J. Quintero[1]
M. Navas[1]
A. Fernández[2]
T. Ortiz[2]

Advances in attention deficit hyperactivity disorder. What does neuroimaging provide us with?

[1] Psychiatrist Service
Hospital Infanta Leonor
Madrid (Spain)

[2] Centro de Magnetoencefalografía Dr. Pérez Modrego
Department of Psychiatry and Medical Psychology
Medical School
Universidad Complutense de Madrid
Madrid (Spain)

In attention deficit hyperactivity disorder (ADHD) is a multifactorial and clinically heterogeneous disorder that is the result of the combination of environmental, genetic and biological factors. Its high prevalence, added to the high level of maladaptation occurring in the children affected and the elevated comorbidity with other psychiatric disorders have lead to new scientific interest in this disorder. Especially in recent years, there has been a considerable increase in its study using neuroimaging techniques. Structural and functional imaging studies suggest that the ADHD pathophysiology would be conditioned by a dysfunction in the fronto-subcortical pathways, as well as imbalances in the dopaminergic and noradrenergic systems.

Key words:
Attention deficit hyperactivity disorder. ADHD. Neuroimagine.

Actas Esp Psiquiatr 2009;37(6):352-358

Avances en el trastorno por deficit de atención e hiperactividad. ¿Qué nos aporta la neuroimagen?

El trastorno por déficit de atención e hiperactividad (TDAH) es un trastorno de la conducta fruto de la combinación de diferentes factores, entre los que se encuentran tanto factores ambientales como genéticos y biológicos. Su elevada prevalencia, el alto grado de desadaptación que produce en los niños afectados, así como la elevada comorbilidad con otros trastornos psiquiátricos, han despertado el interés científico sobre este trastorno. En especial, en los últimos años, su estudio mediante técnicas de neuroimagen ha aumentado considerablemente. Estudios de neuroimagen estructural y funcional sugieren que la patofisiología del TDAH estaría condicionada por una disfunción en las vías fronto-subcorticales así como por un disbalance en los sistemas dopaminérgicos y noradrenérgicos.

Palabras clave:
Trastorno por déficit de atención e hiperactividad. TDAH. Neuroimagen.

INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is a neurologically-based behavior disorder. It is characterized by the chronic and inappropriate development in different grades of lack of attention, impulsiveness and hyperactivity.[1] ADHD is the most prevalent psychiatric problem affecting school-aged children. It prevalence values are stable in regards to different races and cultures that range from 4 to 8%.[2] It also causes serious personal dysfunctions for the child, as well as for the family, school and society.

Although the neurobiological substrate of ADHD is not accurately known, there are currently two hypotheses: 1) The first, frontostriatal hypothesis postulates the existence of a dysfunction of the frontostriatal circuits based on a series of anatomic as well as functional findings, provided by different neuroimaging studies.[3,4] 2) The second, an alternative, is that of the posterior cortical hypothesis that shows the existence of alterations in other posterior cortical regions, equally on the anatomic and functional levels.

The first hypothesis is presently the most popular, the frontostriatal circuit being considered an essential part of the neurophysiological substrate of the executive functions. Different neuroimaging studies show a frontostriatal dysfunction in ADHD. Studies with positron emission tomography (PET) have shown a decrease in brain glucose meta-

Correspondence:
Javier Quintero
Psychiatrist Service
Hospital Infanta Leonor
Gran Vía del Este, 80
28031 Madrid
E-mail: fjquinterog@salud.madrid.org

bolism in the frontal lobe.[5,6] Other studies performed with single photon emission computed tomography (SPECT) have also found the existence of an inverse relationship between cerebral blood flow in frontal regions of the right hemisphere and severity of behavioral symptoms.[7] Consistence with other studies, the neuropsychological studies and the existing cognitive theories seem to agree that the central cognitive deficit of this disorder consists in an executive dysfunction.[8,9]

By unifying the different theoretical models, it can be concluded that difficulties exist in three essential components of the executive functions in ADHD that have been related with adequate functioning of the prefrontal cortex: temporal integration information, working memory and inhibition.[10,11] Of these three processes, inhibitory control has been studied most, possible due to the influence of the Barkley theoretical model, who consider that the primary characteristic of ADHD is a behavior inhibition deficit that secondarily generates a deficit in the executive functions.

