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Functional magnetic resonance studies in eating behavior disorders

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Eating behavior disorders (EBD) constitute a serious somatic and psychiatric condition that occurs mainly in adolescent and young adult women and is characterized by a persistent desire to be extremely thin, pathologic fear of gaining weight and distortion of body perception. From a neurobiological vantage point, it has been suggested that alterations in some neural systems of these patients may exist, either as a cause or effect of their condition. In recent years various research studies have been conducted with the aim of identifying underlying brain disorders in EBD. The purpose of this article was to review the main findings obtained in neuroimaging studies, including PET, SPECT, magnetic resonance spectroscopy (MRS), focusing mainly on functional magnetic resonance imaging (fMRI). Some alterations and changes in metabolism and blood perfusion that accompany the neuroimaging findings will be reviewed, as well as studies designed to determine whether these alterations persist after recovery from the disease.

Key words:
Eating behavior disorders, anorexia nervosa, bulimia nervosa, corporal image, neuroimaging, brain processing, functional magnetic resonance imaging

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Estudios de resonancia magnética funcional en los trastornos de la conducta alimentaria

Los trastornos de la conducta alimentaria (TCA) constituyen una condición somática y psiquiátrica grave, que sucede principalmente en mujeres adolescentes y jóvenes adultas y que se caracteriza por deseo persistente de extrema delgadez, miedo patológico a engordar y distorsión de la percepción corporal. Desde un punto de vista neurobiológico, se ha sugerido la existencia de alteraciones en algunos de los sistemas neurales de estas pacientes, bien como causa o consecuencia de su patología. En los últimos años, se están realizando múltiples estudios de investigación en este ámbito, con el objetivo de determinar las alteraciones cerebrales subyacentes en los TCA. El propósito de este artículo es realizar una revisión de los principales hallazgos obtenidos en los estudios de neuroimagen realizados, incluyendo PET, SPECT, resonancia magnética con imagen espectroscópica (MRS) y centrándonos, principalmente, en la imagen de resonancia magnética funcional (fMRI). Se revisarán también algunas de las alteraciones y cambios metabólicos y de perfusión sanguínea que acompañan a los hallazgos de neuroimagen, así como los estudios encaminados a concretar si estas alteraciones persisten tras la recuperación de la enfermedad.

Palabras clave:
Trastornos de la conducta alimentaria, anorexia nerviosa, bulimia nerviosa, imagen corporal, neuroimagen, procesamiento cerebral, resonancia magnética funcional.

INTRODUCTION

Eating behavior disorders (EBD) are a group of mental diseases that are currently of unknown etiology, although the participation of a number of biological and psychosocial factors has been postulated, as in most psychiatric disorders. The onset of EBD usually takes place in adolescence and the disease occurs mainly in women.

The general clinical characteristics that define these disorders are persistent desire to stay extremely thin, pathological fear of gaining weight and distortion of body perception. These core defining symptoms are accompanied by a characteristic temperament and personality and mood changes. The most common forms of EBD are anorexia nervosa (AN) and bulimia nervosa (BN) with their different subtypes. Although both types of EBD share the characteristics defined, there are differences in the behavior of the patients; patients with AN exhibit a more rigid and perfectionist attitude, with a tendency to obsessive-compulsive behavior, and patients with BN have a greater alteration in impulse control. Most patients recover after a mean disease duration of six years, although 10–20% of cases become chronic. Low

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body weight and onset of disease during the growing years are factors of poor prognosis, although there are few predictors of outcome and they are not very reliable.

Studies to date have identified a series of alterations in the neural mechanisms underlying the clinical syndrome described in patients with EBD, principally in patients diagnosed of AN, who have been chosen for investigation in the majority of cases. The most consistent alterations include: reduction in brain volume[1], alteration of neurotransmitter levels[2], reduced cerebral blood flow and metabolism[3], and deterioration of cognitive test results[4–6]. In any case, the causal relations between cerebral changes and the clinical syndrome are unclear because it is difficult to differentiate the primary disorders from the secondary phenomena that accompany this serious somatic condition, in view of the fact that the malnutrition associated can origínate changes in neuroendocrine function. Some of the dysfunctions found may be inherent to dysregulation of emotions or impulse control, which also appear to be affected in these patients.

With regard to the techniques used to study EBD, preference in the analysis of brain function has been given to non-invasive imaging methods that allow the analysis of different aspects of metabolism, neurotransmission, and cerebral perfusion. The techniques preferred for the study of brain function are positron emission tomography (PET), single photon emission computed tomography (SPECT), magnetic resonance spectroscopy (MRS), and functional magnetic resonance imaging (fMRI). These techniques provide valuable information about the pathophysiology and neurobiological bases of the different psychiatric disorders.

