

K. Tajima
M. Díaz-Marsá
A. Montes
R. Fernández García-Andrade
A. Casado
J.L. Carrasco

Neuroimaging studies in the borderline personality disorder

Servicio de Psiquiatría
Hospital Clínico San Carlos

DSM-IV defines Borderline personality disorder (BPD) as a personality disorder that can be primarily characterized by emotional instability, extremely polarized thought and chaotic interpersonal relations. It is the most common personality disorder. Its prevalence is estimated to be from 0,2% to 1,8% of the general population, and the 76% of them are women. However, despite these data and the different biologic findings, there are few publications on neuroimage about this nosologic entity.

Recent studies suggest that a dual cerebral disorder, including frontal and limbic circuits, could be present in characterize BPD. These cerebral areas would also be involved in the serotonergic dysfunction that seems to be related to the impulse dyscontrol and self-aggressive behaviour, characteristic of these patients. Most authors point out the importance of traumatic precedents in the BPD genesis, with a direct relation between stress and the neurobiological findings observed, including the neuroimage changes. The aim of this article is to make a revision of the main neuroimage data found in BPD, including the new techniques such as functional MRI, diffusion tensor MRI and spectroscopy.

Key words:

Impulsivity. Borderline personality disorder. Traumatic events. Diffusion tensor. Functional MRI. Spectroscopy.

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Estudios de neuroimagen en el trastorno límite de la personalidad

El trastorno límite de la personalidad (TLP) o borderline, es actualmente definido por el DSM-IV como un trastorno de la personalidad que se caracteriza principalmente por disregulación emocional, pensamiento extremadamente polarizado y relaciones interpersonales caóticas.

Es, con mucho, el más común de los trastornos de la personalidad. Se estima que su prevalencia oscila entre un 0,2 % y un 1,8 % de la población general. De ellos, el 76 % son mujeres. Sin embargo, a pesar de estas cifras nada desdeñables y de los diferentes hallazgos biológicos, existen pocas publicaciones sobre neuroimagen en esta entidad nosológica.

La gran mayoría de los estudios recientes sostienen la hipótesis de que en el TLP existiría una patología cerebral dual que incluiría circuitos frontales y límbicos. Estas áreas cerebrales también estarían implicadas en la disfunción serotoninérgica que parece relacionarse con el descontrol de impulsos y la autoagresividad propios de este tipo de pacientes. Muchos autores apuntan a la importancia de los antecedentes traumáticos en la génesis del TLP, existiendo una relación directa entre el estrés y los hallazgos biológicos observados, incluyendo las alteraciones en la neuroimagen.

El propósito de este artículo es realizar una revisión de los principales hallazgos obtenidos en los estudios de neuroimagen realizados en TLP, incluyendo las nuevas técnicas como la resonancia magnética (RM) con tensor de difusión, las pruebas funcionales como la RM funcional y la RM con espectroscopia.

Palabras clave:

Impulsividad. Trastorno límite de la personalidad. Antecedentes traumáticos. Tensor de difusión. RM funcional. Espectroscopía.

INTRODUCTION

Borderline personality disorder (BPD) is currently defined by the DSM-IV as a personality disorder that can be characterized primarily by emotional instability, extremely polarized thinking and chaotic interpersonal relations. Its estimated prevalence ranges from 0.2% to 1.8% of the general population, and 76% of them are women.

Recent studies support the hypothesis that dual brain pathology that would include the frontal and limbic circuits would exist in the BPD. These brain areas would also be involved in the serotonergic dysfunction that seems to be relat-

Correspondence:

M- Díaz-Marsá
Hospital Clínico San Carlos
Servicio de Psiquiatría
Avda. Prof. Martín Lago s/n
28040 Madrid
E-mail: mdiazm.hcsc@salud.madrid.org

ed to impulse dyscontrol and self-aggressive behavior that are characteristic of these patients. Together with this, some authors point out the importance of traumatic background in BPD genesis, there being a direct relationship between stress and the neurobiological findings observed, including the neuroimaging changes.

