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Effect of the HERVAT neuroeducational program on evoked potential P300 in children with attention deficit disorder

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Introduction. Attention deficit disorder (ADD) has been investigated from various perspectives. However, the neurobiological mechanisms underlying this condition remain unknown. Evoked potentials, including P300, can be used to investigate the processes underlying deficient attentional and cognitive functions in children with ADD.

Methods. In this study, we analyze the effect of a neuroeducational program, HERVAT (Hidratación [hydration], Equilibrio [balance], Respiración [breathing], Visión [vision], Audición [hearing], Tacto [touch]), on evoked potential P300 in a group of children aged 7-11 years with ADD.

Results. At the end of the study, the latency of P300 improved and brain activity was reorganized toward frontal areas in children with ADD who undertook the HERVAT program. In the control group, on the other hand, the latency of P300 and the posterior cortical areas remained unchanged during tests to discriminate between multisensory stimuli.

Conclusions. In conclusion, the neuroeducational program HERVAT effectively shortened the latency of evoked potential P300, which is responsible for information processing in the brain, and reorganized brain activity from posterior areas toward frontal cortical areas, which are responsible for the attentional processes involved in executive function.

Keywords: HERVAT, P300, ADD, Parietal area, Frontal area

Actas Esp Psiquiatr 2019;47(2):54-61

Efecto del programa neuroeducativo HERVAT en el potencial evocado P300 en niños con trastorno por déficit de atención

Introducción. El trastorno por déficit de atención (TDA) ha sido estudiado desde muchos puntos de vista, sin embargo todavía se desconocen los mecanismos neurobiológicos subyacentes al mismo. Los potenciales evocados y entre ellos el componente P300 pueden servir para investigar los procesos de las funciones cognitivas y atencionales deficitarios en los niños con TDA.

Metodología. En este estudio analizamos la eficacia del programa del neuroeducativo HERVAT (acrónimo de Hidratación, Equilibrio, Respiración. Visión, Audición, Tacto) en el potencial evocado P300 en un grupo de niños, entre 7 y 11 años con TDA.

Resultados. Los resultados indican que al final del estudio los niños con TDA que han hecho el programa HERVAT han mejorado la latencia del P300 y han reorganizado la actividad cerebral hacia áreas frontales mientras que el grupo control mantiene la misma latencia del P300 y las mismas áreas corticales posteriores durante la tarea de discriminación de estímulos multisensoriales.

Conclusiones. Como conclusión podríamos decir que el programa neuroeducativo HERVAT manifiesta su eficacia en el acortamiento de la latencia del potencial evocado P300, responsable del procesamiento cerebral de la información así como en la reorganización de la actividad cerebral desde áreas posteriores cerebrales hacia áreas corticales frontales, responsables de los procesos atencionales de las funciones ejecutivas.

Palabras clave: HERVAT, P300, TDA, Area parietal, Area frontal

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INTRODUCTION

Attention deficit disorder (ADD) results from abnormalities of executive function, mainly attention, working memory, cognitive flexibility, and inhibitory control[1-3]. This neuroeducational disorder has been studied from several viewpoints, although our knowledge of the underlying neurobiological mechanisms remains insufficient. Evoked potential–based assessment has revealed specific abnormalities of information processing in the brain of children with ADD. The most widely used long-latency component to date for the study of this disorder is evoked potential P300.

P300 is a type of positive wave that occurs approximately 300 ms after initiation of the stimulus and is associated with working memory and attention[4-7]. It is generated within the limits of various structures, including the parietal and temporal lobes and frontal cortices[8,9]. P300 can be used to investigate the processes underlying cognitive and attentional functions, as well as for the analysis, discrimination, and evaluation of a stimulus[10]. Therefore, several studies in children with ADD have found P300 to be associated with various neurophysiological variables, such as decreased amplitude and increased latency of P300[11-14].