NEUROIMAGING STUDIES IN EBD

Most studies of brain morphology in EBD find a loss of both gray substance and white substance and an increase in ventricular volume during the disease[7]. However, techniques like magnetic resonance and magnetic resonance spectroscopy reveal partial normalization of these abnormalities with recovery from the disease, which indicates that these structural changes observed in patients with EBD are reversible and accompany the clinical syndrome[8].

As functional imaging techniques capable of identifying abnormalities in metabolism, neurotransmission and cerebral perfusion have developed, the aim has been to establish relations between the changes observed with these techniques and the characteristic clinical variables of patients with EBD.

Studies of cerebral metabolism with magnetic resonance spectroscopy have found a significant reduction in myo-inositol and other lipid compounds in the frontal white substance and occipital gray substance, as well as an increase in the concentration of all metabolites except lipids in the cerebellum. Nonetheless, the authors indicate that nutritional deficiency could also contribute to these findings[9].

Techniques such as PET have suggested alterations in serotoninergic and dopaminergic neurotransmission, as well as in some neuropeptides (although there is little data on the latter) that seem to persist with the normalization of the eating disorder[10]. Using the same technique and serotonin receptor-specific radioligands, the existence of an important serotoninergic dysregulation at the level of the 5HT1A and 5HT2A receptors and 5HT transporter was later confirmed. An increase in the 5HT1A receptor is observed in purgative type AN and a decrease in the 5HT2A receptor in restrictive type AN in the cingulate, temporo-medial zone of the temporal lobe, parietal lobe, prefrontal and orbito-frontal latero-medial cortex that did not change with recovery from the disease[11,12]. However, it seems that the alteration in the 5HT transporter is not as consistent: a study with SPECT and radioligands for the 5HT transporter concluded that no significant differences were found between patients with BN and controls with respect to this molecule[13].

It is interesting to note the findings encountered with PET and SPECT on cerebral perfusion in EBD. In patients recovered from BN, we observed a fairly nonspecific decrease in blood flow affecting the areas of the bilateral prefrontal cortex, right orbito-frontal medial cortex, left subgenual and right anterior cingulate, left motor and sensorial cortex, bilateral lateral temporal, left occipital and left thalamus. The fact that these data were recorded in patients who had recovered suggests that the alterations produced by the disease did not normalize with improvement, which could indicate that they were trait anomalies[14]. However, these data are inconclusive because the same group of investigators found normalization of blood flow with clinical recovery in both AN and BN in another study[15]. Other authors using PET with 99Tc in patients with AN observed a reduction in cerebral blood flow (rCBF) in the anterior lobes (including the anterior cingulate cortex) and right parietal lobe. In this study they reported the normalization of blood flow with recovery from the disease in almost all areas except the anterior cingulate[16]. Other authors later reproduced the stabilization of blood flow with improvement of the clinical variables in all the areas, including the anterior cingulate cortex[17].

FUNCTIONAL MAGNETIC RESONANCE IN EBD

FUNCTIONAL MAGNETIC RESONANCE (fMRI) is a functional imaging technique that uses the general principles that relate neuronal activity with metabolism and blood flow. Functional MRI can record cerebral hemodynamic changes that accompany neuronal activation using what is

called "BOLD (*blood oxygenation level dependent*) contrast phenomena", i.e. changes in blood oxygen level, which are reflected by the concentration of deoxyhemoglobin, which acts as an intrinsic contrast agent. An increase in local neuronal activity is associated with a greater increase in the cerebral blood flow that supplies oxygen to cells. For this reason, increments in local neuronal activity produce lower concentration of deoxyhemoglobin on the venous side of the capillary bed, generating an increase in the signal intensity that can be detected by fMRI.

Functional MRI has several advantages over PET and SPECT, notably, non-exposure to radiation because the technique does not require the administration of an exogenous contrast agent. In addition, fMRI is an accessible and less expensive technique with better spatial and temporal resolution. Nonetheless, fMRI also has certain disadvantages, such as artifacts that are caused by head movements (or jaw movements, which are very common in studies in EBD, where the stimuli are usually related with food) or the difficulty of isolating and obtaining stimulation exclusively of the neuronal area of interest. Consequently, the preparation of the tests or paradigm to be applied should be carefully thought out and designed.

