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Attention networks in children with idiopathic generalized epilepsy

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ABSTRACT

Attention deficit is one of the most frequent symptoms in children with idiopathic generalized epilepsy (IGE). However, it is unknown whether this is a global attention deficit or a deficit in a specific attention network. We used the attention network test (ANT) in children with IGE, who were not being treated with antiepileptic drugs (AEDs), to determine the efficiencies of three independent attention networks (alerting, orienting, and executive control). Children with IGE showed a significant deficit in their executive control network and in overall reaction time. However, they did not show any deficit in their alerting or orienting networks. These results suggest that IGE specifically affects the executive control network.

1. Introduction

Epilepsy is one of the most common chronic neurological disorders [1]. It is associated with a wide range of cognitive impairments, such as attention deficit, memory impairment, and language problems, that have negative effects on social life, work, or school [2]. These cognitive impairments have a multifactorial etiology that includes biological factors, such as types of seizures, neuropathology, and age at onset, as well as psychosocial problems, particularly those resulting from therapeutic interventions with adverse effects [3]. As a result, patients with different types of epilepsy have different kinds of cognitive impairments. In symptomatic epilepsy, cognitive impairments usually occur in the affected lobe. For example, temporal lobe epilepsy is associated with language difficulties and memory problems [4–7], whereas frontal lobe epilepsy results in executive dysfunction [8]. However, because idiopathic epilepsy does not have any apparent cause or detectable brain lesions, the neurological basis for its associated cognitive impairments remains unknown. Previous studies have shown that patients with idiopathic generalized epilepsy (IGE) have normal intelligence, but they also show learning disabilities, memory impairment, and reduced psychomotor speed [9–11].

Based on numerous neuroanatomical and cognition studies, Posner and Petersen divided the human attention system into three independent networks, namely, alerting, orienting, and executive control (conflict resolution) [12]. Each network performs a distinct function in the attention process [12,13]. First, the alerting network, which is localized to the frontal and parietal areas of the right hemisphere, activates and maintains a vigilant state [14]. Second, the orienting network, which is localized to the subcortical areas of the parietal lobe, such as the pulvinar and reticular nuclei of the thalamus, selects focal information from numerous stimuli [15]. Third, the executive control network, which is localized to the midline frontal areas, such as the anterior cingulate cortex (ACC) and prefrontal cortex, monitors and resolves conflicts between competing information [13,16].

Attention deficit is one of the most frequent symptoms of children with epileptic syndromes [9,11]. However, it is not known whether this is a global attention deficit or a deficit in a specific attention network. To our knowledge, no studies on the attention networks of children with IGE have been published to date. The Attention Network Test (ANT) is designed to assess the efficiencies of the three attention networks in a single experiment [17]. It has been widely used to evaluate the attention of both healthy children [18,19] and those with disorders [20,21], as well as adults with borderline personality disorder [13,22–24] and schizophrenia [16].

In this study, we used the ANT to explore the attention networks of children with newly diagnosed IGE who were not yet being treated with antiepileptic drugs (AEDs).

2. Methods

2.1. Subjects

Thirty-seven children with IGE (IGE group) were selected from the First Affiliated Hospital of Anhui Medical University, Anhui Province,

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China. To be included in the study, patients had to: (a) have been diagnosed with IGE; (b) have been diagnosed with IGE with only generalized tonic–clonic seizures (GTCSs), as defined by the Commission on Classification and Terminology of the International League against Epilepsy [25]; (c) have a normal intelligence quotient (IQ>80), as determined by Raven's Standard Progressive Matrices; (d) have received no prior or current AED treatments; (e) have more than 1 year of education; (f) have normal or corrected vision; and (g) have the ability to understand the procedures of the experiment. Excluded were those with evidence of a neurological or psychiatric disorder, as determined by medical history, physical examination, or neuroimaging.

In addition, 37 age-, IQ-, and education-matched children also were tested as healthy controls (HC group). Descriptive data on the IGE and HC groups are summarized in Table 1. All parents gave written consent before their children participated in the experiment. The ethical committee of Anhui Medical University approved this study.

2.2. Collection of the pertinent demographic and clinical data

Background information on the children in the IGE group was obtained from their hospital records and interviews with their parents. This information included demographic data (e.g., age, sex, education), etiological factors, seizure activity (e.g., age at seizure onset, seizure frequency), neurological and psychiatric findings, and EEG and neuroimaging results. Raven's Standard Progressive Matrices was administered to measure the intelligence of each subject. Children with IQ <70 were excluded from further participation.