A review is made of the principal studies made with neuroimaging techniques in BPD, including novel techniques such as Magnetic Resonance Imaging (MRI) with diffusion tensor, functional MRI or MRI with spectroscopy.

MORPHOLOGICAL STUDIES

Prefrontal cortex is considered fundamental in the cognitive control of behavior, control of impulsivity and regulation of emotions, all of these being severely affected functioning areas in BPD. In spite of this, at present there is no definitive evidence on the existence of morphological abnormalities in the frontal lobes of borderline patients. On the other hand, the limbic system could also be involved in the borderline disorder since it plays an essential role in the regulation of emotions and in memory storage and recovery.

In the first morphological studies conducted in the beginning of the 1990's using the Computerized Axial Tomography (CT scan), a mild decrease in the size of the third ventricle in BPD was observed. However, it seems that this finding could be explained by the predominance of the female gender in the sample more than by the disease itself of BPD, given that women have a smaller sized third ventricle.¹

In the first studies conducted using the Magnetic Resonance Imaging (MRI), volume decreases of up to 62% were found on the frontal level when BPD and healthy control patients were compared.² Along the same line, significant losses in value in the right anterior cingulate and left orbitofrontal cortex were found in these patients.³ More recent investigations on volumetry with MRI suggest alterations in the corpus callosum of subjects with BPD, observing greater thinness of the isthmus of the corpus callosum that becomes visible as the number of traumatic backgrounds in childhood increases.⁴ A larger volume of the left postcentral gyrus of the right precuneus has also been observed on the parietal cortex level. This increases as the dissociative symptoms that have been seen in the clinical features increase.⁵ In addition, it seems that BPD patients have a smaller volume of gray matter of the hippocampus and that the decrease of the volume increases parallelly to the increase of the patient's hospitalizations, which would mean greater clinical severity. Together with this, it seems that the aggressive behavior would be more connected with the decrease of the hippocampus than impulsive behavior,⁶ which would help to discriminate some clinical subtypes of the BPD.

Since there are studies suggesting a dysfunction in the hypothalamo-pituitary axis reactivity in BPD,⁷ the pituitary gland volume was studied because of its close correlation with the activity of this axis. Thus, there seems to be an inversely proportional relationship between the pituitary volume and the number of parasuicidal behaviors in adolescents with recent-onset borderline personality disorder, it having been observed that the decrease of the volume of the pituitary gland increases and the number of suicide attempts increase.⁸ On the other hand, some authors have described a significant correlation between the volume of the amygdala and the presence of depressive symptoms measured with the Hamilton Rating Scale for Depression in borderline disorder patients.⁹

The application of new neuroimaging techniques such as Diffusion Tensor Resonance makes it possible to detect subtle *in vivo* white matter alterations, determining the grade in which the organization of the cell tissue has lost its normal integrity. This technique is based on the macromolecule-water proton magnetization transfer exchange between protons forming a part of the free water and those that form a part of the macromolecule connected water. In the white matter, the perpendicular diffusion in the direction of the axons is restricted due to the myelin sheath and cell membrane so that the parallel diffusion over the axon is greater than the perpendicular diffusion. This characteristic of the diffusion (that differs according to the direction in which they are examined) is called anisotropy. Some high indexes of anisotropy indicate greater directionality and coherence of the fiber tracts, while a low anisotropy index indicates lower directionality and greater random movement of the water in the all the directions measured. Thus, those pathological processes that decrease the number of macromolecules, especially the axon and myelin membranes, would cause a decrease of the anisotropy.