Localization of sources with multichannel EEG systems has made it possible to demonstrate the efficacy of this method of information processingin children with ADD. The results seem to show increased brain activity in the frontal areas (which are responsible for attention processes) during the performance of simple multisensory perception tests in children with ADD compared with a control group[15,16]. Other studies have used structural neuroimaging to confirm gray matter deficits in the frontal lobes[17,18]. If we assume that cerebral neuroplasticity results from environmental stimuli and that the absence of stimuli is therefore associated with a deficit resulting from cerebral hypofunction, then P300 is a good marker for evaluating the efficacy of neuronal plasticity processes associated with neuroeducational interventions in children with ADD: one of the main deficits in these children is in environmental and perceptual attentional function associated with areas of the posterior parietal cortex. These include voluntary, supervisory, and action-regulating functions associated with the anterior cingulate and extensive frontal areas.

In this sense, and even though our knowledge of the neurobiological substrate of ADD is incomplete, the 2 main hypotheses are as follows: first, the fronto-striatal hypothesis, which postulates the existence of fronto-striatal circuit dysfunction based on a series of anatomical and functional findings from neuroimaging studies; second, the cortical-posterior hypothesis, which postulates the presence of abnormalities in other posterior cortical regions that have been verified using recent neuroimaging studies[19,20]. A study based on this neuroeducational method[21] revealed improved brain activity with shorter latency periods of the evoked potentials N200 and P300 and increased parietal activity, that is, in the area of the brain associated with basic processes of attention, analysis, and sensory recognition, as well as increased frontal activity, that is, in the area associated with progression of attentional processes and cognitive control in decision making.

The objective of the present study was to evaluate the behavior of P300 as a neurobiological marker in a group of children with ADD who have been participating in the neuroeducational program HERVAT (acronym of Hidratación [hydration], Equilibrio [balance], Respiración [breathing], Visión [vision], Audición [hearing], Tacto [touch]).

METHODS

Sample

The study sample included 24 children with ADD, of whom 12 made up the HERVAT group (9 children of both sexes aged 7-11 years, and 3 children with attention deficit hyperactivity disorder). The children were from schools in the Autonomous Community of Madrid, Spain and were attending school. No children had neuropediatric or neuropsychiatric disorders, and all had normal intelligence quotients (100-115). The children had undertaken the HERVAT neuroeducational program for 30 minutes during their school timetable. A second group of 12 children comprised the control group (9 with ADD and 3 with attention deficit hyperactivity disorder), whose characteristics were similar to those of the experimental group with respect to age, sex, and academic level. All of the parents signed the informed consent, and the study was approved by the Ethics Committee of Hospital Clínico San Carlos, Madrid, Spain on 18/12/2013. The inclusion criteria were as follows: clinical diagnosis fulfilling the criteria for ADD (DSM-V), signature of the informed consent for the EEG by the father/mother/guardian, and age 7-11 years. The exclusion criteria were low birth weight (<2500 g), preterm birth (requiring care in an incubator), fetal distress or Apgar score lower than 9, pervasive developmental disorder or any other type of brain damage or mental retardation, abnormal EEG findings and/or epilepsy (including febrile seizures in infancy), and learning difficulties. Both groups were similar in age, sex, educational level, and sociocultural level. In order to ensure that medication did not confound the results, we only included nonmedicated children.

Procedure

The diagnosis was made based on the DSM-5 interview (American Psychiatric Association) for the diagnosis of ADD, the diagnostic interview of the Kiddie-Schedule for Affective Disorders and Schizophrenia, Present and Lifetime in its Spanish version (translated, adapted, and validated), and the ADHD Rating Scale-IV .

