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ORIGINAL PAPER

Visual and auditory steady-state responses in attention-deficit/hyperactivity disorder

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Abstract

We designed a study to investigate the patterns of the steady-state visual evoked potential (SSVEP) and auditory steady-state response (ASSR) in adolescents with attention-deficit/hyperactivity disorder (ADHD) when performing a motor response inhibition task. Thirty 12- to 18-year-old adolescents with ADHD and 30 healthy control adolescents underwent an electroencephalogram (EEG) examination during steady-state stimuli when performing a stop-signal task. Then, we calculated the amplitude and phase of the steady-state responses in both visual and auditory modalities. Results showed that adolescents with ADHD had a significantly poorer performance in the stop-signal task during both visual and auditory stimuli. The SSVEP amplitude of the ADHD group was larger than that of the healthy control group in most regions of the brain, whereas the ASSR amplitude of the ADHD group was smaller than that of the healthy control group in some brain regions (e.g., right hemisphere). In conclusion, poorer task performance (especially inattention) and neurophysiological results in ADHD demonstrate a possible impairment in the interconnection of the association cortices in the parietal and temporal lobes and the prefrontal cortex. Also, the motor control problems in ADHD may arise from neural deficits in the frontoparietal and occipitoparietal systems and other brain structures such as cerebellum.

Keywords Attention-deficit/hyperactivity disorder · Electroencephalogram · Steady-state visual evoked potential · Auditory steady-state response · Stop signal

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common mental disorders, afflicting people of all ages and its prevalence varies in childhood, adolescence and adulthood. Meta-analytic studies have estimated the worldwide ADHD prevalence at 5.29–7.1% in children and adolescents and at 3.4% in adults [1–3]. A population-based study has shown that ADHD is the most prevalent psychiatric condition among Iranian adolescents with an estimated incidence of approximately 8% [4]. Subjects diagnosed with ADHD exhibit very different types and severity of symptoms; however, in general, the disorder is characterized by hyperactivity, impulsivity and inability to inhibit inappropriate actions, distractibility and low levels of concentration and attention [5, 6]. Numerous studies have used various objective measures of neuropsychological functioning in subjects with ADHD to investigate and evaluate deficits in sustained and selective attention, target detection, working memory, executive function and inhibitory control [7–14]. Although these studies have reported important neuropsychological and pathophysiological findings, they have focused less on the importance of the effects of steady-state auditory and visual stimuli on sustained and selective attentions.

Steady-state evoked potential (SSEP) is an electrophysiological response by the nervous system which is elicited when a repetitive sensory stimulus is introduced to a person. If the frequency of the stimulation (f_0) is adequately high, SSEP can be supposed as a sinusoidal component in the EEG signal which has the same frequency as that of the stimulation and its harmonics, i.e., $2f_0$, $3f_0$, $4f_0$, etc. [15]. Repetitive visual stimulation such as flickering of a region in the monitor leads to a steady-state visual evoked potential (SSVEP) which has its highest amplitude in the occipital region, whereas a modulated tone sound in a fixed frequency induces auditory steady-state responses (ASSR). Robustness

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of the signal and its high signal-to-noise ratio, as compared to conventional EEG artifacts, make SSEP an appropriate choice for neuroscience studies.

Many researchers have shown that the amplitude and the phase of the response are tightly related to the functions and structure of the brain such as memory, emotion processing and attention [16–18]. Also, SSEP has been applied in many neuropsychological researches. Patients with schizophrenia have been intensively examined for differences with healthy individuals in their SSVEP and ASSR. Silberstein and his colleagues found a correlation between SSVEP latency and auditory hallucination in patients with schizophrenia [19]. They also reported diversities of SSVEP between schizophrenia and control groups during the continuous performance task A-X (CPT A-X) [17]. In addition, the O'Donnel group evaluated 4–40 Hz SSVEPs and gamma-band ASSR in patients with schizophrenia [20, 21], and the Spencer group validated the results of their evaluation of the ASSR [22, 23].

Also, in a few studies, ASSR has been evaluated in patients with bipolar disorder. A significant reduction was reported in both the mean trial power and the phase locking factor in patients with bipolar disorder in contrast to the control group [24]. Then, Rass et al. studied the relation of ASSR with clinical symptoms, cognitive functions and pharmacological treatment of these patients [16]. Another research by Oda and her colleagues, who used MEG instead of EEG, confirms the results obtained by Maharajh et al. [25].