The studies conducted in BPD using this technique support the hypothesis that there is greater involvement of the frontal white matter in patients with BPD and it is precisely the involvement of the lower frontal circuits that determine the impulsive-aggressive behavior. Involvement of the prefrontal white matter microstructure in patients with BPD could condition an incapacity to evaluate the desire of immediate reward versus acknowledgement of the long-term consequences.¹⁰ Together with this, it must be remembered that the orbitofrontal cortex is essential in the regulation of emotions and impulse control. Thus, uninhibited or socially inappropriate behaviors and greater emotional instability could be explained by orbitofrontal cortex lesions, white matter circuits bind the orbitofrontal cortex to other frontal areas, such as the anterior cingulate, basal ganglia and amygdala, and the dysfunction of these neuronal circuits is associated with emotional dysregulation and impulsivity. Patients with BPD often have problems in affective regulation and impulsivity. This could lead to self-harm, affective and impulsive behavior and to unstable interpersonal relationships. In this way, alterations in the orbitofrontal

regions could explain many of the symptoms observed in subjects with BPD.

In another study performed in women with BPD who had comorbidity with attention deficit hyperactivity disorder (ADHD), an association between the values of mean diffusivity in the inferior frontal white matter and some key symptoms of the BPD such as emotional dysregulation, aggressivity, hostility and presence of dissociative symptoms were observed.¹¹ These findings would confirm the relationship between the inferior front white matter microstructure and borderline symptoms in women with borderline personality disorder. Among the different symptoms, the dissociative ones had the lowest significant association, probably because they would be involved in more extensive networks, including temporal, parietal and occipital areas. No correlation between these variables and the values of the anisotropy fraction (AF) nor with the results of the neural psychological tests (Attention Network Test and Degraded-Stimulus Continuous Performance Test) or with the values of the mean diffusivity was detected. In the comparisons of subgroups, a significant decrease of the AF in the lower left frontal white matter of the patients with a background of major depressive episodes compared to those who did not have these backgrounds and an increase of the mean diffusivity on the left side in patients with a concurrent eating behavior disorder in relationship to those who did not have it was observed.

FUNCTIONAL TECHNIQUES

The structural brain image does not provide information that makes it possible to detect and locate the brain activation produced when certain cognitive tasks are performed. These processes may be studied using the cerebral functional imaging techniques, whose objective is to locate the brain areas that are activated in response to any stimulus or cognitive situation. The existence of alterations on the frontal level in BPD has some consistency in the functional imaging tests such as the Positron emission tomography with fluorodeoxyglucose (FDG-PET). Three studies have demonstrated hyperactivity on the frontal level (orbitofrontal and anterior cingulate).¹²⁻¹⁴ Furthermore, there is evidence about alterations in the amygdalar metabolism in BPD patients that is detected by a creatinine peak between 11% and 17% lower in patients with BPD. Creatine plays an important role in the energetic metabolism of the brain and these findings could indicate an alteration in the local energetic metabolism in the patients with BPD.

An important advantage of Functional Magnetic Resonance Imaging (fMRI) is that it provides good spatial resolution (millimetric) and good temporal resolution (below the second). The first step to perform a study with fMRI is the experimental design in which the subject is alternatively subjected to two (sometimes more) situations. The most frequent is that these situations correspond to rest and perfor-

mance of the task, although there may be much more complex designs. Some of the paradigms used in studies performed with fMRI consist in showing images such as faces or images with different emotional burdens (pleasant, unpleasant and neutral). Along this line of investigation, in the study performed with fMRI applying stimulant for 4 seconds and neutral stimulants for another 4 seconds as paradigm, a greater response was observed in bilateral orbitofrontal and insular cortex, left anterior cingulate cortex, medial prefrontal cortex and parietal and parahippocampal areas. This same activation may also be observed for neutral stimuli, which could be interpreted as a difficulty to distinguish between emotional and neutral stimuli.¹⁵

Another study showed greater activity in the left amygdale was observed in BPD patients compared to the control group when using faces with neutral and emotional expressions (happiness, sadness and fear) as paradigm. The emotionally aversive images were related with greater activity in the amygdala and in the medial and prefrontal inferolateral cortex.^{16,17}