In some neuroimaging studies, alterations begin to appear in a posterior cortical circuit that seem to involve at least the posterior superior temporal cortex and the inferior parietal cortex, giving rise to the posterior cortical hypothesis. According to Mirsky's model of attention,[12] both regions would be involved in the capacity to focalize attention, that is, to concentrate the attention resources on a certain task, while ignoring the distracting stimuli.

As a conclusion to these two theoretical models, the first one is capable of explaining what happens to patients who suffer the inattentive subtype of ADHD while the latter could better explain what happens to the patients diagnosed of the hyperactive/impulsive subtype, or even those who suffer the combined type.

The evolution of psychiatry in the diagnosis of mental disorders currently counts on the use of neuroimaging techniques. Although there is still little scientific data to justify these techniques within the clinical diagnostic protocols, there is no doubt that their use will lead to an important advance in the diagnosis and knowledge of many mental disorders, especially ADHD, that are currently unknown. Thus, with the presently available data, the diagnosis of ADHD continues to be highly clinical.

STRUCTURAL STUDIES

The first structural studies to be described mentioned a decrease in global brain volume in ADHD-diagnosed patients.[13,14] Later, this was attributed to the IQ effect of the subjects studied. Seven of 12 studies[13,15-20] have demonstrated that total brain volume in ADHD patients (in about 19 years of age), specifically the right hemisphere, is 3% to 5% less than in the controls. None of the studies have shown a significant increase in volume.

Later, the new works that have appearing have focused on the study of specific brain areas that could have a clinical-biological correlate with ADHD. The most relevant brain areas are located in the cerebellum, callous body and basal ganglia.

The first data from studies on the cerebellum in ADHD-diagnosed patients suggested the existence of a decrease in its volume.[13] Later studies found that after the cerebellum measurements were correlated in relationship with total brain volume, there were no significant differences between total cerebellum volume of ADHD patients and those of the control subjects. However, decreases in volume of the inferior posterior lobules (VIII-X) of the cerebellum vermix were found.[13] These vermix alterations suggest the possible participation of the cerebellum in the circuits related with attention processes. Furthermore, the abnormalities found in any of the structures of the circuit formed by the prefrontal cortex, basal ganglia, and cerebellum could give rise to an executive dysfunction[11] (Barkley's model).

The callous body is considered to be an essential element in the transmission of interhemispheric information via white matter. When using parcellations as a study method of the cerebellum in ADHD diagnosed patients, morphometric changes are detected in the anterior and posterior zone of the callous body.[21,22]

Studies which have been done with the magnetic resonance imaging (MRI) of the caudate nuclei in ADHD subjects offer different conclusions. The first works found an asymmetry of both nuclei, with right predominance, which seemed to be due to a decrease in left caudate nucleus size.[23] However, other studies have described a decrease in the right caudate nucleus.[43]

The prefrontal cortex can be subdivided into five subregions: prefrontal regions (orbital, dorsolateral and mesial), premotor region and motor regions.

All the studies that measured at least one of the prefrontal cortex subregions found decreased volumes in ADHD-diagnosed patients. These studies[13,15,17-20] identified a lower prefrontal volume in areas corresponding to the prefrontal dorsolateral cortex of the left and right hemispheres. Equally, several studies have found significant decreases in the volume of the temporal, parietal and occipital lobes.[4,24]

FUNCTIONAL STUDIES

There are neuroimaging, neuropsychological, neurochemical and genetic studies that mention alterations in the frontal-striatal circuit as a fundamental cause of ADHD.[3,22,25,26] Specifically, the use of functional neuroimaging techniques has been advancing rapidly in the last few decades, offering and providing clarification on the neurobiology of ADHD and on the effects that the different treatments produce in the brain of these patients.