Although ADHD is a common psychiatric disorder, only a few studies have attempted to investigate it by the SSEP method. To the best of our knowledge, only Silberstein et al. utilized the SSEP technique to examine boys with ADHD [9]. They requested the subjects to perform a CPT-AX task on a monitor which displayed a 13 Hz sinusoidal flicker in the background. They reported a reduction in the SSVEP latency at the right prefrontal region in healthy boys simultaneously with the disappearance of A, while it was exactly the opposite in boys with ADHD in the same condition, i.e., they showed increased latency in the same region. Healthy boys also showed a decreased latency in the right prefrontal site during the appearance of the A and X, whereas such a thing was not observed in boys with ADHD. Based on these results and their comparison with the findings of the dopaminergic system, they concluded that SSVEP latency is an index for measuring the coupling and processing speed in neural networks. Furthermore, healthy boys showed a lower SSVEP amplitude during the period between the appearance and the disappearance of A. According to this observation, Silberstein and his group suggested that lower SSVEP amplitude is a marker for increased neural activity.

Motivated by the high prevalence of ADHD and the importance of steady-state responses as informative neurophysiological indices within the electrical activity of the brain, we designed a study to investigate the visual and auditory steady-state response patterns in adolescents with ADHD during a stop-signal task. Therefore, we used 1800 ms steady-state stimulations, as prolonged stimuli, over the frequencies of 15 Hz in visual and 40 Hz in auditory stimulations with 1500 ms interstimulus intervals and measured SSVEPs and ASSRs with EEG. This approach allows us to investigate the extended neural responses to both visual and auditory steady-state stimulations in ADHD for the first time. Also, we had the opportunity to examine neural responses during a cognitive task. Furthermore, it was hypothesized that different steady-state responses will be observed in visual and auditory stimuli during a cognitive control task, because patients with ADHD show a different performance in their visual and auditory working attention.

Method and materials

The study was approved by the Ethical Committee of Tehran University of Medical Sciences. All participants and their parents signed an informed consent to take part in the study.

Participants

Totally, 68 adolescents participated in this study; including 36 individuals diagnosed with ADHD and 32 healthy individuals. The participants had no history of head trauma, substance abuse, any major medical illness or systemic medical diseases, learning disability, clinically documented hearing loss, neurological disorders (such as seizure) and psychiatric treatment (such as neurofeedback). Raven's Progressive Matrices for adolescents was conducted to obtain the estimated intelligence; individuals with an estimated intelligence quotient greater than or equal to 100 were eligible for the study. The Edinburgh Handedness Inventory was used to determine the handedness of participants in a self-reported manner. As determined by a child and adolescent psychiatrist, all subjects in the patient group fulfilled the Diagnostic and Statistical Manual of Mental Disorders (5th ed.; DSM–5; American Psychiatric Association, APA, 2013) diagnostic criteria for ADHD. Of these 36 adolescents with ADHD, recruited from the psychiatry clinic of Roozbeh Hospital in Tehran, Iran, two could not complete the signal recording protocol and four were omitted because of poor cooperation in the signal recording process. Therefore, the ADHD group included 28 boys and 2 girls, with a mean age of 14.43 years (SD = 1.90; age range 12–18 years). 27 ADHD individuals were right-handed, and 3 ADHD individuals were left-handed. In the healthy control (HC) group recruited from a high school, 2 out of 32 subjects were omitted due to poor cooperation during EEG recording. This

resulted in the HC group consisting of 27 boys and 3 girls, with an average age of 15.11 years (SD = 1.71; age range 12–18 years). 28 control individuals were right-handed and 2 control individuals were left-handed. There was no statistically significant difference between the HC group and the ADHD group in age or sex composition.

Data acquisition paradigm

The popular stop-signal task was employed during EEG data recording. The task was manipulated so that it would contain visual and auditory stimuli to generate SSVEP and ASSR within the electrical activity of the brain, respectively. Recordings took place in a silent room, away from any electromagnetic sources like power lines and mobile phones. Subjects sat in front of a monitor on a comfortable arm-chair which was about 70 cm from the monitor. The height of the chair was set in such a way that the subjects' hand rested easily on a keyboard while he/she placed his/her elbow on the arm of the chair. The electroencephalogram signal was recorded by 16 electrodes using a gUSBamp biosignal amplifier (Gtec, Austria). According to the 10–20 standard, electrode locations were selected on Fp1, Fp2, F3, F4, F7, F8, Fz, C3, C4, Cz, T7, T8, Cp5, Cp6, O1 and O2 with the reference electrode on the right ear. Sampling rate was set to 512 Hz. Cutoff frequencies of the amplifier's low pass and high pass filters were adjusted to 0.1 and 60 Hz, respectively.

The recording session included two blocks with 60 ± 20 trials (depending on subject's collaboration): one block for visual stimulation and another for auditory stimulation, in which the order of blocks was randomly selected between visual–auditory and auditory–visual in equal probability to eliminate any bias in the task. Each trial in a block started when a cross appeared in the middle of the monitor as a cue. After 800 ms, the cross sign was replaced with a cartoon picture of an airplane whose head was to the right in one-half of the trials and to the left in the other half. The subjects were trained to press the right or left key depending on the direction of the airplane immediately after its appearance. The picture remained on the monitor for 1000 ms and then the next trial would start after 1500 ms. A quarter of the trials contained stop signals in which subjects should not have pressed any keys (Fig. 1).

