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The neural correlations of spatial attention and working memory deficits in adults with ADHD

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ABSTRACT

Working memory impairment is a typical cognitive abnormality in patients with attention-deficit/hyperactivity disorder (ADHD) and is closely related to attention. Exploring the interaction between working memory and attention in patients with ADHD is of great significance for studying the pathological mechanism of this disease. In this study, electrophysiological markers of attention, posterior contralateral N2 (N2pc), and working memory, contralateral delay activity (CDA), were used to explore the relationship between these two cognitive abilities in patients with ADHD. EEG data were collected from adults with ADHD and age-, sex-, and IQ-matched normal controls while performing a classical visuospatial working memory task that consisted of low-load and high-load memory conditions. In different memory load conditions, the memory array elicited a smaller N2pc (220–260 ms) and a smaller CDA (400–800 ms) in adults with ADHD than in normal controls. Further analysis revealed that the reduced CDA amplitude could be significantly predicted by the earlier and reduced N2pc amplitude in adults with ADHD. Moreover, when the number of memory items increased, the increase in N2pc highly predicted the increases in CDA. Our findings illustrate the relationship between spatial working memory and attention ability in ADHD adults from the neurophysiological aspect that reduced working memory is closely related to insufficient attention ability and provide a potential physiological basis for the pathological mechanism of ADHD.

1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder with a high prevalence rate of 5–6% in children, and the persistence rate of symptoms into adulthood is as high as 50–80% (Asherson et al., 2016). Compared with children, adult ADHD patients have lower hyperactivity levels but still show impulsiveness and inner restlessness. Notably, a lack of attention and attention maintenance to related stimuli is common. Abnormal neuropsychological activity resulting from these symptoms may interfere with a patient's learning ability and life, professional activities, and social functions (Halleland et al., 2012; Wang et al., 2017).

Working memory impairment as a typical cognitive impairment in adults with ADHD has been confirmed in many studies. A meta-analysis summarized that adult ADHD patients showed deficits in both visual space and phonological loop working memory tasks (Alderson et al., 2013). Evidence from event-related potential (ERP) studies has demonstrated that the components related to working memory, such as contralateral delayed activity (CDA) and P3, are reduced in adults with ADHD (Kim et al., 2014; Wiegand et al., 2016). fMRI studies indicated functional abnormalities in working memory-related brain regions, including the bilateral dorsolateral prefrontal cortex (DLPFC), the right parieto-occipital area, the right inferior parietal lobe and the right caudate nucleus and less functional connectivity between frontal and subcortical regions (Burgess et al., 2010; Sheridan et al., 2007). However, the current clinical intervention for impaired working memory in ADHD has not made effective progress, which may require a thorough scientific understanding of the deficient neurocognitive mechanisms of

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ADHD (Chacko et al., 2013; Gibson et al., 2011).

Working memory is the active maintenance of visual information to serve the needs of ongoing tasks, which includes not only the part responsible for information maintenance but also the central executive system related to the active control process, which is closely related to the attention process (Aben et al., 2012; Luck and Vogel, 2013; Nelson, 2008). Research has indicated that working memory processes attention-gathering information and regulates attention through top-down control mechanisms (Gazzaley and Nobre, 2012; Knudsen, 2007). Therefore, it is reasonable to speculate that working memory impairment in ADHD patients is likely to be affected by the attentional process. Indeed, much evidence has been obtained from studies of patients with ADHD. For instance, one behavioral study found that working memory deficits were affected by a defect in the visual coding period in children with ADHD (Barnett et al., 2005). Recent electroencephalography (EEG) studies reported attenuated alpha desynchronization and theta synchronization during the encoding phrase, which is related to impaired working memory performance in patients with ADHD (Lenartowicz et al., 2014; Missonnier et al., 2013). fMRI studies revealed that higher working memory ability predicted increased activation of the left prefrontal cortex (PFC), which is related to attentional control in adults with ADHD (Burgess et al., 2010; Sheridan et al., 2007).

ERP studies have suggested that one specific component, the N2pc, observed contralateral to the attended target, is an enhanced negative potential and emerges over the posterior scalp 200–300 ms after the appearance of stimuli. Many studies have confirmed the N2pc as an electrophysiological marker of visual attentional selection (An et al., 2012; Eimer, 1996; Huang et al., 2015; Luck and Hillyard, 1994a, 1994b; Sun et al., 2018; Yao et al., 2013). Two recent studies have found that the N2pc can reflect attention deficits in ADHD patients, as shown by prolonged latency or decreased amplitude (Cross-Villasana et al., 2015; Wang et al., 2016). More importantly, N2pc can also be induced in the visual short-term memory search paradigm (Kuo et al., 2009; Nobre et al., 2004). Based on the above results, it is feasible to use the N2pc in working memory tasks to study the attention ability of adults with ADHD.

We also used the ERP component to accurately assess the working memory capacity of participants. The CDA, which emerges over the posterior scalp 400–800 ms after the memory array, has been suggested to be a good candidate to assess visual working memory capacity (Luria et al., 2016; Vogel et al., 2005; Vogel and Machizawa, 2004). Related studies have confirmed that the CDA may be a measure of how much information is currently in mind (Luria et al., 2016, 2010) and that the CDA is sensitive to individual differences in working memory. Two studies analyzed the application of CDA in adults with ADHD (Spronk et al., 2013; Wiegand et al., 2016). Spronk et al. (2013) found no difference between ADHD and controls, while Wiegand et al. (2016) demonstrated that decreases in the CDA may be a candidate neurocognitive endophenotype of ADHD. Therefore, this study aimed to further our understanding of the working memory performance of adults with ADHD represented by CDA.

