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Revisión

Executive functions in anorexia nervosa

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Abstract

Introduction: **The pathophysiologic mechanisms that account for the development and persistence of anorexia nervosa (AN) remain unclear. With respect to the neuropsychological functioning, the executive functions have been reported to be altered, especially cognitive flexibility and decision-making processes.**

Objectives: **The aim of this study was to review the current state of the neuropsychological studies focused on anorexia nervosa, especially those highlighting the executive functions.**

Methods: **This was done by means of a searching process covering three relevant electronic databases, as well as an additional search on references included in the analysed papers. Eventually we have to mention other published reviews and a hand-search.**

Results and discussion: **Comparing AN patients and healthy controls the results remain controversial and so remains the comparison of different eating disorders with respect to the neuropsychological dysfunction. The role of variables such as depression, anxiety and obsessionality needs to be clarified. There seems to be some base to state that some commonalities exist in the so-called extreme weight conditions (anorexia, obesity). The link between neuropsychological dysfunction in AN and biomarkers remains unclear. The role of neuropsychological deficits in AN, as initial factors or simply as mere consequences, remains unclear too. The link between the body image disturbances and the neuropsychological dysfunction needs to be clarified. The similarities between the AN neuropsychological dysfunction and that found in other mental disorders may be considered up to date as a mere approach. The same applies to the relationship between the AN patients' neuropsychological performance and personality or gender.**

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FUNCIONES EJECUTIVAS EN LA ANOREXIA NERVIOSA

Resumen

Introducción: **Los mecanismos fisiopatológicos que explican el desarrollo y la persistencia de la anorexia nerviosa (AN) siguen sin estar claros. Con respecto al funcionamiento neuropsicológico, se han señalado alteraciones en las funciones ejecutivas, especialmente en la flexibilidad cognitiva y en los procesos de toma de decisiones.**

Objetivos: **El objetivo de este trabajo fue revisar el estado actual de los estudios neuropsicológicos sobre anorexia nerviosa, especialmente los centrados en las funciones ejecutivas.**

Métodos: **Se realizó un proceso de búsqueda con tres relevantes bases de datos electrónicas, así como una búsqueda adicional con las referencias incluidas en los documentos analizados. Finalmente hay que mencionar otras revisiones ya publicadas y una búsqueda manual de otras fuentes.**

Resultados y discusión: **Los datos de comparación de pacientes y controles sanos siguen siendo controvertidos, así como la comparación entre los diferentes trastornos de la alimentación con respecto a la disfunción neuropsicológica. El papel de variables como depresión, ansiedad y obsesividad necesita ser aclarado. Parece que hay alguna base para afirmar que existen algunos puntos en común entre los llamados trastornos de peso extremo (anorexia, obesidad). El vínculo entre la disfunción neuropsicológica en AN y biomarcadores aún no está claro. El papel de los déficits neuropsicológicos en la AN, como factores iniciales o simplemente como meras consecuencias, tampoco está aclarado. La relación entre los trastornos de imagen corporal y la disfunción neuropsicológica debe asimismo aclararse. Los datos sobre las similitudes, en cuanto a la disfunción neuropsicológica, entre AN y otros trastornos mentales pueden ser considerados, hasta la fecha, como una mera aproximación. Lo mismo ocurre con la relación entre el rendimiento neuropsicológico de los pacientes con AN y la personalidad o el género.**

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Palabras clave: *Anorexia nerviosa. Neuropsicología. Rendimiento cognitivo. Flexibilidad cognitiva. Set shifting. Toma de decisiones. Planificación.*

List of abbreviations

AN-p: Anorexia Nervosa-purging type.
AN-r: Anorexia Nervosa-restrictive type.
AN: Anorexia Nervosa.
BMI: Body Mass Index.
BN: Bulimia Nervosa.
CNS: Central Nervous System.
ED. Eating Disorders.
EDNOS: Eating Disorders Not Otherwise Specified.
EWC: Extreme Weight Conditions.