Stimulation was applied from the beginning of a trial to its end. The type of stimulation and stop signals depended on the modality. In the visual block, stimulation was delivered as the background of the airplane picture kept blinking between black and light gray with a rate of 15 Hz. The key point in delivering accurate stimulations to have robust and strong steady-state responses in EEG, when using an LCD monitor, is that the blinking frequency should be a divisor of the refreshing rate of the monitor, which was 60 Hz in our case. Also, the stop signal was a beep with a frequency of 1.4 kHz, which was played in both ears and lasted for 100 ms in this modality.

For auditory stimulation, a 1 kHz sinusoidal signal was modulated with another 40 Hz sinusoidal signal which was played in both ears through a headset. The stop signal was applied using a thick red bar above the airplane picture in the monitor.

The amplitude of steady-state responses varies at different stimulation frequencies or from one person to another. The stimulation frequency in SSVEP (15 Hz; alpha steady-state response) was selected for two reasons; first, the largest

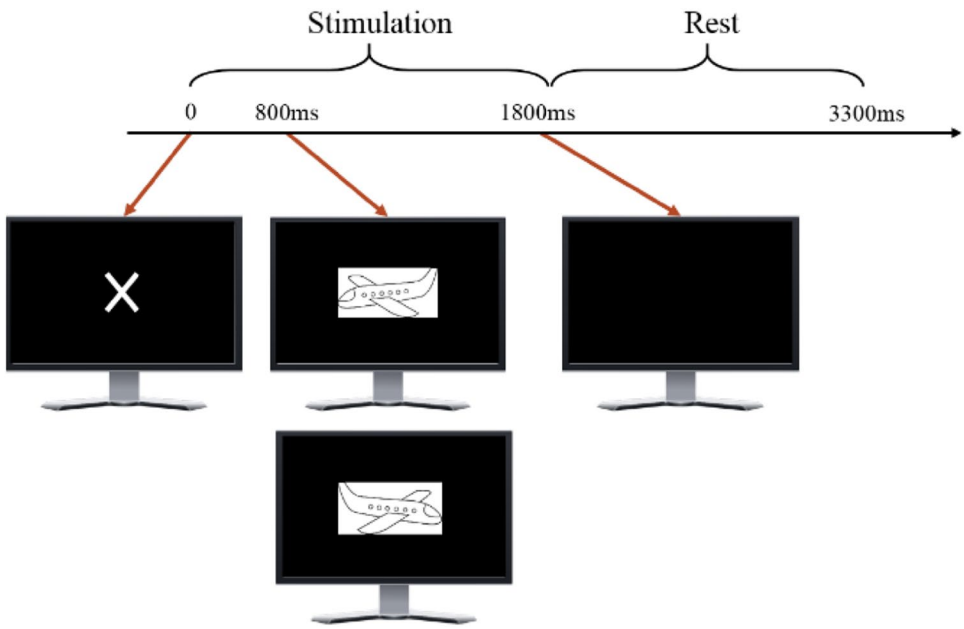

Fig. 1 Procedure and timing of the stop-signal task

amplitude of SSVEPs occurred at a stimulation frequency of around 15 Hz [26, 27]. Second, we intended to prevent the interference between the stimulation frequency and the alpha range (7–13 Hz) of spontaneous activity of the brain in the EEG signal. In the auditory domain, the largest amplitude of ASSRs has been observed at around 40 Hz [28].

During signal recording, we recorded the stop-signal reaction time (SSRT), number of correct responses, omission error and commission error.

Data processing

Steady-state response (SSR) can be considered as a sinusoidal signal which is added up to EEG [9]. The amplitude and the phase of this response are informative for psychophysiological analysis. However, the estimation of these parameters is not straightforward due to the small relative power of the response in comparison with the ongoing EEG. Averaging over the signal can be used with special considerations to enhance signal-to-noise ratio of the SSR. So, the recorded EEG was segmented using a rectangular window with a length of $5/f_{\text{stim}}$ ($5/f_{\text{stim}}$ is the frequency of stimulation). The window was shifted with a step size of $1/f_{\text{stim}}$ over the entire 1000 ms time series of a trial (the first 800 ms of each trial time series was omitted because it may include an event-related response to the onset of stimulation) and then segments were averaged in the time domain. It is quite important that time segments be synchronized. Otherwise, the phase of the sinusoidal response might vary among the segments, and not only does the averaging operation decrease the amplitude, but it also eliminates the phase information. Thus, the window length and shifting steps need to be integer factors of the stimulation period while this is limited by low sampling rate. This issue is well discussed in [15]. Here, to reduce the error of non-integer factors, the signal was up-sampled using an interpolation method with a rate of four.