In summary, this study adopted electrophysiological indicators that effectively characterized individual attention selection and working memory capacity to explore the interaction between attention and working memory in adults with ADHD. To effectively evoke these two components, we used the visuospatial working memory paradigm with a typical selective attention process. In addition, two memory load conditions were designed to describe the performance of ADHD patients on tasks of different complexities (Carlisle et al., 2011; Sigi Hale et al., 2007). Therefore, the present study investigates 1) whether the attentional selection ability reflected by the N2pc of adults with ADHD is abnormal when completing working memory tasks; 2) whether the maintained working memory capacity expressed by CDA is abnormal in adults with ADHD; and 3) whether working memory impairment in adults with ADHD based on CDA is related to the attentional selection ability reflected by the N2pc.

2. Method

2.1. Participants

A total of 66 adults (32 with ADHD, 34 normal controls) participated in the study. Adults with ADHD were recruited from the clinics of Peking University Sixth Hospital/Institute of Mental Health. Normal controls matched for sex, age, and intelligence quotient (IQ) were enrolled from communities in Beijing. All of the participants were interviewed, underwent diagnosis and were screened for any potential comorbidities using the Structured Clinical Interview for DSM-IV Axis I Disorders (First et al., 1996) by a qualified psychiatrist. Conners' Adult ADHD Diagnostic Interview for DSM-IV (American Pyschiatric Association, 2000; Conners et al., 1999) was applied to confirm the diagnosis and subtypes in the ADHD group. Considering the highest proportion of inattentive subtype (ADHD-I) and the more prominent attention deficit and working memory impairment, only adult ADHD-I patients were included in the present study. To exclude the potential effect of ADHD therapeutic drugs, all patients were drug-naïve or stopped taking drugs for > 2 weeks. Full-scale IQ measurements were made using the Wechsler Adult Intelligence Scale, Third Edition. All participants met the following criteria: (a) right-handed, (b) no history of head trauma with a loss of consciousness, (c) no history of neurological illness or other severe disease, and (d) no current diagnosis of schizophrenia, severe major depression, clinically significant panic disorder, bipolar disorder, pervasive developmental disorders, or mental retardation and (e) a full-scale IQ above 80.

Data from 3 participants (1 with ADHD, 2 normal controls) were discarded because of the high ratio of noise and artifacts in the EEG signals (> 10 bad electrodes). Data from another 4 participants (2 with ADHD, 2 normal controls) were excluded due to excessive horizontal eye movement (> 50% trials rejected). Therefore, the group comparisons reported here are from the remaining 59 participants (29 with ADHD, 30 normal controls, 89.4% of the samples) were included for further analyses. Among the adults with ADHD, one had social phobia (SP), one had obsessive-compulsive disorder (OCD), one had posttraumatic stress disorder (PTSD) and two had dysthymia disorder. The participants' demographic information is shown in Table 1.

This study was approved by the Medical Ethics Committee of Peking University Sixth Hospital/Institute of Mental Health. All participants signed informed consent.

2.2. Stimuli and procedure

A schematic of the stimuli and trial design is illustrated in Fig. 1. The stimuli were presented on a 21-in. gamma linearized CRT monitor (1600 × 1200 pixel, 85 Hz refresh rate) with a homogeneous light gray background (54.3 cd/m2, RGB: 80, 80, 80) that was positioned 100 cm

Table 1
Demographic information and clinical symptoms.

	ADHD	Control	χ^2/t	*p*
Sex (male: female)	15:14	21:09	−2.04	0.154
Age in years (Mean ± SD)	26.51 ± 5.41	25.05 ± 2.79	−1.30	0.202
IQ (Mean ± SD)	120 ± 7	122 ± 5	−1.32	0.192
Symptoms scores (Mean ± SD)				
Inattentive	26.45 ± 3.22	13.47 ± 3.01	−15.96	< 0.001
Hyperactive/Impulsive	17.10 ± 3.80	12.57 ± 2.94	−5.14	< 0.001
Total	43.55 ± 5.35	26.03 ± 5.42	−12.49	< 0.001

There were significant differences in symptom scores between the two groups, while there were no significant differences in age and sex distributions.
ADHD, attention-deficit/hyperactivity; SD, standard division; IQ, intelligence quotient.