2.3. Attention network test

The ANT was programmed using E-Prime (Version 1.1, Psychology Software Tools, Pittsburgh, PA, USA). Stimuli were presented on a 17-in. color monitor controlled by a personal computer with a Pentium 4 processor. Participants viewed the stimuli on a computer screen, and responses were collected via two response buttons. Stimuli consisted of a row of five horizontal black lines, with arrowheads pointing toward either the left or the right, against a gray background. Three target conditions were presented: a leftward or rightward pointing arrowhead flanked on either side by lines without arrowheads (neutral condition) or two arrows pointing in either the same direction (congruent condition) or in opposite directions (incongruent condition). A single arrow or line subtended 0.55° of visual angle, and adjacent arrows or lines were separated by 0.06° of visual angle. The stimuli were presented in one of two locations, either 1.06° above or 1.06° below the fixation point. Target location was always uncertain except when spatial cue was presented. Participants were instructed to fixate on a central cross and to respond to stimuli as quickly and accurately as possible (Fig. 1). They were asked to identify the direction of the center arrow by either pressing one button with the index finger of the left hand to indicate the left or another button with the index finger of the right hand to indicate the right. The maximum duration for the target display was 2700 ms. A response with a reaction time (RT) <2700 ms terminated the target display; 400 ms before displaying the target, a cue consisting of an asterisk was presented for 100 ms. Four cue conditions were used: (1) no cue, in which only the central fixation cross was presented for 100 ms; (2) central cue, in which a single cue was presented at the fixation point; (3) double cue, in which two cues were presented simultaneously above and below the fixation point; and (4) spatial cue, in which a single cue predicted the location of the target (either above or below the fixation point). In the first three cue conditions, the location of the target was random.

The ANT consisted of a 24-trial practice set and three experimental sets. Each experimental set consisted of 96 trials (4 cue types × 2 target locations × 2 target directions × 3 congruencies = 48 conditions × 2 repetitions). The order of presentation of the trials was randomized (Fig. 1).

Table 1
Demographic and clinical characteristics of the children with IGE and controls.

Characteristic	Children with IGE	Healthy controls
N	37	37
Age, years	10.9 ± 3.0[a]	11.9 ± 2.8[b]
Gender (male/female)	20/17	19/18[b]
Education, years	4.3 ± 2.3	5.1 ± 2.6[b]
Full Scale IQ	102.4 ± 18.6	104.0 ± 15.1[b]
Age at onset, years	10.3 ± 2.8	
Seizure frequency, events/month	1.5 ± 1.7	
Seizure duration, min/event	3.1 ± 1.6	
AED treatment	None	

[a] Mean ± SD.
[b] No significant difference between the groups, $P>0.05$.

2.4. Calculation of attention network efficiencies

The efficiencies of the alerting, orienting, and executive control networks were calculated from differences in RTs under different testing conditions. Values for attention network efficiency were calculated from the raw RT data as described below. For each test condition (4 cue types × 3 target types = 12 conditions), the mean RT was calculated. To avoid the influence of outliers, only RTs between 100 and 2700 ms were used in the calculations. In addition, incorrect or missed responses were excluded.

Alerting efficiency was calculated by subtracting the mean RTs of the conditions with double cues from those of the conditions with no cue, as neither of these conditions provided information on the spatial location of the target. Similarly, orienting efficiency was calculated by subtracting the mean RTs of the conditions with spatial cues from those of the conditions with center cues. In both conditions, the subject was alert, but only the spatial cue provided orientation information. Likewise, executive control efficiency was calculated by subtracting the mean RTs of congruent target conditions from those of incongruent target conditions.

2.5. Data analysis

Statistical analysis was performed using SPSS Version 11.0 statistical software. The statistical significance of the differences between the IGE and HC groups was evaluated by one-way univariate analysis of variance (one-way ANOVA) and the level of significance was set at $P<0.05$.

3. Results

3.1. Demographic data

There were no significant differences between the IGE and HC groups in terms of age, gender, education, handedness, or intelligence (Table 1).