Finally, two features were calculated from the extracted steady-state responses: amplitude and phase. We used fast Fourier transform (FFT) to compute the amplitude and phase of SSVEP and ASSR.

Statistical analysis

For the purpose of analyzing baseline characteristics, a two-sample *t* test was administered. To compare the steady-state responses of the ADHD group with those of the control group, we used a repeated measures analysis of variance (ANOVA) across the brain regions. For the between-subjects factor, we used the group and for the within-subjects factors we used brain regions [prefrontal (Fp1–Fp2), frontal (F7–F3–Fz–F4–F8), central (C3–Cz–C4), centro-parietal (CP5–CP6), temporal (T7–T8) and occipital (O1–O2)]. Two separate repeated measures ANOVA were administered for SSVEP and ASSR responses, respectively. For multiple comparisons, when needed, the Bonferroni correction was applied. When the result of repeated measures was significant, for between-subject effects the independent samples *t* test was used as a post hoc comparison. Greenhouse–Geisser corrected *p* values were reported when the sphericity assumption was violated (according to Mauchly's test). $p < 0.05$ was considered for the level of significance and all statistical analyses were performed by the SPSS software.

Results

The detailed baseline characteristics data about subjects who participated in the research is listed in Table 1. There was no statistically significant difference between the control group

Table 1 Baseline characteristics of adolescents with ADHD and healthy control adolescents

Variables	Groups		*t*	*p*
	ADHD ($n=30$) Mean ± SD	Healthy control ($n=30$) Mean ± SD		
Age (years)	14.43 ± 1.90	15.11 ± 1.71	1.457	0.150
Handedness	Right = 27 Left = 3	Right = 28 Left = 2		
IQ	108.64 ± 9.12	110.87 ± 8.36	0.987	0.327
SSVEP-SSRT (ms)	646.90 ± 152.43	522.31 ± 113.57	− 3.590	0.0007
SSVEP-cCorrect responses (%)	64.20 ± 12.12	73.54 ± 1.87	4.172	0.0001
SSVEP-omission error (%)	10.59 ± 12.21	1.45 ± 1.88	-4.052	0.0002
SSVEP-commission error (%)	5.77 ± 5.34	3.85 ± 2.70	− 1.757	0.084
ASSR-SSRT (ms)	622.83 ± 132.51	532.23 ± 98.83	− 3.300	0.0017
ASSR-correct responses (%)	68.45 ± 13.69	74.66 ± 0.64	2.482	0.016
ASSR-omission error (%)	6.21 ± 13.78	0.20 ± 0.58	− 2.387	0.020
ASSR-commission error (%)	0.81 ± 1.07	0.15 ± 0.44	− 3.125	0.002

and the ADHD group in age, IQ or sex composition. In addition, Table 1 compares the psycho-physical characteristics of the HC and ADHD subjects in the sense of reaction time in milliseconds, percentage of correct responses (sum of the go trials in which subjects respond and stop trials in which subjects do not respond divided by the number of all trials), percentage of omission error (number of go trials in which subjects do not respond divided by the number of all trials) and percentage of commission error (number of stop trials in which subjects respond divided by the number of all trials). The number of correct answers and errors are normalized to the number of all trials to be comparable within the groups. Also, trials with a reaction time of more than 1000 ms are assumed to be invalid trials and omitted from the analysis.

During the stop-signal task with visual stimulation, on average, healthy subjects had a significantly faster reaction time compared to ADHD subjects ($p < 0.01$). The ADHD subjects had significantly less correct responses ($p < 0.01$). They also showed a larger omission error, ($p < 0.01$), and commission error, ($p = 0.084$), than the control subjects. In visual condition, commission errors did not differ between groups. During the stop-signal task with auditory stimulation, on average, healthy subjects had a significantly faster reaction time compared to ADHD subjects ($p < 0.01$). The ADHD subjects had significantly less correct responses ($p < 0.05$). They also showed a significantly larger omission error, ($p < 0.05$), and commission error, ($p < 0.01$), than the control subjects.

Figure 2 shows the grand average of the amplitude and phase of SSVEP responses of ADHD and HC adolescents. As you can see, the SSVEP amplitude of the ADHD group was larger than that of the HC group in most regions of the brain, which means more activity of the brain in the HC group during the visual stimulation. The SSVEP phase of the ADHD group, as an indicator of visual information processing speed, is less than that of the HC group, which means faster processing of visual information in these regions.

Figure 3 shows the grand average of the amplitude and phase of ASSR responses of ADHD and HC individuals. As you can see, the ASSR amplitude of the ADHD group is smaller than that of the HC group in some brain regions (e.g., right hemisphere). Also, the ASSR phase of the ADHD group is less than that of the HC group in most regions of the brain, particularly the left hemisphere.