Along this same line, the brain activity of subjects diagnosed of BPD and subjects with BPD and comorbidity with post-traumatic stress disorder (PTSD) was compared. It was observed that when negative episodes were recalled, all the patients with BPD had greater brain activation in the orbitofrontal cortex (in both hemispheres), anterior and occipital temporal lobule areas. The BPD group with PTSD had more activity in the right anterior temporal lobule, in mesotemporal, amygdala, posterior cingulate gyrus, occipital and cerebellum areas while activity in the bilateral orbitofrontal cortex and Broca area predominated in the group having BPD without PTSD.¹⁸

Another one of the paradigms used in this study was the determination of pain threshold by heat challenge. These studies are based on the observation that patients with BPD seem to have decreased sensitivity for the pain threshold. Heat challenge produced a greater response in the dorsolateral prefrontal cortex and lower activation in the posterior parietal cortex and disactivation in the anterior cingulate gyrus and amygdala zone in BPD patients in comparison with the control group. It was observed that patients with BPD had lower activity and greater pain threshold than the controls regarding stimuli with equal temperatures.¹⁹

Finally, another one of the novel techniques is the Magnetic Resonance Spectroscopy that permits in vivo and non-invasive examination of the molecular composition of a tissue. Although this technique can be performed with different nuclei, the spectroscopy of the hydrogen nucleus is, by far, the most extended in the clinical practice. Up to now, there have been few studies performed with the spectroscopy in patients with BPD. However a study conducted with this technique which analyzed the relationship between loss of amygdalar volume and neurochemical alteration of the amygdala observed a significant increase of the creatine concentration and phospho-

creatine in the left amygdalar region. In addition, a strong positive correlation was seen between the creatine concentration in the left amygdala and the anxiety scores.²⁰ Both the creatinine and the phosphocreatine play an important role in the energetic metabolism, which is of essential importance for the brain, so that the spectroscopic MRI findings would preliminarily suggest the existence of an alteration in the local energetic metabolism in patients with BPD, as has been previously stated.

Similar studies have observed a frontal hypometabolism (above all in the prefrontal cortical areas), observing a significant decrease of 19% in the absolute concentration of N-Acetylaspartate (NAA) in the dorsolateral prefrontal cortex in patients with BPD compared with the controls.²¹ Furthermore, non-significant decreases were observed in the creatine concentration in the frontal cortex (15%) and striatal cortex (16%). NAA is a molecule present in the healthy neurons, and its decrease is a sign of neuronal death and axonal damage. It could be suggested that decrease of NAA in the prefrontal cortex would be related with impulsivity, emotional instability and aggressive behavior characteristic of BPD.

CONCLUSION

The neuroimaging studies in BPD suggest alterations fundamentally in the frontal circuits and in the limbic area. In fact, a large part of the pathoplasty of the BPD symptoms (impulsivity, emotional instability, aggressivity) could be explained by some of the alterations found on the prefrontal level, in the orbitofrontal cortex, in the frontal-dorsolateral cortex, in the frontal-orbital cortex and in the anterior cingulate cortex. On the other hand, the most conclusive findings in the structural neuroimaging studies seem to have an important correlation with the existence of traumatic background in childhood. Thus, structural characteristics such as the thickness of the isthmus of the corpus callosum, volume of the left postcentral gyrus and right precuneus, hippocampal volume and/or pituitary gland volume seem to be influenced by the history of traumatic background. The new structural neuroimaging techniques, such as MRI with diffusion tensor that make it possible to detect microstructural changes in the white matter, suggest the possible existence of alterations in the white matter of a frontal zone in patients with BPD. Regarding the functional neuroimaging techniques that make it possible to detect cerebral activation when a certain cognitive task is performed, they seem to suggest the existence of hypoactivity, mainly in the frontal area (orbitofrontal and anterior cingulate). All these findings suggest the need to continue with these studies, it seeming that the techniques having functional characteristics are of special importance in order to identify the brain areas involved in the BPD characteristic symptoms, and to thus go further into the study of its genesis and to establish new therapeutic orientations.

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