval of 800 ms. The interval between each S1-S2 pair was 1000 ms. S1 and S2 were the identical face photograph in face match condition and different faces in face mismatch condition. The face pictures were presented in randomly sequence with E-Prime software (version 2.0). Participants were instructed to indicate whether S2 was identical to S1 or not as quickly and as accurately as they can. If their answers were "yes", they should press "1"; If their answers were "no", they should press "2". Each stimulus subtended a visual angle of 4.9° vertically and 4.17° horizontally. The participants were counterbalanced in each participant. All participants achieved above 70% accuracy on the 24 practice trials prior to the 120 formal S1-S2 pairs. The stimulus train is illustrated in Figure 1.

C. ELECTROPHYSIOLOGICAL RECORDING AND PROCESSING

Electroencephalogram (EEG) data were collected from all the participants using the 128-channel electrode system (Electrical Geodesics, Inc., Eugene, OR, United States) at a sampling rate of 1000 Hz. The signal impedance was adjusted to $\leq$50 KΩ. During the experiment, the participants were seated comfortably in a light and sound attenuated room to remove potentially interfering variables from the study. The test consisted of two sections with a short period of rest between each section. Offline EEG data were analyzed and processed with the open-source EEGLAB toolbox [49]. Raw EEG recordings were down-sampled to 500 Hz, using finite impulse response filter (0.1–30 Hz) and notch-filtered

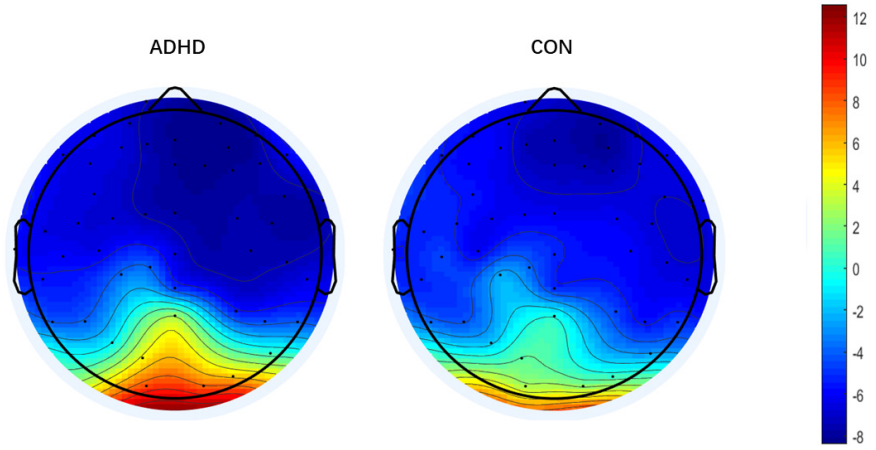

FIGURE 4. Topographical distributions of N170 for the Time-Window of facial stimuli (175–225 ms).