Once the sample was selected, an evoked potentials study was performed using EEG during the auditory, visual, and tactile recognition tests at the beginning and end of HERVAT. The auditory test involved auditory tone stimulation based on the oddball paradigm. The test consisted of 2 tonal stimuli at 2 different frequencies: 2000 Hz, which is considered the target stimulus and accounted for 20% of the stimuli applied and was randomly distributed throughout the test; and 1000 Hz, which is considered the standard stimulus, accounting for 80% of the stimuli applied. The tones were binaural, with an intensity of 60 dB and an up/down duration of 10 ms and a plateau of 50 ms. The time between stimuli was 1 second. The child had to respond by pressing the space bar every time the 2000-Hz tone appeared (target stimulus). The visual test consisted of 2 visual stimuli that took the form of vertical and horizontal lines: the horizontal line, which was considered the target stimulus, appeared in 20% of the stimuli, which were randomly distributed throughout the test; and a horizontal line, which was considered the standard stimulus and had a frequency of 80%. The lines were 0.5 cm wide and 5 cm long, with a duration of 300 ms and a response time of 700 ms. The child had to respond by pressing the space bar every time the horizontal line appeared on the screen (target stimulus). Lastly, the tactile stimulus test involved 2 tactile stimuli that took the form of vertical and horizontal lines. The horizontal line was considered the target stimulus and appeared in 20% of cases and a vertical line, which was considered the standard stimulus and appeared in 80% of cases. The lines were 0.5 cm wide and 5 cm long and were applied to the palm of the hand using a tactile stimulator. The presentation time was 300 ms and the response time 700 ms. The child had to respond by pressing the space bar every time the horizontal line was felt on the palm of the hand (target stimulus).

HERVAT neuroeducational program

The program was held in several schools in the Autonomous Community of Madrid. We applied 5 types of test: hydration, balance, breathing, auditory discrimination, visual discrimination, and tactile discrimination. The tests lasted 5-8 minutes. They were performed 3 times during the school year from Monday to Friday between October and May. The children received around 450 sessions during the school year (see HERVAT neurodegenerative program[22]).

Analysis of EEG data

Evoked potentials were recorded using the 128-channel EEG system ATI-Pentatek®. Data were processed based on a reference mean after acquisition with a band pass filter of 0.05 to 30 Hz and a sampling speed of 512 Hz. Impedance was maintained below 5 kΩ. We applied electrodes to both mastoid areas as on-line references. We used 100-mV "noises" or "artefacts" as exclusion criteria to rule out blinking movements. We visually assessed the tests of each child to ensure that the recordings were clean. The "noise" created by eye and muscle movements was identified visually off-line and eliminated before calculating the data average and analyzing P300. Noisy channels were replaced by moderate linear interpolations of clean channels. Once this process was complete, we calculated the averages for each participant and condition using the previous negative wave that was closest to the motor response, ie, approximately 300 ms before the motor response. Latency values were obtained separately for each condition and participant by analyzing 40 ms, ie, 20 before and 20 after the peak with the greatest amplitude for the Pz electrode, within the time interval 250-350 ms for P300.

The sources of evoked potential P300 were estimated based on 123 electrode recordings for all the participants and localized in the brain based on the solution to the EEG inverse problem using the Bayesian model averaging[23,24]. Individual models were obtained using low-resolution electromagnetic tomography (LORETA, software Neuronic®[25]) for the calculation of electrical tomography of the brain. Each model was defined by restricting the solution to a specific anatomical structure or to a combination of structures using the software package Statistical Parametric Mapping (SPM, MathWorks, Natick, United States). The sources calculated in the evoked potential were used to apply SPM to establish the maps based on a voxelwise Hotelling T2 distribution vs zero[26] with the aim of estimating statistically significant sources for P300. The resulting probability maps from the threshold for the expected proportion of false positives between the tests that were significant were limited to a false discovery rate of q=0.05[27] and were represented as 3D activation images superimposed on the average brain in accordance with the MNI coordinate system[29] and according to the average atlas of the Anatomical Institute of Montreal[29].