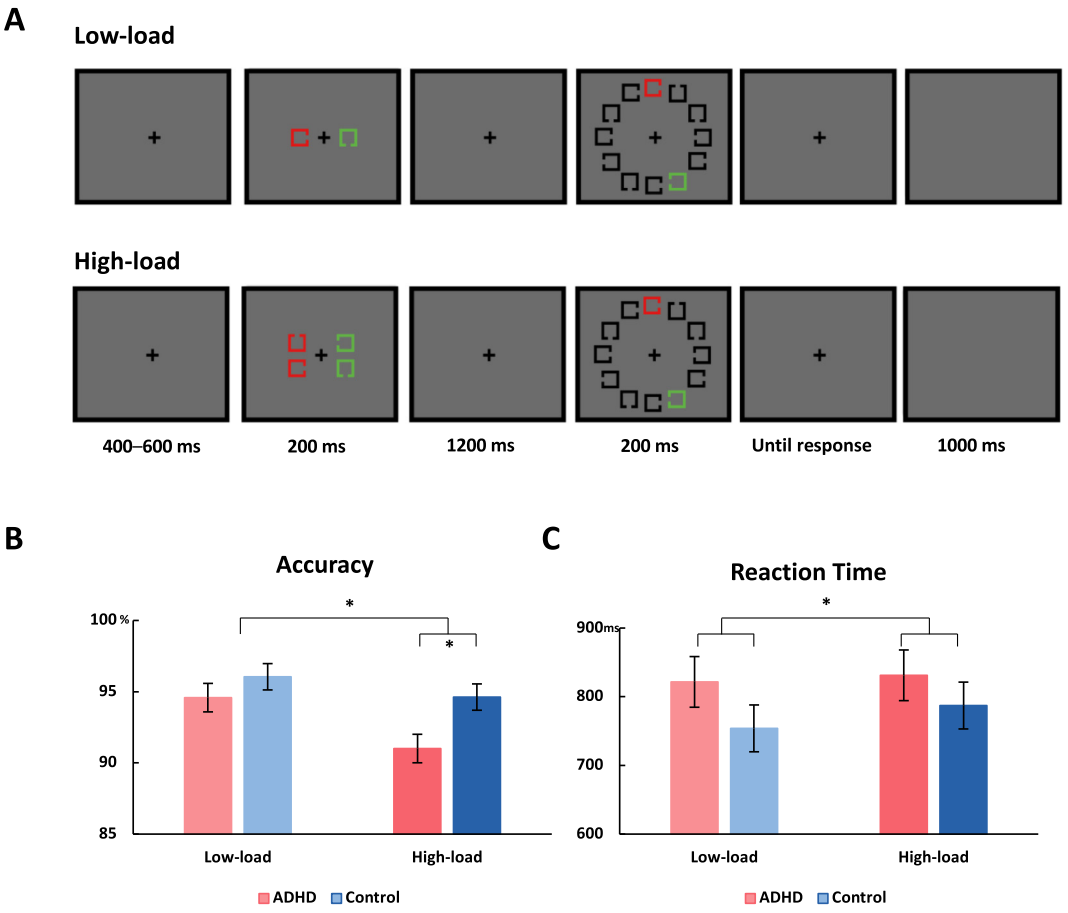

Fig. 1. Experimental paradigm and behavioral results. A. Experimental paradigm. Following an interstimul0075s interval (400–600 ms) with a black central fixation cross, the memory array was presented for 200 ms. Each memory array consisted of red and green Landolt squares, which were presented to the left and right of fixation, respectively. After a delay of 1200 ms, a visual search array was presented for 200 ms. Each visual search array was composed of 12 Landolt squares that were the same size as those in the memory array. Participants were required to respond regarding whether the target-color Landolt square in the following search array matched the target-color Landolt square in the memory array (or whether it matched one of the target-color Landolt squares in the high-load condition). B. The behavior results of accuracy. C. The behavior results of reaction time. *$p < 0.05$.

from the subject. Each trial consisted of a sequence of a memory array and a visual search array. Following an interstimulus interval (400–600 ms) with a black central fixation cross displayed (< 0.01 cd/m2, 0.4° × 0.4° of visual angle), the memory array was presented for 200 ms. Each memory array consisted of a red (25 cd/m2; RGB: 255, 102, 102) Landolt square and a green (25 cd/m2; RGB: 80, 179, 80) Landolt square, which were presented at the left and right of fixation, respectively. Each Landolt square was composed of a colored outer square (1° diameter), an inner square in the background color (0.9° diameter), and a small gap in the background color (0.22°). The gap could appear at 4 possible positions corresponding to the Landolt square orientations (top, right, bottom, left). The gap orientations of Landolt squares in the memory array varied randomly across trials, with the constraint that none of the same orientations appeared within the given memory array.

After a delay of 1200 ms, a visual search array was presented for 200 ms. Each visual search array was composed of 12 Landolt squares with the same size as those in the memory array, which were arranged in a circle with a visual angle radius of 4.15°. Among the Landolt squares, one was red, one was green, and the rest were black (< 0.01 cd/m2, RGB: 0, 0, 0) with randomized gap orientations.

The experiment consisted of low-load (remember-one-target) conditions and high-load (remember-two-targets) conditions. At the beginning of each block, either red or green was designated the target color. The red target and green target blocks were presented in random order with equal probability. Participants were instructed to maintain their gaze on the fixation point while paying attention to the target color-cued visual field and to remember the gap orientation of the target-color Landolt square. In the following search array, a target-color Landolt square was always presented in the cued visual field or on the vertical meridian (100% validity). Participants were required to respond if a target-color Landolt square from the memory array (either of the two target-color Landolt squares in the high-load condition) was present in the subsequent search array and to ignore stimuli presented in the uncued visual field.

This design led to two types of trials, each with equal probability: In 50% of all trials, the target-color Landolt square appeared at one of the two vertical midline positions (upper or lower visual field) and another colored salient-but-irrelevant Landolt square appeared at the lateral position. In the remaining 50% of all trials, the colored salient-but-irrelevant Landolt square was presented at the midline positions, whereas the target-color Landolt square was at the lateral position.