3.2. Reaction times and accuracy

The differences in RTs measured with the ANT correspond to differences in the efficiencies of the alerting, orienting, and executive control networks. During the experiment, some trial responses were incorrect or missed; these data were excluded from the calculation of mean RTs. All RT data were normally distributed. Overall mean RT and accuracy were calculated. For the whole ANT, the mean global accuracies of the IGE and HC groups were greater than 95%. There was no significant difference in global accuracy between the two

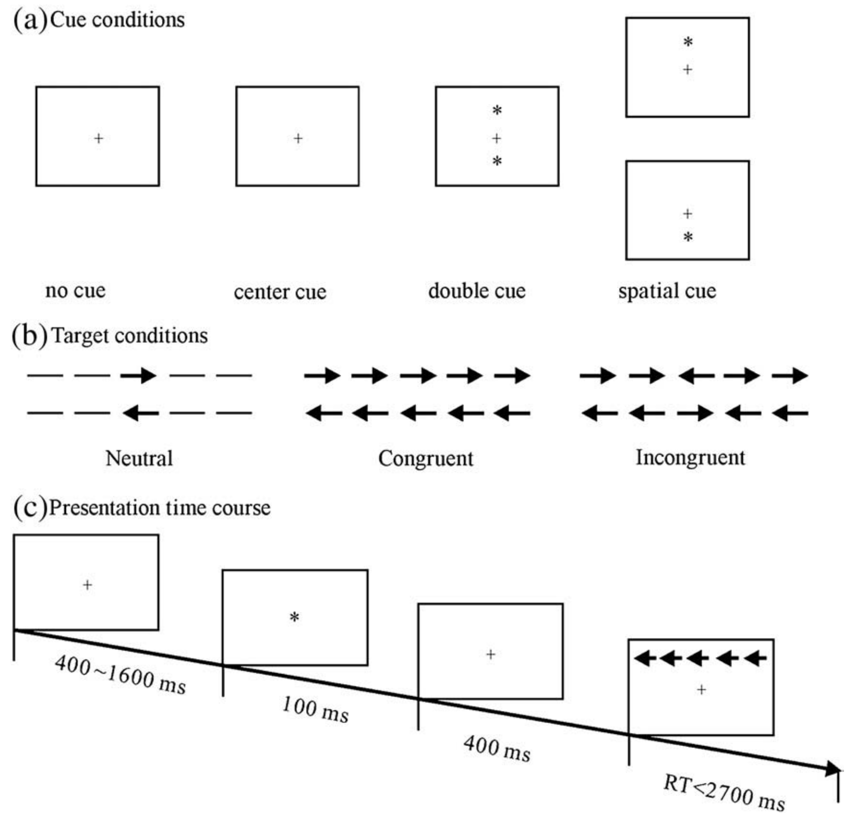

Fig. 1. Experimental paradigm of the Attention Network Test (ANT). (a) The four cue conditions. (2) The six stimuli used in the present experiment. (c) An example of the procedure.

groups ($F[1,72]=0.279$, $P=0.599$). The IGE group had a significantly longer mean RT than that for the HC group ($F[1,72]=5.729$, $P=0.019$) (Table 2).

3.3. Efficiencies of the three attention networks in children with idiopathic generalized epilepsy

The mean RT for the executive control network in the IGE group was significantly longer than that of the HC group ($F[1,72]=5.189$, $P=0.026$). This shows that subjects with IGE took longer to resolve conflicts than did HC subjects. However, there were no significant differences between the two groups in the mean RTs for the alerting or orienting networks ($F[1,72]=0.751$ and $F[1,72]=0.078$, respectively; both $P>0.05$). Thus, children with IGE exhibit specific impairment of the executive control network (Table 2).

4. Discussion

Idiopathic generalized epilepsy is associated with behavioral and cognitive impairments that manifest prior to the onset of seizures and independently of AED treatment [26]. The aim of this study was to use the ANT to investigate the effect of epilepsy on the three attention networks in children newly diagnosed with IGE who were not yet being treated with AEDs.

The results showed that the IGE group reacted more slowly than the HC group. This suggests that children with IGE have a slower cognitive processing speed, and this deficit results from epilepsy alone as none of the children were using AEDs. These conclusions are consistent with those from Berg et al. [26], who showed that IQ, word reading, and spelling scores of patients with IGE were lower than those of their healthy siblings because of slower cognitive processing speed. Their results were not affected by remission status or drug use.