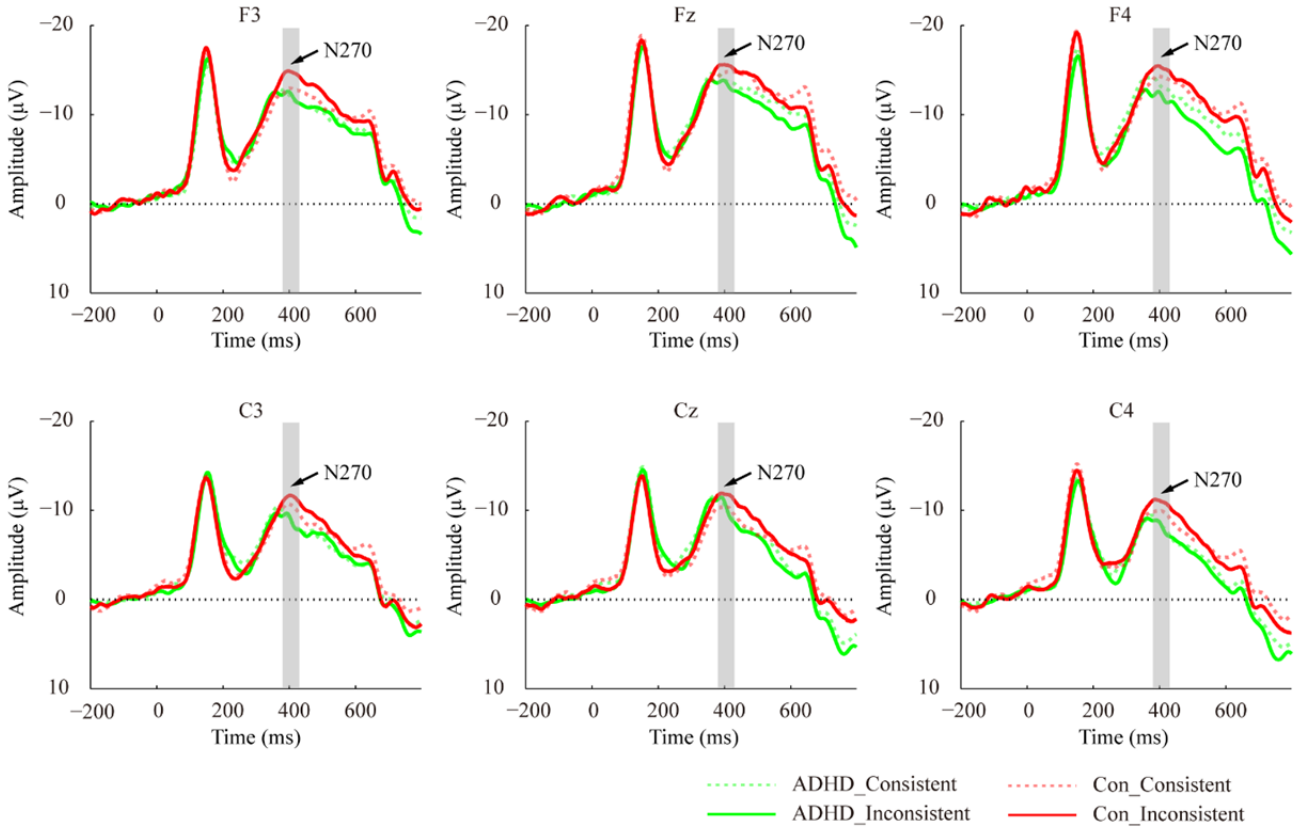

FIGURE 5. The grand-average ERPs of N270 at F3, Fz, F4, C3, Cz and C4 (380–430 ms).

with 50 Hz. EEG data were re-referenced off- contaminations were excluded by independent component analysis (ICA) [50]. The EEG was segmented from 200 ms prior to initiation to 800 ms after the stimulus onset. Sections of data containing artifacts exceeding $\pm 100\ \mu$V were automatically rejected. Baseline correction was applied using the -200 to 0 ms pre-stimulus interval. The peak latency and amplitude were retrieved for N170 (at P7, P8, PO7 and PO8 electrodes) and N270 (at F3, Fz, F4, C3, Cz and C4 electrodes) and were subjected to four factor repeated measure ANOVA. Specifically, 2 (Consistency: Consistent, Inconsistent) $*$ 2 (Region: Parietal, Parietal-Occipital) $*$ 2 (Hemisphere: Left, Right) $*$ 2 (Group: ADHD, Control) for N170 and 2 (Consistency: Consistent, Inconsistent) $*$ 2 (Region: Frontal, Central) $*$ 3 (Hemisphere: Left, Midline, Right) $*$ 2 (Group: ADHD, Control) for N270 with Consistency, Region and Hemisphere