Introduction

Anorexia nervosa (AN) is a severe mental pathology being characterized by a pathological concern with body shape and weight above all. The possibility that there is a dysfunction of the Central Nervous System (CNS) in patients with AN has been explored in several ways, including neuropsychological studies. Thus, several studies assessing the relationship between cognitive processing and certain eating behaviours have been conducted, aiming to achieve a better understanding of the pathophysiology of AN.[1,2]

The specific pathophysiology of AN is not completely known, taking into account that different factors seem to be involved.[2] Up to the date AN has been described on the basis of clinical phenotypes (for example restrictive- vs. purging-type). As far as the aetiology is concerned that description seems to be not effective enough.[3] As a consequence, new ways of study seem to be necessary.[4] In this regard, some authors have suggested these potential new focuses, thus mentioning the study of endophenotypes, the disease-associated traits more useful to determine the relationship with underlying genes and neuropsychological functions.[3,5] It has been said that neuropsychology might lead to an explanatory model of AN.[6]

Neuropsychological studies in AN have supported the hypothesis of a disturbance on the inhibitory control–emotional regulation–executive function circuit.[7] In AN, a relevant cognitive trait appears to be executive dysfunction, which includes three specific neurocognitive elements: decision-making, response inhibition and cognitive flexibility.[8-11] Thus, AN has been consistently associated to alterations on attentional and executive functioning (mainly set shifting and decision-making).[1] In addition some facets of executive functioning, such as cognitive flexibility, have been considered as a risk indicator and are believed to be a possible endophenotype in AN.[12]

Alterations in decision-making, response inhibition and cognitive flexibility in AN highlight the importance of an adequate executive functioning to maintain an proper control of eating behaviour.[7] Executive functions have a biological base (prefrontal brain circuits), which involves different cortical areas such as dorsolateral prefrontal, anterior cingulated and orbitofrontal.[13] A question raised is if differences in these areas could imply different degree of vulnerability.

May be that the most important question is if the neuropsychological findings reported in AN are reversible with an appropriate treatment, so are cognitive deficits an expression of traits or a mere consequence emerged during the course of the disorders?[1] Besides some studies, which have reported that cognitive deficits diminish after weight restoration,[14-17] others [18-20] have not observed such an improvement. As a consequence, a repeated question emerges: What do neuropsychological deficits represent in AN? Are there state-related deficits and trait-related deficits?

The aim of this study was to review the current state of the neuropsychological studies focused on the executive functions in AN.

Methods

Searching process

The searching process covered three relevant electronic databases (Medline, EMBASE and PsycINFO). The general strategy included terms related to anorexia nervosa and neuropsychology. Then some key words and the Medical Subjects Headings were used as well as the Boolean operators AND/OR. The shared terms were ("Anorexia nervosa"[Mesh]) AND ("Decision making"[Mesh]) OR ("Response inhibition") OR ("Cognitive flexibility") OR ("Executive function"[Mesh]) OR ("Planning") OR ("Working memory"[Mesh]).

Additional search was carried out on references included in the papers, published reviews and via hand searching. Literature search was not limited to particular years.

Studies meeting the following criteria were included in the review: (1) studies focused on anorexia nervosa and executive functions; (2) controlled trials and randomized controlled trials as well as cross-sectional studies. Applied exclusion criteria included: (1) case reports; (2) interventions targeting populations with other eating disorders; (3) participants with severe comorbidities; (4) neuroimaging- and neurophysiology-based studies; (5) not available full text. Reviews and meta-analysis were considered as other source of articles, which fitted the inclusion criteria.

The initial search yielded 189 references. These were combined in an EndNote 9 library and screened on the basis of title and abstract; those clearly not meeting the review criteria were excluded as well as duplicates. Thereafter, selected references were screened based on full text. Reasons for exclusion were applied and seventy studies were finally included.