Functional MRI thus allows the regions responsible for sensoriality, motricity, cognition and affective processes in normal and pathological brains to be evaluated functionally. With regard to EBD, fMRI allows us to investigate the pathophysiological basis of eating behavior and its alterations, which makes it possible to search for the brain regions involved in the regulation of eating behavior.

With fMRI, differences have been found in cerebral processing in patients with EBD in response to the presentation of different paradigms, the majority consisting of showing images of body figures, given the importance of the alteration of body perception in these disorders. Distortion of the body image has been considered to be the core symptom of EBD, apparently preceding and conditioning the rest of the symptomatology. Distortion of the body image is manifested by 1) an alteration in perception consisting of systematic overestimation by the patient of his or her body size and 2) cognitive dissatisfaction with the appearance of his or her body. This leads us to think that individuals with eating behavior disorders may have functional alterations in the cerebral systems responsible for processing the body image and its size. These cerebral systems include, on the one hand, the visual perception of body images and, on the other hand, the constitution of the map of one's own body, i.e., the body scheme. Visual perception is located in the occipito-temporal cerebral cortex and responds to images of the human body and parts of the body. The representation of the body scheme depends on the neuronal circuit that includes the right parietal cortex and connects with the thalamus.

Based on these neurophysiological principles, digital images of the subject and other people were used in one study as a paradigm for fMRI. It was observed that the processing of personal images and images of others by control subjects activates occipito-temporal regions (including the secondary visual cortex), as well as the dorso-lateral prefrontal cortex and cerebellum, which indicate cognitive processing. In addition, activation of the parahippocampal and fusiform gyri, both implicated in the processing of emotions, occurred. The fusiform gyrus is recognized as the system specialized in processing the visual appearance of the human body. In patients with AN, the processing of images other than personal images did not differ from controls, but an absence of activation was observed when patients were shown their own body. This suggests a possible suppression of the cognitive, perceptual and emotional processing of personal body image in these patients. On the other hand, important activation of the insula occurred when controls viewed their own body image that did not occur in patients. If we take into account that the insula is a key to the representation of the body scheme, this difference in activity could explain why patients with AN distort their own image[18].

Other studies have been conducted based on the hypothesis of the existence of a "fear network" of the brain centered on the amygdala. This fear network has been used as a paradigm to induce distorted body image symptoms in patients with AN and controls. The presentation of distorted images of one's own body image, principally in AN, would activate psychological mechanisms of anxiety. In patients with AN, activation of the right part of the amygdala when confronted with their own distorted body image was found that was not observed in controls. These results suggest that negative aversive stimuli related to anxiety might activate the right part of the amygdala in patients with AN[19]. Although this study is based on previous findings that suggested an increase in right amygdalar activity in response to this type of stimuli in patients with anxiety disorders, it should be noted that this is a preliminary study of a very small sample and the results are inconclusive[20]. In accordance with these data, a previous study that compared cerebral activity by fMRI when subjects were shown images of high and low-calorie drinks, in which the high-calorie drinks were understood to be the aversive stimulus, specific activation was found in the left amygdala-hippocampus region, insula, and anterior cingulate gyrus in patients with AN[21].

Another study related with body image perception used three different types of images: overweight, normal and underweight. The reason for comparing different body sizes was to be able to specifically identify the cerebral correlation between body size perception and the emotional evaluation. Since this may differ depending on the pathologic subtype, three groups of comparison were made: AN, BN, and healthy subjects. The pattern of cerebral response included less activation of the fusiform gyrus in patients than

in controls in response to overweight and normal weight images (although the difference was not significant with normal weight images), than with underweight images. The perception of overweight images as aversive stimuli explains why the subject exhibited diminished cerebral activity, which was related to a greater aversion toward the image. With respect to the emotional response that the stimulus produces in the subject, more activation was found in the apico-medial prefrontal cortex and medial-inferior temporal lobe, including the amygdala. This difference in activation in relation to the individual's subjective response to the stimulus could be more clearly related to food type stimuli than with body image, as will be discussed below[22].

