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Executive functioning in anorexia nervosa patients and their unaffected relatives

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ABSTRACT

Formal genetic studies suggested a substantial genetic influence for anorexia nervosa (AN), but currently results are inconsistent. The use of the neurocognitive endophenotype approach may facilitate our understanding of the AN pathophysiology. We investigated decision-making, set-shifting and planning in AN patients ($n=29$) and their unaffected relatives ($n=29$) compared to healthy probands ($n=29$) and their relatives ($n=29$). The Iowa Gambling Task (IGT), the Tower of Hanoi (ToH) and the Wisconsin Card Sorting Test (WCST) were administered. Concordance rates and heritability indices were also calculated in probands/relatives. Impaired performance on the IGT and the WCST were found in both AN probands and their relatives, although planning appeared to be preserved. The IGT heritability index suggested the presence of genetic effects that influence this measure. No evidence for genetic effects was found for the WCST. The results suggest the presence of a shared dysfunctional executive profile in women with AN and their unaffected relatives, characterized by deficient decision-making and set-shifting. Concordance analysis strongly suggests that these impairments aggregate in AN families, supporting the hypothesis that they may constitute biological markers for AN. Decision-making impairment presents a moderate heritability, suggesting that decision-making may be a candidate endophenotype for AN.

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1. Introduction

Anorexia nervosa (AN) is characterized by disordered eating behaviors where the patient's attitudes toward weight and shape, as well as their perception of body shape, are disturbed (American Psychiatric Association, 2000). It has been suggested that the clinical phenomena seen in AN reflect executive functioning impairments (Frampton and Hutchinson, 2007). For example, AN patients persist in restrictive behaviors despite serious risks to their health (Fairburn et al., 1999) and despite psychosocial consequences. These pathological eating behaviors reflect their preference to opt for choices that yield high immediate gains in spite of higher future losses, and they can be conceptualized in term of impairments in planning real-life strategies and decision-making abilities (Cavedini et al., 2004). Furthermore, AN patients are characterized by rigidity, perfectionism, compulsive traits, and need for control. These characteristics could be the results of set-shifting impairments (Tchanturia et al., 2012). An increasing number of neuropsychological studies have investigated the relationship between executive functions and disordered eating behaviors (Braun and Chouinard, 1992; Lauer, 2002; Duchesne et al., 2004; Southgate et al., 2005; Tchanturia et al., 2005). Consistent findings have emerged for set-shifting (Tchanturia, et al., 2002, 2004, 2012) (for review see Roberts, et al., 2007) and central coherence (Lopez et al., 2008). Poor set-shifting has also been found in unaffected sisters of women with AN, providing some evidence for this cognitive feature as a candidate endophenotype (Holliday and Tchanturia, 2005; Roberts et al., 2010; Tenconi et al., 2010). Deficient decision-making has been reported in AN patients (Cavedini et al., 2004, 2006; Tchanturia et al., 2007), but recently Guillaume et al. (2010) found normal decision making in these patients, so this neuropsychological domain needs further elaboration. Unfortunately, even if AN pathological eating behaviors strongly suggest an impairment in planning strategies, only one study has investigated this function (Fowler et al., 2006) and no study has been conducted on their unaffected relatives.

At present, findings regarding executive dysfunctions in AN patients remain unclear and many question that remains to be resolved. Particularly, there is uncertainty regarding the reversibility of some neurocognitive impairments after re-feeding. Thus,

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whether executive deficits are state or trait related is a question still unresolved (Lindner et al., 2012; Cavedini et al., 2006).

The use of endophenotype approach may facilitate our understanding of AN executive functioning and pathophysiology. In the last few years, neurocognitive dysfunctions have been considered among the most promising endophenotype candidates in many psychiatric disorders (Leboyer, 2003; Flint and Munafo, 2007; Bulik et al., 2007). This approach is an attractive strategy for the exploration of genetic predisposition because endophenotypes represent a means of dissecting the clinical phenotype into biological variables that are hypothetically more proximal to genetic effect (Leboyer, 2003; Flint and Munafo, 2007). This aspect is even more important if one takes into account that several decades of trying to discover causative genes in AN have, as yet, yielded disappointing results (Slof-Op't Landt et al., 2005; Scherag et al., 2010; Clarke et al., 2012).

Endophenotypes have to be heritable, co-segregating with a psychiatric clinical phenotype in the general population, state independent, and present in unaffected family members at a higher rate than in the general population (Flint and Munafo, 2007). Specific susceptibility gene variants may underlie endophenotypes, which in turn may predispose individuals to develop AN and related conditions. If a characteristic fulfils these criteria but is not proven to be heritable, it is termed a "biological marker" (Holliday and Tchanturia, 2005).

This study was designed to explore simultaneously planning, set-shifting and decision-making in AN patients and their unaffected first degree relatives. We used a test battery composed by the Tower of Hanoi (ToH), the Wisconsin Sorting Card Test (WCST) and the Iowa Gambling Task (IGT). We analyzed the proband/relative concordance rates for the cognitive performances. This is a relatively novel approach and could be useful to better understand the familiality of the neurocognitive traits, but it should not be considered as a measure of heritability since all family members live/lived in the same household and share genes as well as environments. To better understand if these executive functions could be considered a candidate endophenotype for AN, we calculated heritability indices (h^2) using a parent–offspring regression model.