RESULTS

Latency of evoked potential P300

The latency of evoked potentials is associated with the ability of the brain to process sensory information. The la-

Table 1 **Latencies of evoked potential P300 during auditory, visual, and tactile stimulation**

Test	HERVAT GROUP START	HERVAT GROUP END	Statistical significance	CONTROL GROUP START	CONTROL GROUP END	Statistical significance
Auditory	328±8	300±6	p 0.01	322±25	319±17	NS
Visual	310±12	289±3	p 0.01	330±28	331±26	NS
Tactile	328±22	319±12	p 0.05	320±22	321±17	NS

NS: nonsignificant

tency of P300 has been associated with the speed of information processing and stimulus classification, and its prolongation is considered a marker of slower information processing. Our results revealed a similar latency profile for P300, with no significant differences in the auditory, visual, and tactile tests between the groups at the beginning of the study. However, at the end of the study, the group that most benefited, with statistically significant differences between the beginning and the end, was the HERVAT group, thus indicating a positive effect of stimulation throughout the school year on the attentional processes associated with information processing and stimulus classification underlying P300 (Table 1).

Localization of sources of evoked potential P300 at the beginning and end of the study

The main significant differences between the beginning and the end of the study in the HERVAT group were found at the beginning of the study during auditory tone recognition in the right superior temporal areas (MNI coordinates: X 62, Y –35, and Z 8), whereas at the end of the study, the significantly most active areas were the right medial frontal area (MNI coordinates: X 10, Y 66, and Z 8) and the right superior parietal area (MNI coordinates: X 22, Y –61, and Z 66). During the visual line recognition test at the beginning of the study, the main differences were found in the right medial occipital areas (MNI coordinates: X 34, Y –95, and Z 2); at the end of the study, the main differences were found in the left inferior frontal areas (MNI coordinates: X –50, Y 40, and Z 6) and right precentral areas (MNI coordinates: X 42, Y –11, and Z 61). Lastly, during the tactile line recognition tests (palm of the hand), the main differences were found in the right supramarginal parietal areas (MNI coordinate: X 66, Y –31, and Z 35), whereas at the end of the study, the main differences were in the left lower frontal areas (MNI coordinates: X –50, Y 40, and Z 7).

The results for the control group indicate that during the auditory tone recognition study, the main differences at the beginning of the study were found in the left medial temporal areas (MNI coordinates: X –54, Y –2, and Z –29), whereas at the end, the significantly most active areas were the right medial temporal areas (MNI coordinates: X 58, Y –55, and Z 21). During visual line recognition, the main differences at the beginning of the study were in the area of the right calcarine sulcus (MNI coordinates: X 10, Y –77, and Z 2), in the area of the right angular gyrus (MNI coordinates: X 46, Y –64, and Z 37), and in the left cuneus (MNI coordinates: X –6, Y –82, and Z 24); at the end of the study, the main differences were in the right medial temporal area (MNI coordinates: X 58, Y –52, and Z –2). Lastly, during the tactile line recognition study (palm of the hand), the main differences at the beginning of the study were found in the left medial temporal area (MNI coordinates: X –70, Y –35, and Z -10), whereas at the end of the study, they were found in the right superior temporal area (MNI coordinates: X 66, Y –34, and Z 11) and right medial temporal area (MNI coordinates: X 66, Y –43, and Z –3) (Figure 1).

DISCUSSION

Our results indicate that if we carry out a daily systematic activity based on simple tests can improve internal biological status and sensory perception defined in terms of frequency, intensity, systematization, and daily repetition, we can create the necessary, temporally synchronized minimum automatisms to generate new connections between