Currently, there are several techniques that may be considered as «functional neuroimaging.» Within these, those having high spatial resolution are: single photon emission computed tomography (SPECT), positron emission tomography (PET), and functional magnetic resonance imaging (fMRI). Mention should be given to other techniques that are useful to know in which area the brain activity appears, such as those derived from the electroencephalography (EEG), and the discrete event related potentials (DERP). To achieve better knowledge on how brain activity is organized regarding a certain cognitive process, a functional neuroimaging technique is needed to integrate high spatial resolution with high temporal resolution. The combination of the MRI with the magnetoencephalography (MEG) offers this possibility. This makes it one of the most promising procedures for the study of cognitive function.[27]

The studies performed with fMRI have focused on the study of brain activation in children with ADHD with inhibition tasks which, as we have previously commented on, have been proposed as one of the primary deficits in ADHD.[9] These studies have found hypoactivation in the prefrontal cortex of the right cortex[44,28] and in the caudate nucleus.[28] According to Casey et al.,[44] since greater activation of the caudate nucleus is observed in both inhibition function and control condition, it could be related to the execution of the behavioral responses while activation of the prefrontal cortex that only occurs when there is inhibition would be task specific for suppressing responses to salient, although not relevant, stimuli.

One of the greatest contributions that the fMRI may have contributed to knowledge on ADHD is the finding of alterations in the anterior cingulate. The anterior cingulate, also called the cingulate «cognitive division» plays a crucial role in attention, cognition, motor control and reward based decision making.[29] In a study focused on this region, in which the Stroop test was used as the cognitive activation paradigm, Bush et al.[30] observed that the anterior cingulate was hypofunctioning in ADHD-diagnosed adults. Similarly, Rubia et al.[31] found mesial prefrontal hypoactivation in the anterior cingulate area using *stop signal* tasks and motor tasks. Recently, Durston et al.,[25] using *go/no go* type tasks in children, found that it produced an activation in the anterior cingulate of healthy volunteers, but this did not occur in ADHD-diagnosed subjects.

However, studies performed with fMRI do not make it possible to distinguish when the brain activation in the cognitive processing in children with ADHD begins to differ from those of their respective controls. To do so, techniques with elevated temporal resolution such as the magnetoencephalography (MEG)[32] would be more useful.

Other studies performed with functional neuroimaging techniques, principally PET and SPECT, are generating much information regarding where the activity appears in ADHD-diagnosed children. Gustafsson et al.,[7] in a study performed with SPECT, showed the existence of abnormal blood flow distribution in the brain of children with ADHD. Furthermore, these authors found an inverse relationship between regional blood flow in frontal areas of the right hemisphere of the brain and severity of behavioral symptoms. In adolescents with ADHD, the PET has shown a decrease in regional glucose metabolism in the frontal lobe of the brain, while global brain metabolism was not affected.[6] In the studies conducted by Zametkin et al.,[6] it was also reported that there were no significant differences when the data were analyzed separately by gender. Taking these findings into consideration, it would be more prudent to conclude that these data simply suggest the existence of a decrease in global metabolism in ADHD-diagnosed subjects and that the effects of gender should be taken into account in future studies. This point of view correlates well with the findings of Castellanos et al.,[16] who suggested that although the brain size of the female children studied was generally smaller or brain size of the male counterpart, those diagnosed of ADHD had a smaller brain size than their controls of the same gender, the same occurring with the male subjects. Thus, it is concluded that gender, together with other variables, such as complying with the treatment, should be controlled even though it seems that ADHD affects the brain size and functionality independently.