Steady-state visual evoked potential: statistical description

Amplitude

The repeated measures ANOVA of SSVEP amplitudes revealed no significant differences between groups [$F(1,58) = 1.742$, $p > 0.05$]. So, there was no need to perform a post hoc comparison for SSVEP amplitudes of the whole brain between groups. The repeated measures of SSVEP amplitudes revealed significant differences

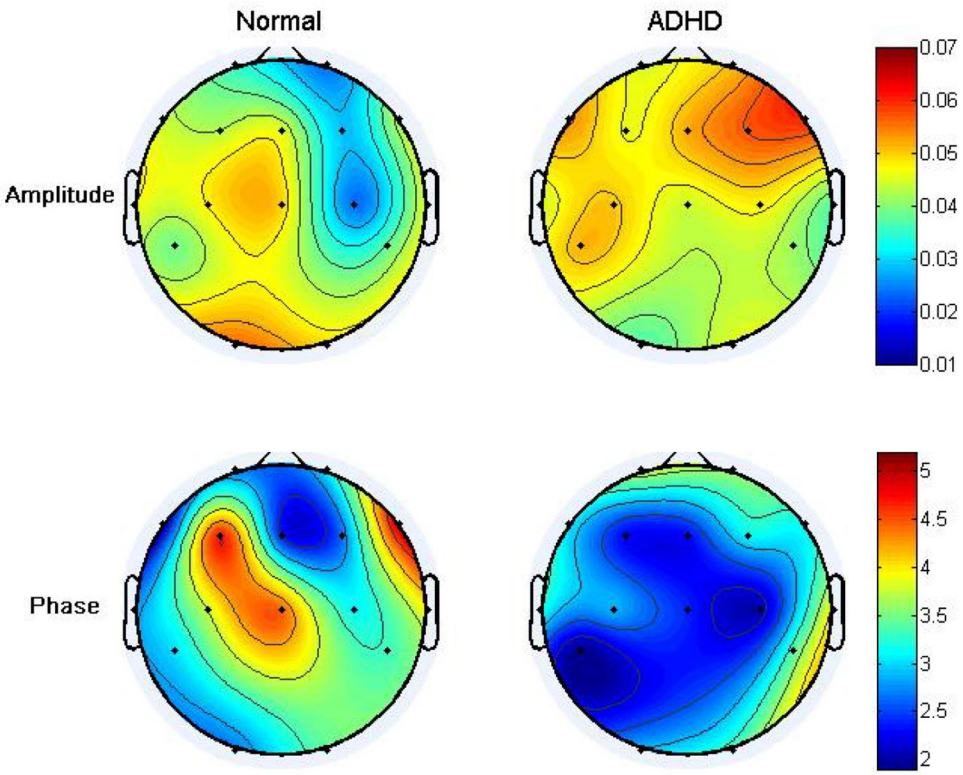

Fig. 2 The amplitude and phase of the steady-state visual evoked potential (SSVEP) in adolescents with (right panel) and without (left panel) ADHD