Procedure

Taking into account the most used neuropsychological tests focused on the explored functions, those stud-

ies including the Wisconsin Card Sorting Test (planning, cognitive flexibility, ability of shifting among stimuli and control of impulsive responses not aimed at achieving and objective), the Stroop Colour and Word Test (inhibition and switching skills) and the Iowa Gambling Task (decision making, risk and reward and punishment value) were specially considered.

A thematic analysis was used to analyse the papers. The six-step framework of Braun and Clarke[21] were followed for this proposal: becoming familiar with the data; creating initial codes; searching for themes; reviewing themes; defining and naming themes and producing the report. Fragments of data that identify a significant feature of such data were acknowledged and grouped together into related themes.[21,22] As a result, the following different topics were obtained: a) Cognitive deficits in AN: Are they generally confirmed? ; b) Are there any differences between the cognitive deficits in AN and those found out in other ED? ; c) Variables usually associated to cognitive deficits in AN; d) Is there any support for the continuum spectrum of ED based on the findings of cognitive disturbances-related studies?; e) Biological bases of cognitive alterations in AN; f) Do cognitive deficits precede the onset of AN or are they a mere consequence (e.g. of starvation)?; g) Is there any relationship between cognitive deficits and body image disturbances in AN?; h) Are cognitive deficits in AN similar to those found out in other mental disorders?; i) Personality and gender.

Results

Cognitive deficits in AN: Are they generally confirmed?

Despite cognitive functions such as decision-making have been reported to be reduced in ED, some authors[23] have found out no significant differences in the Iowa Gambling Test when compared ED patients (including AN, n = 49) and healthy controls. These authors suggest that previous reported alterations could be related to other clinical characteristics. It must be noted that patients included in this study were euthymic and free of psychotropic medication. Similarly, Kingston et al. did not find differences between AN patients and controls by means of cognitive flexibility tasks.[19]

Other studies have found out that AN patients perform worse than healthy controls, for example in set-shifting tasks,[24,25] visuospatial memory and central coherence,[26] visual constructional ability[27] and ability to master a conflict situation over time.[28]

Are there any differences between the cognitive deficits in AN and those found out in other ED?

In the case of bulimia nervosa (BN), decision-making abnormalities and executive reductions can be demonstrated and might be neuropsychological correlates of the patients' dysfunctional everyday-life decision-making behaviour.[29] By means of the Iowa Gambling Test, AN patients, BN patients and obese patients have shown significant impairment comparing to healthy controls, the three groups not being significant different from each other.[30] Recently, by means of the concept of "extreme weight conditions" (EWC) executive functions have been explored with the Iowa Gambling Test, the Wisconsin Card Sorting Test and the Stroop and Word Test. As a result, authors conclude that EWC (AN and obesity) have similar dysfunctional executive profile.[7] In a recent review, both AN patients and BN patients are reported to show cognitive deficits. Nevertheless it seems that cognitive rigidity is more frequent in AN patients and alterations in decision-making or central coherence are more often found out in BN.[31] Within the group of patients with AN, the cognitive profiles of restrictive (AN-r) and purging (AN-p) types seem to be different. By means of the Block Design and Object Assembly, AN-r perform significantly worse than AN-p. In addition no differences were found between AN-p and healthy controls. Exploring set shifting there were not differences among the three groups.[32] Including AN-r, AN-p, BN and healthy controls, cognitive flexibility and motor inhibition have been shown to be unaltered in BN patient while AN patients showed a deficient motor inhibition compared to healthy controls.[33] Others, studying four groups of patients (AN-r, AN-p, BN and Eating Disorders Not Otherwise Specified -EDNOS-), have not observed differences in executive functions among them.[34] It must be noted that only 30% of the patients showed impaired performance in executive functions.