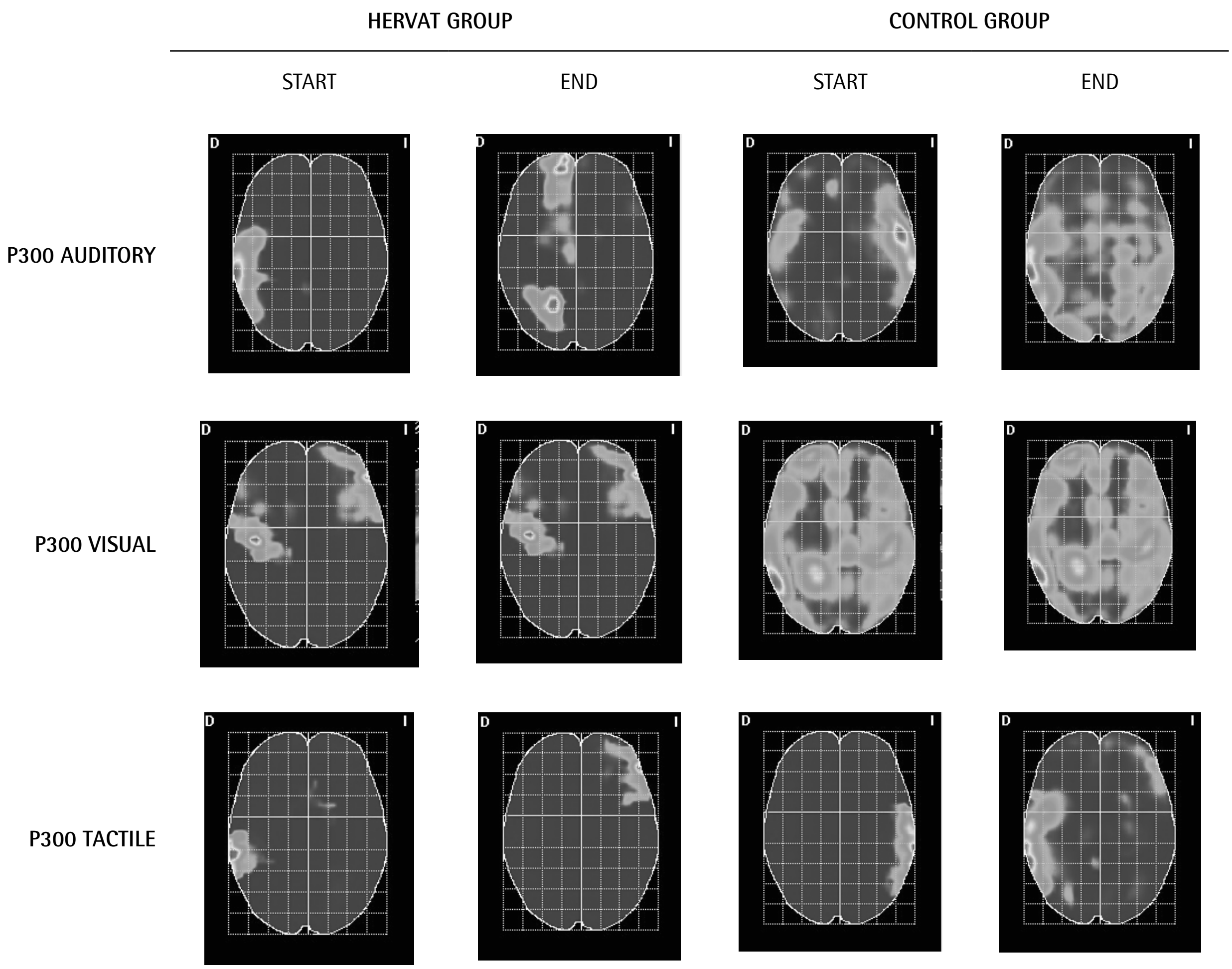

Figure 1 *Differences in localization of sources using Bayesian model averaging of evoked potential P300 at the beginning and end of the study. White indicates the highest activity (statistically significant) in this area of the brain*

cortical areas and thus enhance the latency of evoked potentials, which are essential for robust academic learning and brain maturation.