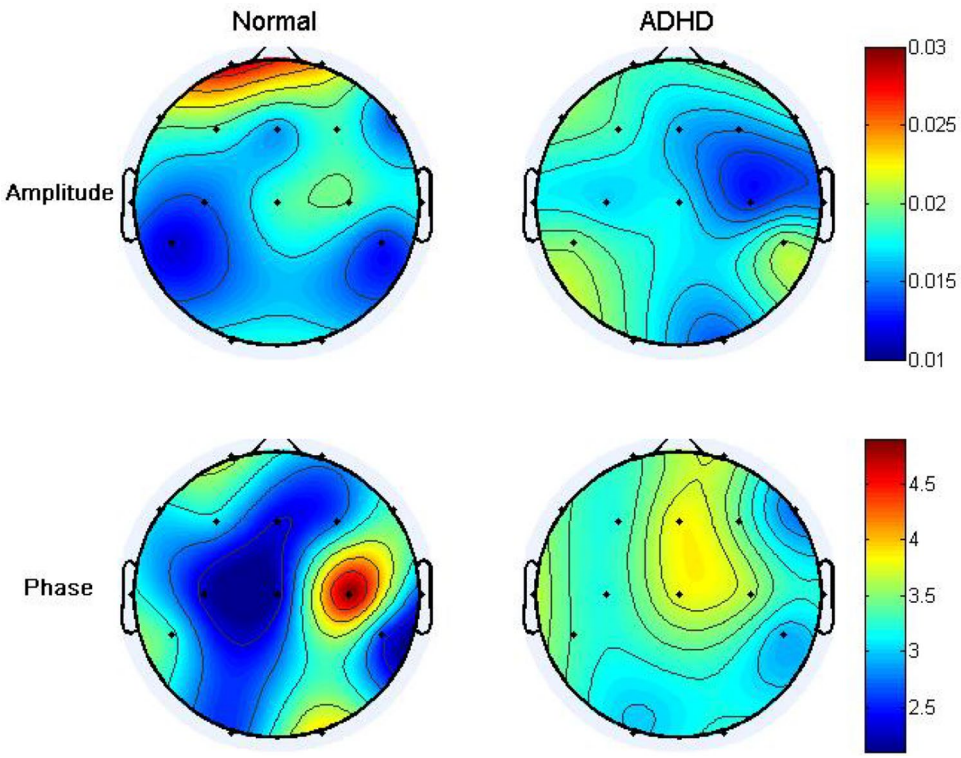

Fig. 3 The amplitude and phase of the auditory steady-state response (ASSR) in adolescents with (right panel) and without (left panel) ADHD

between regions [$F(3.86, 224.32) = 7.654$, $p < 0.001$]. Also, the interaction between region and group was significant [$F(3.86, 224.32) = 12.160$, $p < 0.001$]. Post hoc comparisons (Table 2) showed that the amplitude of SSVEP responses of the ADHD group was significantly higher than that of the HC group at the prefrontal and frontal regions ($p < 0.01$), but the SSVEP amplitude of the ADHD group was significantly less than that of the HC group at the temporal and occipital regions ($p < 0.01$).

Table 2 Pairwise comparison of SSVEP between ADHD and healthy control individuals using independent samples *t* test

Dependent Variable	Group (I)	Group (J)	Mean Difference (I-J)	Partial Eta Squared	*t*	*p*	95% confidence interval for difference	
							Lower bound	Upper bound
SSVEP amplitude								
Prefrontal	ADHD	HC	0.019	0.330	5.344	< 0.0001	0.011	0.025
Frontal	ADHD	HC	0.012	0.383	6.002	< 0.0001	0.008	0.016
Central	ADHD	HC	0.005	0.042	1.591	0.852	− 0.052	0.063
Centro-parietal	ADHD	HC	0.002	0.004	0.484	0.625	− 0.007	0.012
Occipital	ADHD	HC	− 0.016	0.173	− 3.488	0.0009	− 0.025	− 0.006
Temporal	ADHD	HC	− 0.011	0.171	− 3.455	0.001	− 0.017	− 0.004
SSVEP phase								
Prefrontal	ADHD	HC	0.164	0.004	0.493	0.624	− 0.501	0.830
Frontal	ADHD	HC	− 0.183	0.039	− 1.539	0.129	− 0.420	0.054
Central	ADHD	HC	− 1.029	0.254	− 4.449	< 0.0001	0.639	1.684
Centro-parietal	ADHD	HC	− 0.324	0.021	− 1.102	0.275	− 0.912	0.264
Occipital	ADHD	HC	0.162	0.010	0.762	0.449	− 0.263	0.587
Temporal	ADHD	HC	− 0.155	0.006	− 0.593	0.555	− 0.679	0.368

HC healthy control

Phase

The repeated measures of SSVEP phases showed that there was no significant main effect for the groups [$F(1, 58) = 1.394$, $p > 0.05$]. The repeated measures of SSVEP phases revealed significant differences between regions [$F(2.86, 116.11) = 21.209$, $p < 0.001$]. Also, the interaction between region and group was significant [$F(2.86, 116.11) = 4.660$, $p < 0.05$]. Post hoc comparisons (Table 2) showed that the phase of SSVEP responses of the ADHD group was significantly less than the HC group at the central region ($p < 0.01$).

Auditory steady-state responses: statistical description

Amplitude

The repeated measures of ASSR amplitudes showed that there was no significant main effect for the groups [$F(1, 58) = 2.544$, $p > 0.05$]. The repeated measures of ASSR amplitudes revealed significant differences between regions [$F(3.327, 192.964) = 11.742$, $p < 0.001$]. Also, the interaction between region and group was significant [$F(3.327, 192.964) = 12.846$, $p < 0.001$]. Post hoc comparisons (Table 3) showed that the amplitude of ASSR responses of the ADHD group was significantly less than the one for the HC group at the prefrontal region ($p < 0.01$), but at the centro-parietal region, that of the ADHD group was significantly higher than that of the HC group ($p < 0.01$).