Variables usually associated to cognitive deficits in AN

Different variables have shown to be associated to cognitive rigidity and decision-making impairments in AN patients. In this regard, illness duration is associated to the score on the Hayling Sentence Completion Task. It seems to be a partial effect of years of education and body mass index (BMI) on neuropsychological performance as a whole (including Trail Making Test, Wisconsin Card Sorting Test, Iowa Gambling Test and the Hayling Sentence Completion Task). In addition, response inhibition processes and verbal fluency impairment were not associated to BMI and years of education but were associated to depression severity.[35] With respect to the depression symptoms, Giel et al. have found out that set-shifting ability was intact in AN patients without comorbid depression. On the contrary, patients with depression performed significantly poorer in the three tasks (Trail Making Test, Wisconsin Card Sorting Test and a Parametric Go/No-Go Test). The authors concluded that impairments of set-shifting ability in AN patients may partly be due

to comorbid depression disorders.[36] Another variable to consider, which have shown to be associated to the impairment in executive functions, is state anxiety.[34] In the study of Wilsdon et al., three groups were examined (AN patients, women who were high in obsessionality and women who were low in obsessionality) with no significant differences among the groups in executive functions (as measured with the Wisconsin Card Sorting Test). When controlling for depression and obsessionality, AN patients and the high-obsessional group showed significantly more perseverations. Depression appeared to supress variance that was irrelevant to the prediction of perseverance thus enhancing the importance of group membership.[37] Finally, the concept of metacognition has been related to the neuropsychological basis of insight into illness in AN patients, suggesting that metacognition might be an important mediator between basic cognitive deficits and poor insight.[38]

Is there any support for the continuum spectrum of ED based on the findings of cognitive disturbances-related studies?

A continuum model has been proposed for ED, this model comprising of from anorexia nervosa to stable obesity. In this continuum the different subtypes of eating disorders are included, so AN-r, AN-p and BN along with obesity frame the continuum spectrum. According with this theory, all patients included in the spectrum may share certain neuropsychological features, for example those relate to executive functions. In this regard it has been shown that different ED patients have reduced ability on tasks such as the Rey-Osterrieth Complex Figure or the Tower of London Task.[27] In the case of BN and obesity, decision-making disturbances and executive reductions have also been demonstrated.[29,30] Cserjési reported a common deficit in attention capacity in both AN and obesity, specifically when considered shifting capacity and mental rigidity (associated to frontal lobe based executive functions).[39] The recent study of Fagundo et al. highlights a similar dysfunctional executive profile with respect to the extreme weight conditions (AN and obesity).[7] Despite considering similarities, the review of Idini et al. concludes that cognitive rigidity would be more frequent in AN while alterations in decision-making or central coherence are more often found out in BN.[40]

Biological bases of cognitive alterations in AN

A sort of meeting point has been established between overeating and under eating, which would be the dopamine brain reward system. To sum up, impairments on decision-making, response inhibition and cognitive flexibility lead to unsatisfactory control of eating behaviour.[7] In this regard, different studies have reported some biological bases of the neuropsychological impairment thus leading to a research of biomarkers. In this field of study, Dmitrzak-Weglarz et al. have found out significant correlations between neurotrophin factor 4 and glial cell line-derived neurotrophic factor serum levels and executive function as measured by the Wisconsin Card Sorting Test.[41] Seeking those biomarkers, the effect of a functional polymorphism (Val158Met) in the catechol-O-methyltransferase gene on the set-shifting abilities in AN have been explored. In this regard, only in the underweight AN patients that polymorphism affected cognitive performance. Moreover underweight AN patients who were Met homozygotes had significantly higher levels of perseveration.[42]

The suggested substantial genetic influence for AN are based on works with results mainly inconsistent. Trying to investigate the neurocognitive endophenotypes approach of AN, Galimberti el at. analysed functions such as decision-making, set-shifting and planning in AN patients. Impaired performance on the Iowa Gambling Test and the Wisconsin Card Sorting Test were found out in AN patients and their relatives. Nevertheless planning kept preserved. Applying a heritability index, the results suggest a genetic effect influencing the performance in the case of the Iowa Gambling Test but not in the case of the Wisconsin test. The authors concluded the presence of a shared dysfunctional executive profile in AN patients and their unaffected relatives. This dysfunction is shown by way of deficient decision-making and set-shifting, suggesting that these impairments might constitute biological markers for AN.[43]

