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ARTICLE

Error related negativity and multi-source interference task in children with attention deficit hyperactivity disorder-combined type

La negatividad relacionada al error en una tarea de interferencia multifuente en niños con trastorno por déficit de atención-hiperactividad tipo combinado

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ABSTRACT

Objective: To compare performance of children with attention deficit hyperactivity disorders-combined (ADHD-C) type with control children in multi-source interference task (MSIT) evaluated by means of error related negativity (ERN). **Method:** We studied 12 children with ADHD-C type with a median age of 7 years, control children were age- and gender-matched. Children performed MSIT and simultaneous recording of ERN. **Results:** We found no differences in MSIT parameters among groups. We found no differences in ERN variables between groups. We found a significant association of ERN amplitude with MSIT in children with ADHD-C type. Some correlation went in positive direction (frequency of hits and MSIT amplitude), and others in negative direction (frequency of errors and RT in MSIT). **Conclusion:** Children with ADHD-C type exhibited a significant association between ERN amplitude with MSIT. These results underline participation of a cingulo-fronto-parietal network and could help in the comprehension of pathophysiological mechanisms of ADHD.

Keywords: attention deficit hyperactivity disorder, multi-source interference task, event related potentials, error-related negativity, cingulo-fronto-parietal network.

RESUMEN

Objetivo: Comparar el rendimiento de un grupo de niños con trastorno por déficit de atención-hiperactividad de tipo combinado (TDAH-C), con niños controles, en la tarea de interferencia multi-fuente (TIMF), evaluado por la negatividad relacionada al error (NRE). **Método:** Estudiamos 12 niños con TDAH-C con una mediana de 7 años, los controles estuvieron pareados por edad y género. Los niños realizaron la TIMF con registros simultáneos de NRE. **Resultados:** No encontramos diferencias en los parámetros de la TIMF entre grupos. No encontramos diferencias en las variables de la NRE entre grupos. Encontramos asociaciones significativas entre la amplitud de la NRE en niños con TDAH-C. Una correlación fue en dirección positiva: (frecuencia de aciertos y amplitud de TIMF), y otras fueron en dirección negativa (frecuencia de errores y el tiempo de respuesta en la TIMF). **Conclusión:** Los niños con TDAH-C presentan una asociación significativa entre la amplitud de la NRE con la TIMF. Los resultados sugieren la participación de la red cíngulo-fronto-parietal y pueden ayudar en la comprensión de los mecanismos fisiopatológicos del TDAH-C.

Palabras clave: trastorno por déficit de atención-hiperactividad, tarea de interferencia multi-fuente, potenciales relacionados a eventos cognoscitivos, negatividad relacionada al error, red cíngulo-fronto-parietal.

Attention deficit-hyperactivity disorder (ADHD) is an alteration whose main symptoms are inattention, hyperactivity, and impulsivity[1]. Children with ADHD present difficulties in several areas, such as those related to school, home or different social environments that affect their Quality of Life (QoL)[2]. Children with ADHD present alterations in other domains, such as executive functions (EF)[3]. Children with ADHD can be classified in three groups as follows: predominantly

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hyperactive (ADHD-H), inattentive (ADHD-I), and combined type (ADHD-C). The more frequent is ADHD-C type[2,3].

Higher cerebral functions alteration research in children with ADHD is poor. Event-related potentials (ERP) become a valuable tool in cognitive neurosciences[4]. The discover of Falkenstein et al. of ERP whose amplitude is different depending on a failure of action was a landmark, it was later called error-related negativity (ERN)[5]. ERN is characterized by a prominent voltage negative wave distributed fronto-centrally in scalp. Its neuronal generator was proposed to be located in medial frontal cortex[6].

ERP has been studied in children with ADHD, but the ERN with multi-source interference task (MSIT) in children with ADHD-M to test the cingulo-fronto-parietal cognitive/attention network (CFPCAN) has not been studied previously. Our objective was to compare the performance of group of children with ADHD-C type with healthy control age- and gender-matched children in MSIT evaluated by means of ERN.

METHOD

Subjects

We evaluated children from 7-12 years of age from elementary schools referred for ADHD. Children were examined by means of neurological, psychiatric, and electrophysiological tests. ADHD diagnosis was carried-out in agreement with recommendations of the American Psychiatry Society guidelines[1], in a three-step level as follows[2,3]. The first, was the at-school screening; the second, was conducted by means of DSM-IV-R questionnaire, and the third, comprised a semi-structured interview, taking into account the persistence of the disorder for a period > 6 months in at least two environments, such as school and home. Children with ADHD were classified into three sub-types as follows: mainly with inattention symptoms (ADHD-I), with hyperactivity-impulsivity (ADHD-H), and combined type (ADHD-C). In this research we studied only children who have ADHD-C type because they are the more frequent disorder type. All patients were medication-free. Exclusion criteria were the following: mental retardation, epilepsy, cerebral, palsy, autism, blindness, deafness, or other pediatric neurological-psychiatric alteration. We constructed a control group of healthy children age- and gender-matched. This investigation was approved by the Research and Ethics Committee of the hospital. Parents and children of both groups were widely informed about the study and the importance of their participation. Informed consent was signed by the parents of children according to Declaration of Helsinki.