Phase

The repeated measures ANOVA of SSVEP amplitudes revealed significant differences between groups [$F(1,58) = 13.346$, $p < 0.01$]. Post hoc comparisons showed that the phase of ASSR responses of the ADHD group was significantly less than that of the HC group ($p < 0.05$). The repeated measures of ASSR phases revealed no significant differences between regions [$F(3.94, 202.64) = 1.601$, $p < 0.05$]. However, the interaction between region and group was significant [$F(3.94, 202.64) = 12.846$, $p < 0.001$]. Post hoc comparisons (Table 3) showed that the phase of ASSR responses of ADHD group was significantly less than that of the HC group at the central, occipital and temporal regions ($p < 0.05$), but that of the ADHD group was significantly higher than that of HC group at the prefrontal region ($p < 0.01$).

Discussion

Behavioral data considerations

In this study, we examined the visual and auditory steady-state responses in adolescents with ADHD compared to healthy adolescents during a stop-signal task. Actually, we looked for the neurophysiological evidence for links between abnormalities in the steady-state responses of the brain's electrical activity and attention in adolescents with ADHD. In addition to pathophysiological investigations, a neuropsychological test was performed to assess the cognitive

Table 3 Pairwise comparison of ASSR between ADHD and healthy control individuals using independent samples *t* test

Dependent variable	Group (I)	Group (J)	Mean difference (I − J)	Partial eta squared	*t*	*p*	95% Confidence interval for difference	
							Lower bound	Upper bound
ASSR Amplitude								
Prefrontal	ADHD	HC	−0.011	0.182	−6.185	<0.0001	−0.013	−0.006
Frontal	ADHD	HC	−0.001	0.038	−0.916	0.363	−0.002	0.001
Central	ADHD	HC	−0.002	0.019	−1.086	0.282	−0.005	0.001
Centro-parietal	ADHD	HC	0.007	0.166	4.235	<0.0001	0.003	0.009
Occipital	ADHD	HC	−0.001	0.011	−0.874	0.386	−0.004	0.001
Temporal	ADHD	HC	−0.001	0.002	−0.364	0.717	−0.004	0.003
ASSR phase								
Prefrontal	ADHD	HC	0.053	0.118	2.792	0.007	−1.581	−0.262
Frontal	ADHD	HC	−0.052	0.001	−0.218	0.828	−0.527	0.424
Central	ADHD	HC	−0.381	0.224	−4.095	0.0001	−1.483	−0.509
Centro-parietal	ADHD	HC	0.067	0.001	0.189	0.851	−0.645	0.779
Occipital	ADHD	HC	−0.075	0.071	−2.107	0.039	0.037	1.455
Temporal	ADHD	HC	−0.259	0.248	−4.372	0.0001	−1.720	−0.639

HC healthy control

functions of participants. For this purpose, motor response inhibition, as indexed by the stop-signal task, was evaluated during steady-state stimulations (both visual and auditory). The reaction times of the ADHD group were slower than those of the HC group in both conditions. Significantly lower correct detection of ADHD group implies reduced attentional capacity in the presence of both stimulations in these individuals. Higher omission error of the ADHD group indicated that they could not pay attention to stimuli or they had a sluggish response. In other words, this may indicate that visual and auditory stimulations have led to distraction in ADHD subjects. Furthermore, high commission error along with high omission error and slow reaction time, in general, imply inattention in ADHD subjects [29]. However, participants with ADHD performed worse than those of the HC group in the auditory condition only (i.e., they showed more commission errors).

Additional to performance of different tasks, there were some differences between adolescents with and without ADHD in both steady-state visual and auditory responses (amplitudes and phases) at different brain regions when performing cognitive control tasks.

SSVEP considerations

SSVEPs display neural activities within the pyramidal cells of the neocortex as the main sources of cortical glutamate [30]. Previous works have shown that the amplitude and phase of SSVEP are sensitive to emotional and cognitive manipulation [31]. Indeed, the SSVEP amplitude has been compared to alpha activity and cortical arousal in relation to cognitive tasks, whereas the phase or latency has been taken as an index of processing speed in synaptic excitatory processes [9, 17, 18, 30]. Decreased SSVEP amplitude in the occipital region demonstrates that the visual cortex of ADHD adolescents seems to be more activated compared to healthy controls. However, no reduction was observed in the SSVEP phase, indicating that increased neural activity at the occipital region did not lead to an increase in the speed of information processing in the visual cortex of the ADHD. Therefore, this increased neural activity (due to small SSVEP amplitudes) during visual stimulation in ADHD adolescents may be attributed to: (a) the inability of the occipital or visual neural circuits for synchronization to periodic external stimuli, and (b) an abnormality in the retinal response, leading to propagation of an anomalous signal to the visual areas. Furthermore, the rise of SSVEP amplitude in the anterior region (prefrontal and frontal cortices) of the ADHD brain can be interpreted from two perspectives: (a) decreased activity of the anterior areas, which is responsible for executive functions including decision making and cognitive inhibitory control, thereby decreased performance in performing cognitive tasks, and (b) deficiency in connectivity of the anterior and posterior regions of the brain, since increased regional activity in the posterior region has not resulted in an increase in neural activity in the anterior region. The latter, in fact, can demonstrate deficits in the functional networks of frontoparietal and dorsal attention. A recent meta-analysis of 55 functional magnetic resonance imaging (fMRI) studies reported substantial hyperactivation in the visual circuits as well as default network in ADHD [32]. The authors stated that this hyperactivation comes from abnormal inter-regulation between the default network and the dorsal or ventral attention and frontoparietal networks. As a result, the observed hyperactivation in the visual circuits in our work can be interpreted as a possible compensatory mechanism during cognitive tasks in ADHD.