In all conditions, the targets were presented in half of the trials. Participants were instructed to respond by pressing a button on a keyboard. Participants were instructed to respond as accurately and quickly as possible. Each participant performed at least 20 practice trials to ensure that they understood the task and could maintain proper fixation. The formal experiment would begin if the participant's accuracy in the practice trials was higher than 70%. Across the blocks of the trials, the target-color switched between red and green to rule out physical stimulus explanations for the lateralized ERP effects (Woodman, 2010). There were 60 trials for each block; the entire

experiment contained 12 blocks (6 blocks for each condition) and lasted approximately 80 min with enough break time after each block. The experiment was conducted in a dimly lit, sound attenuated and electrically shielded room.

2.3. EEG recording and analysis

EEG data were acquired from 128 channels (HydroCel Geodesic Sensor Net, Electrical Geodesics, Inc., Eugene, OR) with Net Station EEG Software. The impedance of all electrodes was kept below 50 kΩ during the data acquisition. All electrodes were physically referenced to Cz (fixed by the EGI system). The EEG recordings were amplified with a bandpass filter of 0.01–400 Hz (half-power cutoff) and digitized online at 1000 Hz.

Offline EEG processing and analyses were performed using custom scripts from the EEGLAB toolbox in the MATLAB environment. The resampling frequency was 250 Hz, and the bandpass filter frequency band was 0.5–40 Hz. The signals were then re-referenced to the average of the left and right mastoid channels. Electrodes containing excessive artifacts (exceeding 20% of the total recording time) were excluded from further analysis. The time series was subsequently inspected for outlier epochs with muscle artifacts, and epochs with excessive artifacts were removed. The trimmed data were then decomposed to perform an independent component analysis (ICA) via the extended infomax method. ICA components associated with vertical eye movements, head movements, heartbeats and other obvious artifacts were visually identified and removed according to their spatial, spectral, and temporal properties. The data were then segmented relative to the memory array onset (−200 to 1000 ms), and the baseline preceding the memory array (−200 to 0 ms) was subtracted. Epochs were then sorted according to the remembered visual field (left, right) for each group. To further remove the horizontal eye movements in the data, we rejected all signal segments when the difference waves of electrodes F9/10 exceeded ± 50 μV. To further remove artifacts due to blinks during the presentation of the stimulus, we also rejected all signal segments when the mean waves of electrodes Fp1/2 exceeded ± 50 μV during 0–200 ms from the original data. Epochs contaminated by incorrect responses and responses faster than 200 ms or slower than 2000 ms were also excluded from the ERP averages.

We analyzed the N2pc and CDA components obtained from the difference waves. ERP difference waves were computed by subtracting the ERP waveforms measured from electrodes located on the hemisphere ipsilateral to the target from the ERP waveforms of symmetrical electrodes on the contralateral hemisphere. Note that the contralateral waveform for the target was the average of the left-hemisphere electrode when the target was in the right visual field and the average of the right-hemisphere electrode when the target was in the left visual field. Similarly, the ipsilateral waveform for the target was the average of the left-hemisphere electrode when the target was in the left visual field and the average of the right-hemisphere electrode when the target was in the right visual field. Because the overall optical luminance of the stimuli was bilateral, this subtraction eliminates most common ERP components, with N2pc and CDA remaining in the difference waveform. We measured the N2pc and CDA components of the mean waveforms recorded at eight electrode sites, namely, 64, 65, 58, and 59 and 90, 91, 95, and 96 (Fig. 3E, F) at the PO7/8 electrode sites, where these components showed the largest amplitudes. The time windows are 220–260 ms for N2pc (Luck and Hillyard, 1994a, 1994b) and 400–800 ms for CDA (Vogel et al., 2005; Vogel and Machizawa, 2004). The presence of N2pc and CDA were first tested by paired *t*-tests between contralateral and ipsilateral waveforms to the remembered items. Then, the differences in ERP components between the two groups were tested by using 2 group (ADHD, controls) × 2 load (low, high) repeated measures two-way ANOVA. To further investigate the relationship between attention and working memory, we performed a Spearman correlation analysis between the mean amplitudes of the N2pc and CDA components.

3. Results

The demographic and clinical symptoms of the subjects are shown in Table 1. No significant difference was found in age, sex or IQ between adult ADHD subjects and controls. Higher inattentive and hyperactive/impulsive symptom scores were found in adults with ADHD than in controls.

3.1. Working memory task performance of adults with ADHD

As illustrated in Fig. 1, the accuracy showed a significant main effect of group ($F_{1,57} = 6.63$, $p = 0.013$, $\eta^2 = 0.104$), indicating that the accuracy of the ADHD group was significantly lower than that of the control group. The main effect of load ($F_{1,57} = 20.01$, $p < 0.001$, $\eta^2 = 0.26$) was also significant. The interaction of group × load was marginally significant ($F_{1,57} = 3.69$, $p = 0.060$, $\eta^2 = 0.061$). Further simple effect analysis showed that the accuracy of adult ADHD subjects was significantly lower than that of normal controls only in the high-load condition ($F_{1,57} = 7.61$, $p = 0.008$, $\eta^2 = 0.118$), while this effect was absent in the low-load condition ($F_{1,57} = 2.51$, $p = 0.118$, $\eta^2 = 0.042$).