The link between neuropsychological dysfunction in AN and biomarkers remains unclear. Considering that animal studies have established that glutamatergic pathways in the prefrontal cortex play an important role in set-shifting ability, Nakazato et al. tried to determine whether serum concentrations of glutamatergic neurotransmission-related amino acids were associated to set-shifting ability un both acute and recovered AN patients. As a result the authors did not found correlation between serum glutamine concentration and set-shifting performance.[44] In other study, Nakazato et al. measured serum brain-derived neurotrophic factor and set-shifting again in both current and recovered AN patients. In the same line, there was no significant correlation between serum brain-derived neurotrophic factor concentrations and performance on the Wisconsin Card Sorting Test.[45]

Do cognitive deficits precede the onset of AN or are they a mere consequence (e.g. of starvation)?

There are studies, which have reported that as a result of treatment patients did not improve their cognitive performance.[18] Other studies have reported the impaired cognitive functions to be improved but with an absence of association between cognitive and clinical rectifications, leading the authors to suggest the

existence of mediating factors.[24] In the same line that improvement seems not to be associated with changes in BMI.[46] In other cases a persistence of some altered cognitive functions has been observed after weight restoration.[47] With respect to set-shifting tasks in AN, Tchanturia et al.[48] have concluded that difficulties in these tasks did not show any improvement follow re-testing after weight recovery.

Recent studies try to direct the attention to the neuropsychological impairments as predisposing factors and/or specific eating disorder-related findings. An example of these efforts to search endophenotypes of ED is the several articles of Lopez et al. about the concept of central coherence.[49-51] Nevertheless, the potential confounding factors, comorbid pathologies, use of different medications, etc. make difficult to ascertain conclusions.[23]

Aimed to summarize these controversial results, Duchesne et al. conclude that some cognitive dysfunction tend to disappear after treatment, thus supporting the hypothesis that these are functional deficits. Nevertheless, other deficits tend to persist, so they might precede the development of ED or even contribute to their development or to a worse prognosis.[2] In this line, the study of Favaro et al. shows that starvation affects dopamine release in the prefrontal cortex of AN patients with different effects on executive functions according to the catechol-O-methyltransferase genotype.[42] Respecting set-shifting performance, some findings suggest that this function may be a consequence of AN.[52] On the contrary, Tchanturia et al. suggest that impaired executive function in terms of set-shifting tasks could represent a vulnerability factor.[53] Similarly, Tenconi et al. did not find any differences among long-term recovered individuals, weight restored AN patients and those in acute phase with respect to set-shifting tasks with poor performance in the three groups. The authors suggest that set-shifting and central coherence seem to be promising cognitive endophenotypes of AN.[54] In the follow-up study of Gillberg et al. AN seems to be associated to a range of neuropsychological alterations that remain present long after the AN per se is no longer an important feature[17] Another longitudinal study showed that ten years after the AN onset, patients had poor results on the Object Assembly Test, thus indicating weak central coherence with a tendency to focus on details at the expense of configural information.[55] With respect to planning, it has been shown that this function remains impaired even after full recovery from AN.[40]

On the contrary Hatch et al. concluded that cognitive impairments in AN patients appear to normalize with refeeding and weight gain.[56]

Is there any relationship between cognitive deficits and body image disturbances in AN?

There is a shortage of studies based on the relationship between neurocognitive deficits and neurological bases of body image disturbances. Studying the body schema, it has been reported that AN patients may have subtle cognitive dysfunctions which could interact with processing of body-schema-related information. In addition it is suggested that body image distortion may not be secondary to bottom-up perceptual disturbances.[57]

Body image disturbances in AN patients have been shown to be related to frontal alterations, specifically these disturbances might be linked to the alterations of abstraction and critical abilities and with an obsessive frontal functioning. Pathological preoccupation with body shape would lead to intensive focus on the body and the search of perfection, which is typical of rigid personalities.[58]

Are cognitive deficits in AN similar to those found out in other mental disorders?