As mentioned, another paradigm frequently used in fMRI studies are images of food. A study of this type demonstrated the existence of activation of the anterior cingulate and prefrontal medial cortex in response to images of food in patients diagnosed of EBD but not in controls. In a later study, this group proposed to demonstrate that the alterations found were a trait marker rather than a state marker. They chose a sample of female patients who had completely recovered from the disease, given the difficulties that a prospective study would have entailed. The paradigm of photographs of foods and emotional stimuli obtained from the IAPS (International Affective Picture System) was used in three groups of comparison that included patients with chronic AN, patients recovered from restrictive AN, and healthy subjects. The findings suggest that the alterations observed previously (activation of the anterior cingulate cortex, which is implicated in self-esteem based on decision-making and conflict resolution, and of the medial prefrontal cortex, which is responsible for coding the emotional value of the stimulus and how it influences behavior toward one's self) appeared in both patients with chronic disease and in recovered patients in response to food stimuli but not in response to aversive emotional stimuli. Therefore, the authors considered these anomalies as possible trait markers for AN[23].

Investigations in the same line made by the same team have corroborated these data and have also suggested diminished activation of the inferior parietal lobe and occipital cortex in response to visual food stimuli in both AN and BN[24]. Activation of the inferior parietal lobe is associated with appetite and food intake-related behaviors. In view of these findings, it was postulated that patients with EBD might have weaker inferior parietal lobe activity than controls in response to food stimuli in a situation of satiety, and that this hypothesis may offer a neurobiological explanation of the behavior that these patients present in response to eating. The results of our study not only confirmed this hypothesis but yielded the observation that the activation was more marked in relation to more intense restriction (central characteristics of AN). In addition, the difference in activation of these patients could explain the ease with which they can fast, due to the interconnection of somatosensorial and gustatory projections with the inferior parietal lobe. Less occipital activity in response to a visual food stimulus was also found in patients in a situation of hunger, which could be related to the subjective importance of the stimulus for the individual[25].

Although this has been less studied, functional neuroimaging studies have been made with fMRI in patients who binge eat, are obese or have a normal weight. Again using images of food as the stimulus, the working hypothesis was that overweight patients would have more activation of the frontal and prefrontal areas because these areas participate in inhibition, decision-making, the execution of behavior, and in reward-seeking. The data obtained confirmed the existence of more cerebral activation in obese subjects, which could reflect an alteration in the motor planning of food intake. This activation would be even greater if the foods shown were the foods typically consumed during binge eating[26].

Finally, several studies have tried to evaluate hypothalamic function in the regulation of body weight using fMRI. In one study, the activity of two specific zones of the hypothalamus (ventromedial and paraventricular nuclei) decreased with exposure to glucose administration 10 minutes before making the recording[27]. The neurophysiological explanation would be that the foods directly inhibit the hypothalamic activity that would be elevated in situations of hunger[28]. These findings were reproduced in a later investigation in which satiety was observed to be associated with reduced hippocampal activity, which was more reduced in obese subjects than in control subjects[29].

Finally, in another study with fMRI, an attempt was made to evaluate the neurophysiological correlates of "the pleasure of eating", which would consist of two phases: a first phase characterized by anticipation of the reward and a second phase involving the consummation of that anticipation by eating. As dopaminergic areas are involved in both phases, including the amygdala and ventral striate or nucleus accumbens, the results suggest that the activity of these areas was greater in the phase of anticipation than after receiving the reward[30]. These data should be taken into account in studies of the differences between states of hunger and satiety.

CONCLUSIONS

Neuroimaging studies, especially fMRI, in eating behavior disorders suggest that the distortion of the body image that these patients have could be explained by a difference in cerebral processing of the body image concept at both the perceptual and emotional level, corresponding to a neuronal level with less activity in key areas: the insula

(representation of the body scheme), dorso-lateral prefrontal and cerebellum (cognitive processing), and the parahippocampal and fusiform gyri (both involved in processing emotions). A reduction of perceptual processing could underlie the distorted vision, whereas insular inactivity could be the cause of failure of the feedback loop in correcting this alteration of personal image. On the other hand, the aversive stimuli for the subject apparently cause an increase in cerebral activity at the level of the amygdala, the zone where anxiety processing is located. In the case of patients with eating behavior disorder, these alterations seem to be related to both foods with a high calorie content and personal body image. As regards the normalization of these neural correlates after clinical recovery from the disease, evidence suggestive of the existence of different cerebral substrates for the disease state and the vulnerability trait has been found, although it is difficult to draw significant conclusions. Thus, the medial prefrontal response to one of the specific disease stimuli is present after recovery and may represent a trait marker, whereas the lateral prefrontal and antero-dorsal cingulate activity is greater after clinical improvement, which suggests that it is a state factor of the disease. These findings are very interesting but many of them are inconclusive, so investigation in this line must continue in order to identify the brain areas involved in the clinical syndromes that characterize EBD. Better knowledge of the possible causes of these conditions might allow us to make advances in their therapy.

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