Marginal significant main effects of group ($F_{1,57} = 3.83$, $p = 0.055$, $\eta^2 = 0.063$) and load ($F_{1,57} = 34.86$, $p < 0.001$, $\eta^2 = 0.379$) were found for reaction time, while the interaction of group × load was not significant ($F_{1,57} = 0.05$, $p = 0.832$, $\eta^2 = 0.001$).

3.2. ERP wave analysis

The averaged contralateral and ipsilateral activity at the occipital and parietal sites in the control and ADHD groups for the two task conditions is shown in Fig. 2. During the 220–260 ms and 400–800 ms time windows, there was significant separation between the contralateral and ipsilateral waveforms. Paired *t*-tests revealed significant differences in bilateral activity in both controls (220–260 ms: low-load: $t_{29} = 6.83$, $p < 0.001$; high-load: $t_{29} = 7.35$, $p < 0.001$; 400–800 ms; low-load: $t_{29} = 4.66$, $p < 0.001$; high-load: $t_{29} = 7.57$, $p < 0.001$) and patients with ADHD (220–260 ms: low-load: $t_{28} = 3.97$, $p < 0.001$; high-load: $t_{28} = 6.08$, $p < 0.001$; 400–800 ms: low-load: $t_{28} = 2.48$, $p = 0.020$; high-load: $t_{28} = 4.49$, $p < 0.001$), revealing the presence of N2pc and CDA in both groups.

Grand-average ERPs (contralateral minus ipsilateral activity) showing the N2pc and CDA components at the occipital and parietal sites in the two groups for both load conditions are depicted in Fig. 3. In this experiment, the transient wave after the memory array (220–260 ms) is N2pc, which reflects attentional selection in the encoding stage (Hickey et al., 2009; Luck and Hillyard, 1994a, 1994b; Sawaki and Luck, 2010). The negative activity during the maintenance period (400–800 ms) is likely the CDA component, which reflects memory capacity in the memory retention process (Carlisle et al., 2011; Jolicœur et al., 2008).

3.3. N2pc analysis

The mean amplitude of parieto-occipital N2pc within the time window of 220–260 ms was entered into a 2 group (ADHD, control) × 2 load (low, high) repeated measures ANOVA. The significant main effect of group ($F_{1,57} = 13.26$, $p = 0.001$, $\eta^2 = 0.189$) indicated a smaller N2pc in the ADHD group than in the normal control group. A significant main effect of load ($F_{1,57} = 28.36$, $p < 0.001$, $\eta^2 = 0.332$) was also found, but the interaction effect was not significant ($F_{1,57} = 1.53$, $p = 0.221$, $\eta^2 = 0.026$), suggesting that the N2pc amplitude increased with increasing memory load in both groups.

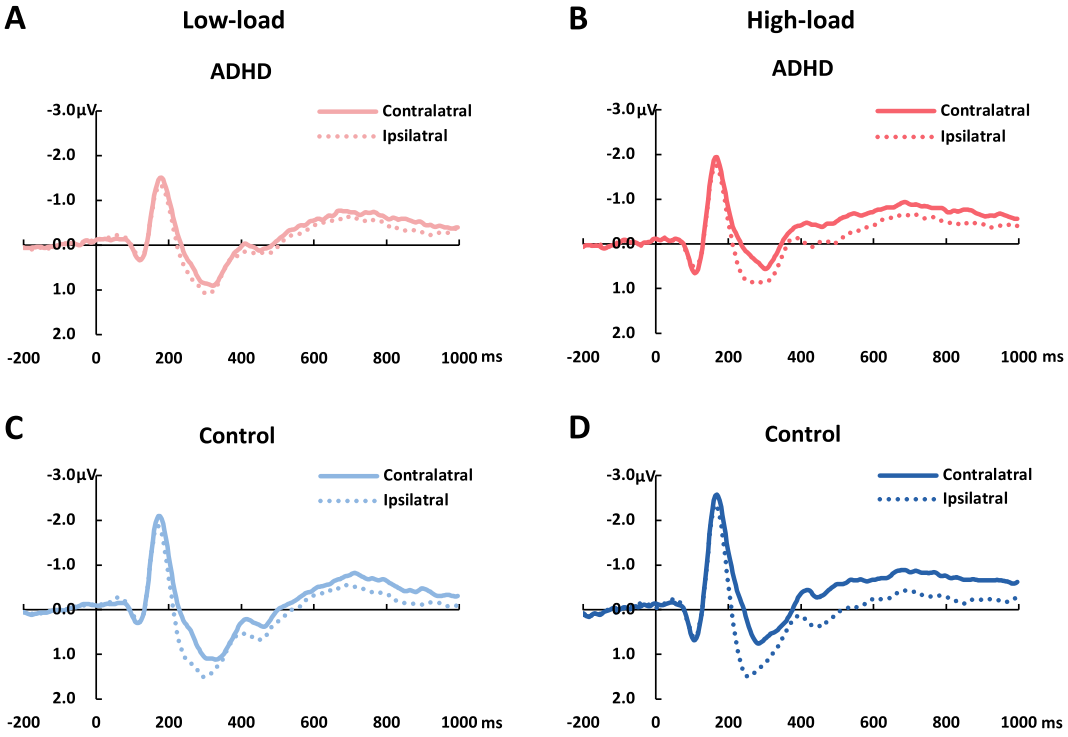

Fig. 2. Original ERP waveforms. Grand-average ERPs at contralateral (solid line) and ipsilateral (dashed line) electrode sites relative to the memory targets. A. ERPs for adults with ADHD in the low-load condition. B. ERPs for adults with ADHD in the high-load condition. C. ERPs for controls in the low-load condition. D. ERPs for controls in the high-load condition.