Recently, PET and fMRI studies have demonstrated that reaction speed in cognitive tasks correlates with activity in the ACC [27,28]. Moreover, neuropsychology studies demonstrate that patients with focal ACC lesions have slower responses during cognitive tasks [29]. Other neuroimaging studies also reveal that the structure and function of the ACC in children with IGE are abnormal [30,31]. On the basis of these results and the findings in this study, it is possible that the longer RT in children with IGE may be due to an abnormal ACC.

The most important result of this study is that the mean RT for the executive control network in the IGE group was significantly longer than that of the HC group. This shows that children with IGE resolve conflicts more slowly than HC subjects. This conclusion is consistent with early studies that used the Stroop and Wisconsin card sorting tests to show that patients with IGE were impaired in executive control functions [1]. The executive control network is part of the executive attention network that is responsible for monitoring and resolving conflicts in the presence of competing information. Executive control activity is localized to the frontal cortex, specifically the ACC and prefrontal cortex [32,33].

Table 2
Attention network reaction time (RT) and inaccuracy (%) of patients and controls.

	Children with IGE	Healthy controls	F	P
Overall mean RT (ms)	814.7 ± 185.3[a,b]	702.8 ± 215.8	5.729	0.019
Accuracy (%)	97.2 ± 3.5	96.7 ± 3.4	0.279	0.599
Executive control RT (ms)	166.9 ± 111.1[b]	115.9 ± 79.0	5.189	0.026
Alerting RT (ms)	92.1 ± 45.3	82.2 ± 52.6	0.751	0.389
Orienting RT (ms)	66.6 ± 50.2	63.7 ± 39.1	0.078	0.781

[a] Mean ± SD.
[b] $P<0.05$.

Epileptiform activity may be a possible explanation for the lower efficiency of the executive control network in patients with IGE. The amplitude of the generalized spike waves that are characteristic of epileptiform activity is greatest in the frontal region. In addition, epileptiform discharges arising in the temporal lobe, hippocampus, or amygdala spread to the prefrontal cortex, and then cellular abnormalities emerge in the prefrontal lobe [34]. IGE also is associated with bilateral frontal lobe metabolite abnormalities [35]. The neural network changes have been identified in epilepsy [36–40], and a recent article that explored the specific sub-networks in IGE suggested that the frontal lobe, perinsular, and subcortical/thalamic areas were most often involved [37]. Consequently, a frontal lobe abnormality may disrupt executive control functions by facilitating seizure spread and activation of abnormal neural circuitry [34].

To our knowledge, this study is the first to examine the alerting and orienting attention networks in children with IGE. There were no significant differences in mean RT for these networks between the IGE and HC groups. The alerting attention network maintains the alert state needed to physically respond to a stimulus. Neuroimaging evidence reveals that the alerting attention network is localized to the frontal and parietal areas of the right hemisphere. The orienting attention network selects focal information from numerous stimuli. It is localized to the superior and inferior parietal lobe and subcortical areas such as the superior colliculus of the midbrain and the pulvinar and reticular nuclei of the thalamus [41]. In animal models of IGE, there is evidence of structural abnormalities in the thalamus [42]; however, thalamic atrophy is not observed in patients with IGE [43]. The latter result is consistent with the absence of cognitive impairment of the orienting attention network in IGE.

Similar selective impairment of attention networks has been observed in other disorders such as schizophrenia and borderline personality disorder [16,20,22]. Several lines of evidence demonstrate that executive function is localized to the ACC and prefrontal cortex [17,44,45]. Furthermore, abnormalities in the structure and function of the ACC and prefrontal cortex are associated with IGE [30,31]. As a result, we hypothesize that the slower cognitive processing speed and selective impairment of conflict resolution in children with IGE are due to abnormalities in the ACC and prefrontal cortex.

Whether the impaired executive functions are a general feature of IGE still needs to be confirmed [1]. Childhood absence epilepsy (CAE) and juvenile myoclonic epilepsy (JME) are also common types of IGE [46]. Previous studies have shown patients with JME to be impaired in executive functions [1]. Nevertheless, few studies focus on the executive function in CAE [1,47]. Therefore, studies concerning the executive function in CAE will be more informative.

In conclusion, this study shows that selective impairment of the executive attention network slows reaction speed in children with IGE who are not under AED treatment. We propose that the neuroanatomical basis for this impairment may involve the ACC and prefrontal cortex. Further investigation of the functions of the ACC and prefrontal cortex in children with IGE using fMRI is warranted.

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