Multi-source interference task (MSIT)

Children were given a keyboard and instructed that the keypad buttons represented one, two, and three from left to right. They were told to use the index, middle and ring fingers of the right hand to respond. They were instructed that sets of three numbers (1, 2 or 3) would appear in the center of a screen every second, and that one number would always be different from the other two (matching distractor). Subjects were asked to press button of the number that was different from the other two.

Children were informed that test could begin and end with fixation of a white dot. In control trials, the target number would always match its position on the button-press (i.e. the number '1' would appear in the left position). In contrast, during the interference trials, the target could never match its position. Children were instructed to answer as quickly as possible but to make sure that they gave the right answer.

Prior to recording, children completed a 5 minutes practice of the task. Reaction time (RT) was measured. Wrong answers were discarded. Children completed 192 trials, 96 trials for control condition, 96 interference trials. The order of presentation, was randomized, in a Mind-Tracer software (Neuronics, La Habana, Cuba) to obtain RT in milliseconds (ms), and frequency of wrong answers, and hits[7].

Error-related negativity (ERN)

We performed ERN recordings simultaneously. A cap with electrodes were set in the scalp according to 10-20 electrode system and referenced to linked earlobes. Impedance was always < 3 Kilo-Ohms in all sites. Electroencephalogram (EEG) and electro-oculogram were recorded by means of a Neuronics ERP device (La Habana, Cuba). Band-pass was set among 0.01-100 Hertz (HZ). Sampling frequency was 256 Hz. EEG signals containing muscular, respiratory, electrocardiographic artifacts were rejected from analysis. ERN was defined as the lower negative response between 50-300 milliseconds (ms) after stimuli in Fz location EEG band-pass filtering was performed between 0.5-30 Hz. Information from each stimuli was obtained 400 ms before and 500 ms after[8]. Wrong responses were separated from hits and were separately analyzed.

Statistical analysis

We compared average differences between groups by means of the Student's t-test. We measured association among variables by means of the Pearson's correlation coefficient in children with ADHD-C type. We chose an *alpha* value ≤ 0.05 to accept differences and correlations as significant.

RESULTS

We studied 12 children with ADHD-C type with a median age of 7 years (range 7-12 years of age), a median total intelligence quotient of 88 (range 80-102), 83% were male, all patients were right-handed. Frequency of hits in children with ADHD-C was 67.73 ± 16.83, while in control children was 71.24 ± 17.39.

We observed a RT mean in control trials, in children with ADHD-C type of 623.42 ± 100.27 ms, while in control children was 661.19 ± 154.16 ms. No significant differences among groups was observed ($p = 0.48$). We obtained a RT mean in interference trials in children with ADHD-C type of 668.52 ± 140.62 ms, while in control children was 664.14 ± 188.25 ms. No significant differences among groups was disclosed ($p = 0.94$).

We obtained a NRE latency in children with ADHD-C type of 131.67 ± 7.79 ms, while in control children was 126.52 ± 16.50 ms. No significant differences was observed ($p = 0.36$). We observed a NRE amplitude mean in children with ADHD-C type of 10.79 ± 5.12 microvolts (μV), while in control children amplitude was 11.64 ± 5.59 μV. No significant differences was observed ($p = 0.70$) (Figure).

We found a significant correlation with positive direction among ERN amplitude with frequency of hits in MSIT ($r = 0.542$, $p = 0.008$) in children with ADHD-C type, while we found significant correlations with negative direction between: frequency of errors in MSIT ($r = -0.48$, $p = 0.01$), and RT in MSIT ($r = -0.44$, $p = 0.03$).

DISCUSSION

Main findings

We found that children with ADHD-C presented significant association of ERN amplitude with MSIT. Some correlation went in positive direction (frequency of hits), and others in negative direction (frequency of errors and RT). Our data support the evidence that CFPCAN engagement alteration in children with ADHD-C type. To our knowledge this is the first study in report correlation among NRE and MSIT in children with ADHD-C type.

ERN usefulness

ERN has been used to study several alterations. For example, ERN was elicited by a Go/no-Go task in children with anxiety disorder and controls. ERN in children with anxiety disorder was characterized by more negative wave, evident by the age of 6, independently of influence of maternal anxiety[9].

In other study, youths with major depression were compared with healthy controls by means of ERN. Youths with depression has significant smaller amplitudes than controls, and did not exhibit the normative increases of ERN amplitudes in function of age[10].