3.4. CDA analysis

For the mean amplitude of CDA within 400–800 ms, repeated measures two-way ANOVA showed that the main effect of load was significant ($F_{1,57} = 28.85$, $p < 0.001$, $\eta^2 = 0.336$), demonstrating the increased CDA amplitude with increasing memory load (Luria et al., 2016). The main effect of group was significant ($F_{1,57} = 4.58$, $p = 0.037$, $\eta^2 = 0.074$), while the interaction between group and load

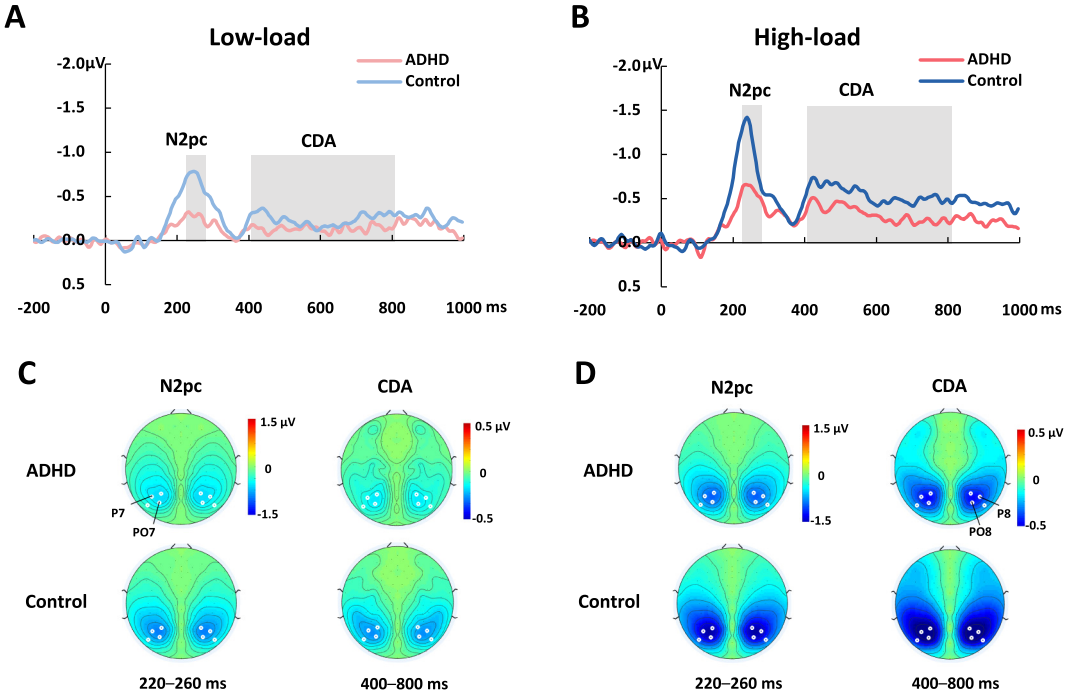

Fig. 3. Difference wave and topographic map. Grand-average difference waveforms obtained by subtracting the ipsilateral waveforms from the contralateral waveforms relative to the memory targets. A. The difference wave in the low-load condition. B. The difference wave in the high-load condition. C. Topographic maps of N2pc and CDA in the low-load condition. D. Topographic maps of N2pc and CDA in the high-load condition. The white dots represent the electrodes chosen for data analysis.

did not reach significance ($F_{1,57} = 1.68$, $p = 0.201$, $\eta^2 = 0.029$), indicating a smaller CDA amplitude of ADHD patients in working memory tasks in both low- and high-load conditions.

Next, we correlated the N2pc/CDA components (the N2pc amplitude, The N2pc peak latency and the CDA amplitude) with the behavioral results (accuracy, reaction times and symptom scores). Both ERP components were not associated with ADHD symptoms. We only found two significant effects under high-load conditions. That is, the smaller N2pc was correlated with the lower accuracy in ADHD patients ($r = -0.449$, $p = 0.014$, two-tailed), and the larger N2pc was correlated with the shorter reaction times in control subjects ($r = 0.410$, $p = 0.025$, two-tailed).

Lastly, we further analyzed other ERPs components (P1, N1, P2 and P3) from the original waveform. Source analysis using BESA software was also performed on N2pc and CDA (Please see supplementary materials).