The DERP provides very specific information on the physiological changes related with this specific situation, giving that its temporal resolution is approximately milliseconds.[33] The DERP studies in ADHD have focused on two aspects. The first, on attention based on sensorial modality (visual or auditory), using continuous performance tasks. The second focuses on inhibition processes, using *go/no go* and stop signal tasks, as in the studies with fMRI. [27]

Studies on attention have observed a decrease in the amplitude of the processing negativity (PN), of the frontal N2 component[34] and the P3b component with deviant sti-

muli. There are differences regarding the amplitude of the PN wave and the N2 component in children with ADHD and healthy controls. These differences appear at 6 years of age and disappear two years later while the differences in the P3b component amplitude would be evident at 8 years of age. This would agree well with the hypothesis of Rubia et al.[35] who speak about a delay in frontal maturation of children with ADHD.

The studies on inhibition of response, a decrease in the frontal N2 component amplitude is observed.[36] This seems to be an electrophysiological reflection of the inhibition process.

The ADHD has been studied using electrophysiological techniques such as the **electroencephalogram** (EEG). The EEG has been used in many studies to differentiate subjects with ADHD from control subjects according to a review performed by Hughes and John.[37] They concluded that there would be a pattern consisting in an increase of theta activity and decrease of the alpha activity. This same pattern may be indicative of other diseases such as dementia, schizophrenia, obsessive-compulsive disorder, alcohol poisoning, mood disorders, among others. Currently, its use as a diagnostic tool in patients with ADHD is limited, this being reduced to ruling out comorbid diseases such as epilepsy which may generate diagnostic doubts in a small percentage of causes.

Magnetoencephalography studies

The MEG is a non-invasive technique that makes it possible to record the magnetic fields generated by intracellular electrical current flow into the dendrites of the pyramidal neurons.[38] The MEG offers an excellent temporal resolution, of milliseconds, while offering elevated spatial resolution.[39] Thus, it could be an especially useful technique to help understand the essential neurolobiological aspects of ADHD and, consequently, what the primary cognitive deficit of ADHD is.

MEG is a good tool to be able to evaluate and create functional images of brain activity in this type of patient. This allows the psychiatrist to integrate the contributions of the structural neuroimaging with those provided by functional neuroimaging, as occurs with the MEG that integrates the functional image within the structural image. This new study approach of the brain will give rise to concepts differing from those we currently manage. This would help us understand our brain from a more temporal than structural approach to the understanding of mental disorders.

There are few works that have studied brain functioning is ADHD-diagnosed children from the perspective of the Magnetoencephalography. In a preliminary study,[40] the magnetic activity of the brain during the performance of a modified version of the Wisconsin cards test was recorded. The results point towards the existence of lower activation of the prefrontal dorsolateral cortex than in the anterior cingulate of the left hemisphere during the first 400 milliseconds (excluding the primary sensorial processing) after reception of a negative feedback.[40] Thus, it reflects an alteration in children with ADHD on two levels. In the first, hypoactivation is observed in prefrontal regions essential for correct executive functioning.[27] Emphasis can be placed on the hypoactivation observed in the anterior cingulate cortex, a structure which, as we have previously stated, is involved in the allotment of attention resources. An alteration is also observed in the temporal areas, this showing the differences between control children and ADHD-diagnosed children in early phases of cognitive processing, that is, during the first 400 ms.

In a recent work, Tannock et al.[41] manifested the differences observed in ADHD-diagnosed adults in relationship with their control pairs in the basic somatosensorial processing measured with MEG. They examined the cortical rhythm patterns of the primary (S1) and secondary (S2) somatosensorial cortex in response to median nerve stimulation in 9 ADHD-diagnosed adults and 10 healthy controls. They measured the changes in strength, synchronicity and frequency of cortical rhythms. As a conclusion to the study, they found that there was an alteration in the somatosensorial processing in adults with ADHD that could partially explain why these individuals score low on tasks that require somatosensorial feedback, especially when the performance of these tasks makes it necessary for the tactile information to be integrated in the upper processing areas.