Gillberg et al. studied a group of AN patients in which there was a subgroup of participants with autism spectrum disorders. In that subgroup there were cases with test profiles similar to those observed in autism and Asperger syndrome.[55] The study of Oldershaw et al. adds similar data. In this case, by means of Wisconsin Card Sorting Task to assess executive function, cognitive profiles of the two groups (AN patients and published data about autism spectrum disorders) were similar with respect to executive functions.[59] Considering AN-r, it has been reported that theses patients have several common features (shifting capacity, mental rigidity) with anxiety disorders.[39] The deficient motor inhibition found out in AN patients has been considered to be similar to the cognitive profile of obsessive-compulsive spectrum disorders.[33]

Personality and gender

Pignatti et al. have indicated that there exists a relationship between cognitive rigidity and fixed psychological traits in AN patients. Specifically perfectionist stable traits support this idea as excessive cognitive control can either improve or damage set-shifting and decision-making procedures.[60]

As far as we know, the study of Tchanturia et al. is the only one devoted to clarify the role of gender in this field of study. Concretely they studied decision-making by means of the Iowa Gambling Test and they found out that both male and female AN patients performed significantly worse than healthy controls. Despite male had higher impulsive scores, that impulsivity did not predict poor decision-making performance. The authors concluded that both males and females had a similar decision-making performance.[61]

Discussion

Many studies have reported deficits in executive functions in AN patients[37,58,60-64] generally related to

fronto striatal systems. In two previous reviews, it has been shown that the most repeated results about these deficits seem to involve the dorsolateral prefrontal cortex and the orbitofrontal cortex.[35,65]

Despite being lots the studies in this regard, the fact of finding different results between AN patients and healthy controls remains not to be completely agreed.[23] Patients' characteristics have been an explanation for those who do not find out a worse performance in AN patients. In fact, it has been said that serotonergic drugs might influence the cognitive performances and in many cases patients enrolled in different studies were taking such a type of drugs.

Comorbidity is another factor potentially capable to lead to different results. It is known that depressive symptoms can affect decision-making performance[66] and in many cases this variable has not been taken into account. Moreover there are authors who consider that depressive symptoms do not influence executive functions such as decision-making.[67] Do depressive symptoms affect the decision-making process in AN patients or the eating-related symptomatology? That point seems to remain unclear.

Based of the above-mentioned results it is difficult to catch a general idea about the specificity of the executive dysfunction in AN when comparing with other ED. As a result of the studies of several authors, ED could share a general deficit in executive functions[7,29,30,34] while for others it would have some differences among subgroups of ED.[33,40] Finally, it must be noted that some findings point out that both similar dysfunctions and different dysfunctions might be observed in AN patients compared to other ED.[32] One more time another point in this field of study is not completely consensual.

With respect to the possible variables associated to the cognitive deficits, medications, depressive symptoms, anxiety trait or obsessionality have been involved in the results of different studies. Not always the studies have controlled for these variables adequately[6,62] or these variables have not been considered simultaneously.[34] May be that the main controversial factor to analyse is the one referred to the role of starvation in the cognitive performance. Some authors have found out a correlation between decision-making skills and BMI while others did not report that correlation.[23,68] In this regard, Hatch et al. conclude that cognitive impairments AN patients appear to normalize with refeeding and weight gain.[56] In view of the controversial results in this topic, we agree with Duchesne et al. considering that it might be concluded that some cognitive dysfunctions tend to disappear after treatment while other deficits tend to persist, so they might precede the development of ED or even contribute to their development or to a worse prognosis.[2]