3.5. Relationship between attentional selection and working memory capacity

Compared with normal controls, adults with ADHD showed a reduced N2pc and a reduced CDA in both low- and high-load conditions. To investigate whether the working memory capacity in adults with ADHD was related to abnormal attentional selection, we further analyzed the correlation between the amplitudes of N2pc and CDA. The results showed that for the ADHD group, there were significant correlations between the N2pc and CDA amplitudes under the low- ($r = 0.379$, $p = 0.042$, two-tailed) and high-load ($r = 0.674$, $p < 0.001$, two-tailed) conditions. This result suggested that the working memory defects reflected by the reduced CDA in adults with ADHD might partly be due to the attentional selection deficits reflected by the reduced N2pc. For the control group, the correlation between the N2pc and CDA amplitudes also reached significance under the high-load condition ($r = 0.516$, $p = 0.003$, two-tailed), but this effect was absent under the low-load condition ($r = 0.249$, $p = 0.185$, two-tailed). This result suggested that the working memory capacity in the normal controls was also closely related to the attentional selection ability when the task became more challenging and demanded more attentional resources (See Fig. 4).

Additionally, we further measured the rise in N2pc amplitude and the rise in CDA amplitude from one item to two items and found that there was also a highly significant correlation between the rise in the N2pc amplitude and the rise in CDA amplitude for both adults with ADHD (r = 0. 532, p = 0. 003, two-tailed) and controls (r = 0. 487, p = 0. 006, two-tailed). This result further demonstrated that, similar to the control group, the increment in attentional selection recourses highly predicted the increases in working memory biomarkers in ADHD patients when the number of memory items increased.

4. Discussion

In the current study, we investigated the neural substrate of attentional selection and working memory deficits and the relationship between them in adult ADHD subjects by using the N2pc and CDA components as indicators. This study employed a visual working memory paradigm to elicit a typical attention process, which included active attentional selection to the defined object, memory maintenance of the selected objects and subsequent object matching (Carlisle et al., 2011; Kim et al., 2014). Analysis of behavioral performance and simultaneous EEG recordings revealed remarkable differences when comparing the normal and adults with ADHD groups. Most importantly, our data indicated that the working memory deficit in ADHD was partly related to poor covert visual spatial attention.

4.1. Working memory deficit in adults with ADHD

The behavioral results showed lower accuracy and longer reaction times for adults with ADHD, indicating persistent defects in visual working memory (Alderson et al., 2013). Additionally, the interaction effects between group and load conditions for accuracy showed worse working memory performance in the high-load condition, revealing the load-dependent working memory impairment of ADHD. Previous research has revealed that the defective manifestations of ADHD are more prominent while performing more complex tasks. Therefore, some researchers have postulated that defects involving complex processes may be the core defects of ADHD in the performance of working memory (Chacko et al., 2013; Gibson et al., 2011; Luria et al., 2010), which is also suggested by the worse behavior performance under the high-load condition observed in our study.

ERP analysis revealed the neural basis for reduced visual storage in adults with ADHD. As a reliable indicator of the maintained capacity (Luria et al., 2016; Vogel et al., 2005; Vogel and Machizawa, 2004), the CDA amplitude in adults with ADHD decreased significantly compared with normal controls, suggesting insufficient short-term working resources were allocated to the remembered targets in ADHD subjects. The reduction in CDA amplitude in ADHD patients was not only observed in the early stage, as found previously (Wiegand et al., 2016), but also throughout the maintenance period in the present study. This result may be due to the more typical visual spatial working memory impairment in ADHD patients (Alderson et al., 2013).

The intraparietal sulcus (IPS) is a potential source of CDA. The BOLD response of the IPS was found to be strongly modulated by the number of tracking items (Jovicich et al., 2001) and to be sensitive to individual differences in working memory capacity (Todd and Marois, 2005). One fMRI study also found hypo-activation in the IPS in children with ADHD when performing spatial reasoning tasks, indicating a poorer ability to process spatial information (Tamm and Juranek, 2012). However, it seems fairly unlikely that such a larger and

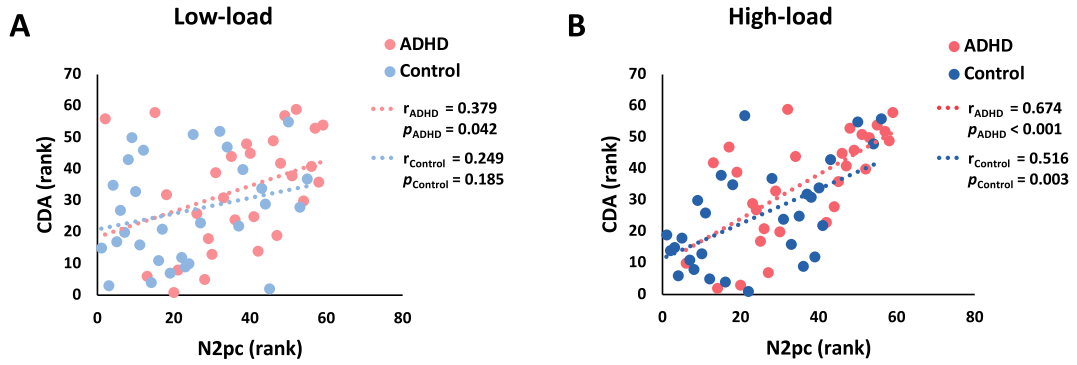

Fig. 4. CDA amplitude (working memory biomarker) as a function of N2pc amplitude (attentional selection biomarker). A. The significant correlation between N2pc and CDA in the low-load condition. B. The significant correlation between N2pc and CDA in the high-load condition.

sustained component is generated by a single cortical source. It is more likely the result of several coordinated sources among which the IPS may play a significant role (Luck and Kappenman, 2012). Thus, the decreased CDA amplitude in adult ADHD subjects may be due to the insufficient function of the IPS.