Our group is conducting several projects in ADHD and MEG. In a recently published project[42] that is working on brain complexity models of *Lempel-Ziv*, we found significant differences between the cases and controls focused on the anterior regions of the brain. The model in this work proposed achieved 93% sensitivity and 79% specificity, also finding a strong correlation with age. Thus, the higher the age, the more reliable the behavior of the model to differentiate the patients with ADHD from the controls, reaching 100% specificity in children over 9 years. This is also supported by other investigations that find the etiopathogenic base of ADHD in a neurodevelopment alteration, or what is the same, in a delay in maturation.[41] In figure 1, the averages of the complexity in the 148 channels (color scale) can be seen. A significant increase of the LZ complexity is observed in all the anterior central zone for the control group compared with the hyperactive group.

CONCLUSIONS

The advances in the knowledge of ADHD in the last decade have lead to a significant change in the perception

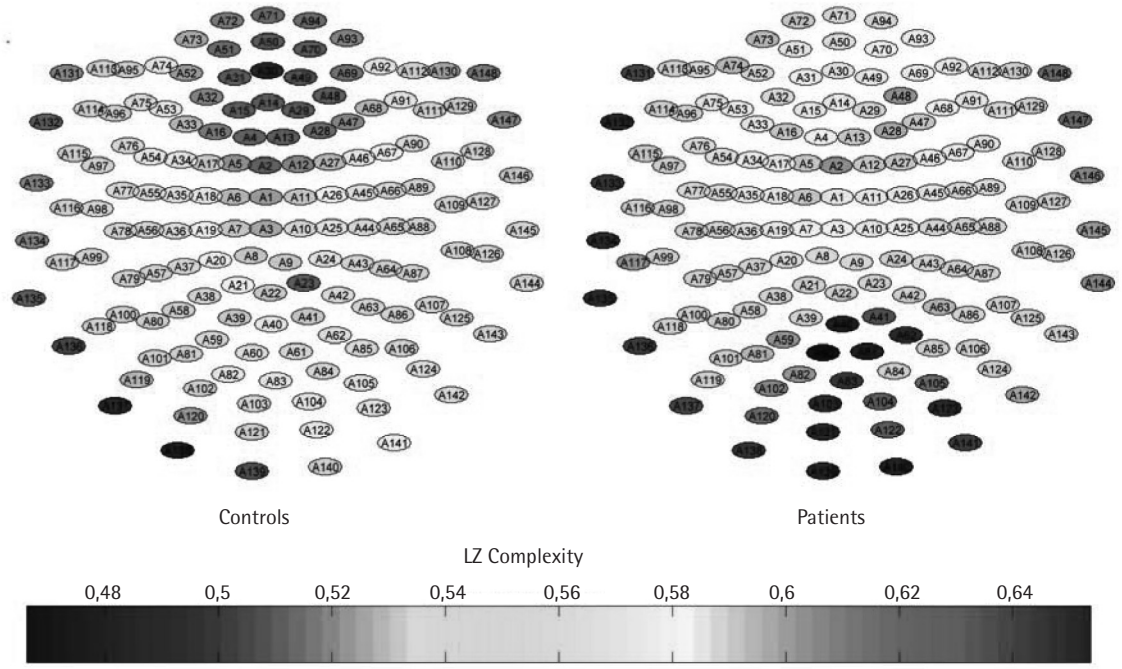

Figure 1 *Analysis of the complexity. MEG.*

of the etiopathogenesis of ADHD. In this sense, the neuroimaging techniques not only open a window to knowledge and better understanding of the disorder but also provide a glimpse into the possibilities of finding diagnostic applicability in the future for some of these techniques, even though the data that we presently have can only be considered within future concepts and that we should stress that the current diagnosis of ADHD is basically clinical.

In this sense, the MEG is being positioned to be a technique which, in the future, can help us understand better the specific and differentiated participation of our brain in the cognitive processes and in mental disorders in general in the ADHD specifically. This can be either from a temporal approach of them or a distributed process of the brain activity, as the current neuroscience proposes or as a combination of both processes.[43]

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