The continuum spectrum of ED is a theory which remain as object of debate. It is not something new. In fact, the notion of a common psychopathology in ED was established in 1982.[69] The concept of extreme weight conditions adds a new element to support that to some extent all ED share psychological, psychopathological and neuropsychological features. In this regard, the study of Fagundo el al.[7] represents a summary about this topic. This study hypothesizes with the idea that cognitive deficits observed in AN and obese patients might partially be an expression of their incapacity to successfully regulate reward and punishment which might be affect the planning every day functioning. Their cognitive performance and their eating behaviour seem to have similarities. Seeking for biomarkers, perhaps the cognitive mechanism underlying the decision-making process in different ED would be different. Impulsivity (obesity) and rigidity (AN) could be the two extremes in which would be possible to place all ED. Summarizing, individuals with either excessive food intake or food restriction show a similar dysfunctional executive profile. Nevertheless, the need to find specific biomarkers has not been followed by successful findings up to date despite having obtained some promising results.[41,42]

Being a core of the AN symptomatology, the shortage of studies focuses on the relationship between neuropsychological functioning and body image disturbances may be the most relevant conclusion. Body image disturbances in AN patients have been related to frontal alterations (abstraction and critical abilities) and with an obsessive frontal functioning. In this regard, morbid concerns about body shape would lead to intensive focus on the body and the search of perfection. It must be noted that a linear correlation has been found out between body image disturbances and the greater rigidity of frontal functioning.[58]

With respect to the neuropsychological findings in AN, several studies have reported similarities with other pathologies such as autism,[55,59] anxiety disorders[39] and obsessive-compulsive disorders.[33] In other cases, the cognitive alterations observed in AN have been related to different levels of depression and anxiety[34,56] as well as to obsessive traits.[35] Considering the obsessive-compulsive spectrum, Cavedani et al. and Liao et al. have suggested that obsessive-compulsive symptomatology would be behind of the Iowa Gambling Test performances while in another study of Cavedani et al. this was not confirmed.[6,62,68] As a result of these finding it might be said that there are some similar findings in other mental disorders, thus is very difficult to state that the neuropsychological findings in AN are strictly specific of this disorder.

The neuropsychological functions in AN have been accompanied by studies based on neuroimaging and neurophysiology in order to correlate structural and functional brain changes with neuropsychological findings.[65,70] Having the enormous amount of involved variables (weight, duration of illness, medications, etc.) in mind, it has been strongly difficult to demonstrate the correlation between brain changes and functional changes. In order to establish a cause-effect relation it would be necessary to develop longitudinal neuroimaging studies as well as more neuropsychological lon-

gitudinal designs. Studies about the cognitive function in AN not only are relevant in order to seek biomarkers, biological traits laying the clinical expression, but just to implement new forms of treatment to specifically focus on the neuropsychological impairment of these patients.[1] The proposed dysfunction in prefrontal circuitry that mediates executive functions, reward and behavioural regulation (not only in AN but also in obesity) could be a starting point to be considered in future treatments.[7]

Conclusions

Different neuropsychological alterations have been described in AN. Nevertheless there are many inconsistencies among studies mainly due to methodological biases. Comparing AN patients and healthy controls the results remain controversial. Bearing in mind different ED, some authors consider several common disturbances while others have reported some differences among them. The role of different variables such as depression, anxiety, obsessionality, etc. needs to be more clarified. There seems to be some base to state that some commonalities exist in the so-called extreme weight conditions (from AN to obesity). With respect to the biological basis of executive functioning alterations, the link between neuropsychological dysfunction and biomarkers remains unclear. The role of neuropsychological deficits in AN, as initial factors or simply as mere consequences, remains unclear too. Another topic, which needs to be clearly improved, is that which refer to the link between the body image disturbances in AN and the neuropsychological dysfunction. The similarities between the neuropsychological dysfunction in AN and that found in other mental disorders may be considered up to date as a mere approach. The same applies to the relationship between the AN patients' neuropsychological performance and personality or gender.

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