4.2. Attentional selection deficit in adults with ADHD

As expected, the lateral targets elicited a robust N2pc in both the normal and ADHD groups, and the adults with ADHD showed a much smaller N2pc amplitude in both the low- and high-load conditions. Recent studies have revealed that the N2pc component can be used to reflect defects in attentional function of ADHD patients in visual search tasks, as shown by prolonged N2pc latency in adults with ADHD (Cross-Villasana et al., 2015) or decreased N2pc amplitude in children with ADHD (Wang et al., 2016).

Although the N2pc component can be used to reflect the attentional selection process during working memory tasks (Kuo et al., 2009; Nobre et al., 2004), none of the currently published studies have examined the N2pc component in adults with ADHD during working memory tasks and its relationship with the following CDA. In light of the current findings, as a temporal precise measure of attentional capture and by removing the effect of basic activation in ERPs (Luck and Hillyard, 1994b), this lateralized component more objectively reflects the attentional characteristics of adults with ADHD during working memory: The smaller N2pc in adults with ADHD indicated deterioration of the ability to allocate attention resources to memory items, regardless of whether the memory load was low or high. The reduced N2pc amplitude in ADHD patients predicted their worse behavioral accuracy, further suggesting that attentional selection is impaired in ADHD, and this impairment may be related to poor task accuracy. In contrast, attentional selection did not seem to be the limiting factor for performance accuracy in the control group and was only involved in accelerating the behavioral response speed.

4.3. The close relationship between attentional selection deficit and working memory deficit

As described previously, the attentional selection process played a complex and important role in working memory. Clinical studies of ADHD reported that working memory impairment in ADHD patients may be mainly manifested as a deficiency of attention-related processes (Barnett et al., 2005; Chacko et al., 2013; Gibson et al., 2011; Lenartowicz et al., 2014). Inadequate attention ability may lead to abnormal working memory performance, which may be reflected in ADHD patients.

By combining the classical experimental paradigms and the fine temporal evolution of ERPs, we could effectively distinguish between the attentional selection process and the memory maintenance process during visual working memory. The novel and most critical point of our study was that the reduced CDA was predicted by the earlier and reduced N2pc in the ADHD group, indicating that abnormal working memory performance in ADHD patients may be closely associated with attention deficit. Therefore, it was reasonable to further find that when the number of memory items increased, the increment of attentional selection recourses (the rise in N2pc) also highly predicted increases in the working memory biomarker (the rise in CDA). We hypothesized that during visual working memory tasks, early ineffective top-down attentional selection to memory goals leads to reduced processing information at the maintenance stage and eventually to working memory deficits in adults with ADHD. From a clinical perspective, the findings of the present study indicated that attention training would be of great significance for improving working memory and the overall ability of patients with ADHD.

Several previous studies have found that for ADHD children and adolescents, only the performance of simple memory tasks improved after working memory training, while the performance of complex memory tasks and other cognitive tasks as well as ADHD symptoms did not change significantly after working memory training (Chacko et al., 2013; Gibson et al., 2011; Roberts et al., 2016). These results suggest that the core processes in working memory are impaired in ADHD and cannot be improved by training. Unfortunately, our study did not involve attentional training or working memory training. Therefore, it currently remains unknown whether training of our task could improve the core processes of working memory. On the other hand, attentional control is an important part of the central executive system, which might be involved in the top-down control process of the working memory system, including the formation, retrieval and processing of working memory (Gazzaley and Nobre, 2012; Knudsen, 2007). For example, Gaspar et al. (2016) demonstrated that high working memory-capacity individuals could actively suppress salient distractors (as revealed by the larger distractor-elicited P_D component), whereas low working memory-capacity individuals were unable to suppress salient distractors in time to prevent those items from capturing attention (as revealed by the smaller distractor-elicited P_D component), indicating that individual differences in visual working memory capacity are associated with the timing of specific attentional control operations. Further research is critical to investigate whether intervention and attentional control training could improve executive processing in working memory.

ADHD is a highly heterogeneous disease with three subtypes: ADHD-inattention type, ADHD-impulsive/hyperactive type and ADHD-combined type. To reduce the influence of different subtypes, only subjects with the ADHD-inattention type, the dominant of the three types, were included in this study. The present conclusions may not be directly applicable to other subtypes of adults with ADHD, and the higher IQ levels of ADHD patients included in this study may also limit the broad applicability of the findings.

N2pc appears to be a robust yet relatively unexplored putative biomarker of attentional impairment in ADHD that might subsequently impact performance on working memory and other executive function tasks. Moreover, the effects of prestimulus N2pc on group differences have not been systematically compared with the effects of the target-evoked N2pc on group differences. Further research is critical to ascertain whether attentional control deficit is indeed predictive of the clinical features typically associated with working memory deficits, especially the core executive processing deficits in working memory.

5. Conclusion

Combining the classical experimental paradigm with the fine temporal evolution of ERPs, we measured attention processes and working memory processes under different load conditions. Our study provides novel neurophysiologic evidence that working memory deficits in ADHD patients are partly influenced by their insufficient attentional selection ability, which provides a neurophysiological basis for the objective reports of attention and working memory deficits in adults with ADHD and highlights the importance of spatial attention during working memory in humans.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2019.101728.

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