ASSR considerations

The 40 Hz ASSRs reflect the neurons' tendency to oscillate at a certain gamma resonant frequency induced by an external periodic stimulation [20]. The present findings of ASSR deficits are consistent with hypotheses of N-methyl-D-aspartate (NMDA)-receptor dysfunction in ADHD. In fact, new evidence supports NMDA dysfunction as a possible pathogenesis of ADHD from the neurodevelopment, impulse inhibition and attentional circuitry perspectives [33]. The normal function of NMDA receptors is important for normal gamma modulation, and dysfunction of these receptors results in decreased/increased gamma amplitude and shortened/prolonged gamma duration [34]. NMDA disturbance most likely affects the GABA receptors-mediated inhibition [35]. GABAergic inhibition is involved in several neurodevelopmental disorders including ADHD. Cortical inhibitory function mediated by GABAergic neurotransmission is necessary for filtering sensory information and choosing proper behavioral responses [36]. Therefore, disturbance of this inhibitory function due to GABAergic abnormalities, especially within the auditory association cortex, can result in ASSR deficits and consequently disorder-based behavioral dysfunctions in ADHD.

Other potential pathophysiological mechanisms

Individuals with ADHD showed a different activity pattern in the prefrontal region in both SSVEP and ASSR amplitudes. This finding is consistent with previous observations from neuroimaging studies in which dysfunctions were reported in the dorsolateral and bilateral inferior prefrontal cortex (PFC) during inhibitory control tasks in ADHD [37–40]. Actually, hypo-activation of the inferior prefrontal cortex is one of the most consistent findings among the neuroimaging literature of ADHD during motor response inhibition tasks [41–44]. However, the PFC, as a main part of higher-order association, is very important to regulate

attention and organize behavior or thought in a task-relevant manner [45]. Furthermore, structural brain imaging in patients with ADHD indicates that the cortical thickness of their orbitofrontal cortex (OFC) is smaller and the connectivity of the OFC with other brain regions is reduced [46, 47]. In general, the frontal lobe, including PFC and OFC, is responsible for the important functions such as executive functions including decision making, cognitive inhibitory control and selective or sustained attention [48–50].

The SSVEP amplitude of ADHD adolescents was smaller in the temporal and occipital regions. In other words, the neural activity of these regions increased in the ADHD group during visual stimulation. Moreover, the ASSR amplitude of ADHD adolescents was larger in the centro-parietal region. The inferior part of the temporal lobe, as a temporal association cortex, plays a primary role to explore visual features for recognizing objects or places, whereas the parietal association cortices play an important role to orient attentional resources in time or space [45]. These posterior association cortices are sensitive to the physical characteristics of a stimulus such as color and movement [51]. Therefore, poorer performance of adolescents with ADHD when performing tasks can be attributed to the dysfunction of these association cortices and the flow of information between them.

One limitation of this study was that subjects did not undergo a cognitive assessment of their selective attention when faced with visual and auditory tasks. Furthermore, various stimulation frequencies result in different steady-state responses depending on neurophysiological impairments. Thus, various stimulation frequencies in different modalities should be further investigated in the future.

Conclusion

In general, it seems that the visual stimulation has a greater impact on neural activity in the anterior and posterior regions of the brain, whereas the auditory stimulation has a greater impact on the local synaptic excitatory processes in ADHD. This is probably the reason why the commission error of ADHD individuals has had a significant difference with the those of healthy group only in the auditory condition. Nonetheless, deficiencies have been observed in PFC in both conditions. These deficiencies affect the executive functions of ADHD individuals and reduce their cognitive performance when facing different cognitive tasks. In conclusion, poorer task performance (especially inattention) and neurophysiological results in ADHD demonstrate a possible impairment in the interconnection of the association cortices in the parietal and temporal lobes and the PFC. As a result, the visual cortex cannot well extract the relevant information from incoming sensory information and visual pathways to integrate the appropriate signals into a coherent and unified perceptual experience. The results of the present study could also support the hypothesis of NMDA and GABAergic dysfunctions in ADHD. Also, the motor control problems in ADHD may originate from neural deficits in the frontoparietal and occipitoparietal systems, and even from other brain structures such as cerebellum.

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Compliance with ethical standards

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