On the other hand, ERN responses in a group of youths with obsessive-compulsive disorder (OCD) and controls were compared. Youths with OCD showed an increase in ERN amplitudes when compared with controls, treatment with serotonergic antidepressant or cognitive-behavioral therapy had no effects in ERN[11].

A group of heavy regular drinkers female young adults were studied by ERP, and ERN. Patients presented longer RT, and retard in P3 latency; they also presented a smaller ERN amplitude suggesting a deficit in performance monitoring[12].

Learning from errors is important for adaptive behavior, it requires detect errors, and adjusting an adequate conduct. In the future, studied with ERN has been suggested as an endophenotype in several neuropsychiatric disorders[13,14].

Comparison with other studies

ERP parameters included wave latency and amplitude measurements[15]. Latency is the time from stimuli onset to the peak of a wave. NRE latency was retarded in children with ADHD-C type, although it was not statistically significant. More research, with a large number of patients, is mandatory to verify this tendency. Wave amplitude depends on the synchronization of neuron populations engaged in some task. Differences among groups were no significant, but a tendency in children with ADHD-C to had lower amplitudes than control children, was observed. Our results are in partial agreement with data observed from a research performed with MSIT evaluated by means with functional magnetic resonance imaging. Children with ADHD, showed lower CFPCAN activation than controls[16]. Comparison must be made with careful, because technique differences between studies.

Engagement of dorso-medial cingular cortex (DMCC) in pathophysiological mechanisms of ADHD has been suggested, because it plays central role in cognitive processes[17]. If DMCC is disrupted, dysfunction could produce signs of ADHD: inattention, impulsivity, and hyperactivity. Some intracranial recording studies in humans suggested that DMCC operates in a feedback mediated decision-making framework, integrating

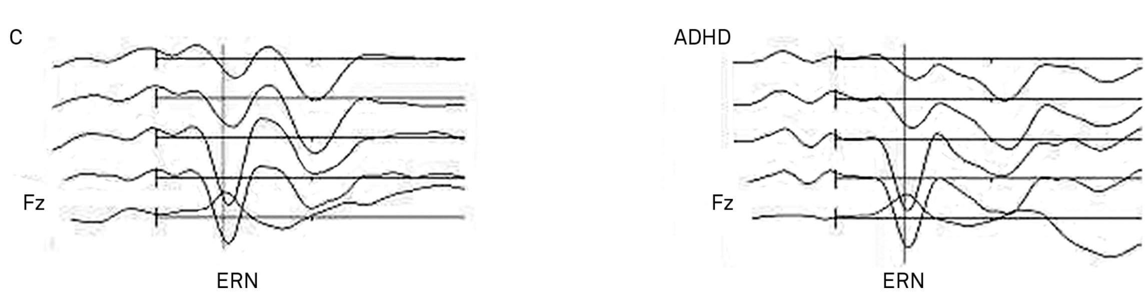

Figure. Grand-averages of error related negativity (ERN) recorded at midline and Fz site of the International 10-20 electrode system. Left panel, controls (C), and right panel children with attention deficit hyperactivity disorder (ADHD) combined type. No differences in latency and amplitude of the wave are evident.

information about planned operations and expectations with rewards and negative outcomes, shaping decisions, and modulating motor output[18]. Animal studies further suggest that dopamine modulates the decision-making functions in DMCC[19]. Dysfunction of the DMCC could also explain why patients with ADHD performing normally on motivated tasks but showing deficient performance when the task is not deemed motivating. Exact roles that the DMCC plays in distributed cognitive/attention networks remain to be established to improving our understanding of the pathophysiological mechanisms of ADHD that have been implicated in attention, and motor control: including the dorso-lateral prefrontal cortex (DLPFC), parietal cortex, caudate nuclei, premotor cortex, thalamus, and cerebellum. This was expected because these structures subserve cognitive processing in a parallel-distributed manner[20]. The DLPFC is activated with DMCC during cognitive tasks; the premotor cortex is responsible for planning and execution of non-automatic tasks; the parietal cortex has been activated during target detection, and the striatum has been implicated in ADHD pathophysiology. Although the roles that these structures play in ADHD remain to be determined, the data argue that they interact as a distributed network.

Limitations of the study

It necessary to study larger population of children with ADHD with ERN technique with MSIT paradigm of the three recognized types, in order to obtain stronger conclusions. Power of observations will be more with a prospective follow-up instead a cross-sectional design. Thus additional research is required to reinforce our results.

In conclusion we found a significant association of ERN amplitude with MSIT in children with ADHD-C type. Some correlation went in positive direction (frequency of hits), and others in negative direction (frequency of errors and RT). These results underline participation of a CFPCAN and could help in the comprehension of pathophysiology of ADHD.

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