At the end of the study, we found reduced latency for evoked potential P300 in the group that had undertaken the HERVAT program. Therefore, we understand that there is a considerable improvement in information processing, given that latency was associated with the time for a subject's brain to process information from the external environment[30]. Consistent with these results, various studies have reported a significant increase in the latency of evoked potential P300 in children with ADD compared with controls[11-13,31]. These data seem to indicate a major improvement in the attentional capacity of children with ADD as a result of their participation in the HERVAT neuroeducational program. If we assume that neuronal plasticity is a process by which connections between neurones increase, thus making them more stable as a consequence of experience, learning, and cognitive and sensory stimulus[32], and that evoked potential P300 is a reliable means of measuring neurofunctional processing associated with the attentional processes necessary for working memory to access superior cognitive processing[33,34], then the results we obtained for evoked potential latency indicate a major improvement in multisensory attentional processes. Consistent with our findings, other authors reported that the latency of P300 was shortened at the end of a 2-month study after treatment with methylphenidate in a group of adolescents with ADD[35]. Lastly, a study based on physical exercises in children with ADD showed that the exercises were effective for shortening reaction time and increasing P300 activity; this could be associated with increased capacity for inhibitory control, which is usually impaired in these children[36].

The results for source localization point to greater participation of anterior areas at the end of the study in the HERVAT group than in the control group, in which activity in posterior areas at the end of the study remained unchanged. These results indicate that the HERVAT program led to a marked improvement in cerebral structures associated with voluntary attentional processes, whereas the control group maintained activity in the posterior structures responsible for involuntary environmental attention. Other studies have also shown increased brain activity in the frontal areas, which are responsible for attentional processes during the performance of simple multisensory perception tests in children with ADD compared with the control group[15,16], thus indicating an increase in brain resources in these children when faced with recognition of very simple stimuli.

Our results showed a reorganization of brain activity at the end of the study that was very similar in the auditory, visual, and tactile recordings: the left frontal areas were activated in the visual and tactile recordings, as were the right frontal areas in the auditory recording. This finding has enormous neurofunctional relevance, since frontal lobe hypofunction has been reported in children with ADD, and some studies have even demonstrated significant gray matter deficiency in this area[17,18].

Our results confirm cerebral neuroplasticity associated with greater participation of the frontal areas. This in turn points to the presence of fronto-parietal circuit dysfunction in children with ADD[19,20,37] that could point to major biological markers in the attentional processes of these children. Thus, Merzernich and Syka[38] showed that attention is essential for the creation of new neuronal connections and for the formation of stable brain circuits: stable and long-lasting neuronal connections and circuits can only be established when a person pays attention. The improvement in attentional processes and the latency of evoked potential P300 in the HERVAT group is consistent with results from other studies that report considerable neurophysiological improvement in sensory and cognitive training, in cortical plasticity, and in learning and memory[21]. In fact, some studies report very poor connectivity in the parietal areas in children with ADD as a consequence of the low attention they manifest[20,39]. This in turn entails major academic learning difficulties[31]. Consistent with these findings, a recent study[40] reported significant differences for evoked potential P300 between the beginning and the end of the study in the group of children who undertook a passive tactile stimulation program targeting wide parietal areas. Other authors reported increased cortical activity in P300, as well as improved inhibitory processes in a group of children with ADD after training based on neurofeedback and physical exercise[41]. The increased activity in the frontal areas of the HERVAT group at the end of the study could be associated with a greater need for frontal inhibitory processes during the execution phase[42], as well as in "top-down" cognitive processes[43], which are necessary when carrying out attentional tasks and are usually impaired in children with ADD.

In conclusion, the neuroeducational program HERVAT proved to be efficacious for shortening the latency of evoked potential P300, which is responsible for information processing in the brain, and for reorganization of brain activity toward frontal cortical areas, which are responsible for the attentional processes of executive function.

ACKNOWLEDGMENTS

Project funded by Fundación para el Conocimiento Madri+d.

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