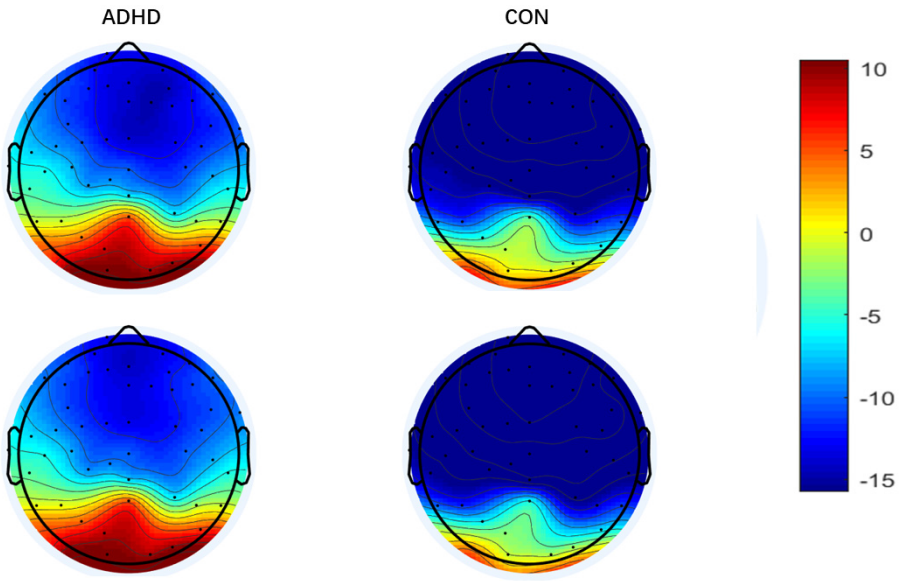

FIGURE 6. Topographical distributions of N270 for the Time-Window of interest for all the Stimulus Types (380–430 ms).

as within-subject factor and Group as between-subject factor. The time epochs of N170 (175–225 ms), N270 (380–430 ms) were observed. The location of electrodes used for analysis was shown in Figure 2.

III. RESULTS

A. N170

No significant effect was found on neither the peak latency nor the peak amplitude of N170. The grand-average ERPs at P7, P8, PO7 and PO8 were shown in Figure 3. The topographical distribution of N170 is illustrated by the voltage map in Figure 4.

B. N270

Both the main effect of Region [$F(1, 56) = 12.96$, $p = 0.001$, $\eta_p^2 = 0.188$] and the interaction among Consistency, Region and Group [$F(1, 56) = 5.13$, $p = 0.027$, $\eta_p^2 = 0.084$] were significant. Simple effects analysis showed that ADHD group's peak latency was delayed under inconsistent condition ($M = 399.29$ ms) than consistent condition ($M = 393.70$ ms) at central region. No other significant effect was found. Figure 5 showed the grand-average ERPs at F3, Fz, F4, C3, Cz and C4. The topographical distribution of N270 is illustrated by the voltage map in Figure 6.

IV. DISCUSSION

Expanding previous studies, the current studies modified S1-S2 paradigm by using faces with neutral emotion from standard dataset as stimuli and investigated the potential difference on neurophysiological markers of face recognition in children with ADHD. The stimuli in previous studies were mostly simple stimuli, and the research participants were mainly adults. This work complements research previously conducted with adults and we applied this paradigm innovatively to the early diagnosis of ADHD. We found that children usually have larger event-related potentials with a longer latency compared with adults [51], [52]. N270 was delayed under inconsistent condition than consistent condition for ADHD group and no significant difference was revealed between ADHD group and control group on N170, which partially supported our hypothesis. Compared with consistent face pairs, the peak latency of inconsistent condition was longer for children with ADHD, while this effect was only observed at central region. This result replicated previous studies using S1-S2 paradigm in other mental disorders or medical conditions [31], [36]–[38]. Employing the facial S1-S2 paradigm, the current study provided novel insight into the face recognition research in ADHD and found N270 might be a sensitive index for face recognition for children with ADHD.

No significant difference on peak latency and peak amplitude on N170 between ADHD group and control group was found, which was agreed with the null results of previous research [20], [21] while contradicted with Tye *et al.*, [21] and Ibáñez *et al.*, [22]. These discrepancies might due to the differences on methodology. For instance, Ibáñez *et al.*, [22] employed happy and sad emotions while we used faces with neutral emotion. The children were instructed to count the number of flags appeared among the fixation stimuli [21] while the participants in the current study were asked to identity whether the second face was identical to the first face in the face pair. The null results on N170 might demonstrate that ADHD group did not differ from control group at early stage on face processing.

Compared with consistent face pairs, the peak latency of inconsistent condition was longer for children with ADHD,

while this effect was only observed at central region. This result replicated previous studies using S1-S2 paradigm in other mental disorders or medical conditions [31], [36]–[38]. Employing the facial S1-S2 paradigm, the current study provided novel insight into the face recognition research in ADHD and found N270 might be a sensitive index for face recognition for children with ADHD.

Though enriching the face recognition research in ADHD, some limitations should be mentioned. Firstly, the current investigation only recruited children as participants, whether the current findings could be transferred to adult group still need empirically tested. In addition, we did not make distinction among different subgroups of ADHD. It would be interesting to investigate face recognition in different ADHD subgroups.

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