Finally, instead of looking at each neurocognitive performance separately, we analyzed the combination of performances together in order to define complex neurocognitive profiles. Results from this study might provide further supporting evidence for the possible qualification of planning, decision-making and set-shifting performance as a candidate endophenotype for AN.

2. Methods

2.1. Subjects

The study sample consisted of 116 subjects: 29 pairs of AN probands and their unaffected first-degree relatives and 29 pairs of healthy comparison probands and their unaffected first-degree relatives. All participants were female. The AN relatives group consisted of 18 mothers and 11 sisters. In the HC relatives group, there were 15 mothers and 14 sisters.

AN probands were recruited consecutively from a clinical population referred to the Department of Neuropsychiatric Sciences, San Raffaele Hospital, Milan. Inclusion criteria for AN probands were: (a) the willingness to participate and to involve their relatives in the study; (b) diagnosis of AN according to DSM-IV-TR (American Psychiatric Association, 2000); (c) absence of lifetime Axis I diagnosis; (d) absence of mental retardation and/or neurological illness and/or brain injury or trauma; (e) history of drug or alcohol abuse; and (f) age between 18 and 65 years. For 1 year, all patients receiving treatment within the units for the treatment of eating disorders were asked to participate in the study. During a clinical interview, a senior psychiatrist verified if patients fulfilled all inclusion criteria and administered the Mini-International Neuropsychiatric Interview (MINI-DIS) (Sheehan et al., 1998), a well-validated screening instrument for Axis I disorders. If patients satisfied the study's inclusion criteria, with their permission, the relatives were contacted and invited to take part in the study. If the patient had more than one sister, the sister closest in age was recruited. In order to participate in the study, AN relatives had to satisfy the same inclusion criteria of their probands (excepted for AN diagnosis). Fourteen patients satisfied criteria for AN restricting subtype (AN-Re) and 15 patients for binge-purge subtype (AN-Be). All patients were unmedicated.

HC probands of normal weight with no history of eating disorders and their relatives were recruited in the local community. Exclusion criteria were: (a) lifetime Axis I diagnosis according to DSM-IV-TR (American Psychiatric Association, 2000); (b) history of mental retardation; (c) neurological illness; (d) brain injury or trauma; (e) history of drug or alcohol abuse; and (f) age between 18 and 65 years. During an interview, a senior psychiatrist verified if HC probands and their relatives fulfilled all inclusion/exclusion criteria and administered the MINI-DIS (Sheehan et al., 1998).

This study was designed in accordance with the Declaration of Helsinki and approved by the Milan Area Health Authority Ethics Committee. Written informed consent was obtained from all participants after the procedure had been fully explained.

2.2. Assessment

In AN probands, severity of illness was assessed using the Yale–Brown–Cornell Scale for Eating Disorders (Mazure et al., 1994) and the body-mass index (BMI), expressed as kg/m^2, was measured for each patient. Onset and duration of illness were also collected.

The following validated neuropsychological tasks were administered: (1) the Iowa Gambling Task (IGT) (Bechara et al.,1994), which assesses decision-making, the ability to acquire a preference through reward and punishment as represented by money gains and losses; (2) the Tower of Hanoi (ToH) (Shallice, 1982), which assesses planning, the ability to achieve a goal through a series of intermediate steps; and (3) the Wisconsin Card Sorting Test (WCST) (Bergh, 1948), which explores set-shifting, the ability to shift to a different thought or action according to the situation's context. A full description of the administered tasks is provided in a previous publication (Cavedini et al., 2010).

2.3. Procedure

If participants satisfied the study's inclusion criteria, executive functions were then assessed. The neuropsychological tasks were administered by a trained psychologist in a single session and in a randomized tasks sequence. The complete testing session never lasted more than 90 min, and all participants completed the tests without problems of cooperation or fatigue.

2.4. Statistical analysis

Data were collected and analyzed using the Statistica 6.0 software package (StatSoft, Inc., Tulsa, Oklahoma). The four groups were compared on demographic and neuropsychological variables by using an analysis of variance (ANOVA).

Analysis of data from relatives pairs need to account for the fact that measures are not independent. Because members of the same family share a number of characteristics, observations from the same family pair might be positively correlated. We deal with this by using ANOVA to compare exclusively AN vs. HC probands, AN vs. HC relatives and AN relatives vs. HC probands. Since age might potentially influence neuropsychological performances, this variable was included as a covariate to control for this potential confounder factor.

The *t*-test for dependent groups was used to carry out comparisons between probands and relatives in both groups, because of the lack of independence between family members.

In order to exclude possible differences in neuropsychological performances, using the same statistical model, we compared performance of mothers vs. sisters, probands vs. sisters, and probands vs. mothers in both clinical and healthy groups.

In a subsidiary analysis, to assess the possible influence of clinical subtype on neuropsychological performances, the ANOVA was used to compare AN patients who met criteria for the Restrictive subtype and those belonging to the Binge-Purge subtype.

Spearman's correlation coefficient was used to determine relationships between clinical variables and neuropsychological test scores.

In a subsidiary analysis, heritability indices (h^2) for neuropsychological tasks were calculated. Since there was no difference in neuropsychological performances between sisters and mothers in both HC-R and AN-R groups (see results Section 3) and considering the relatively small sample size, we used a parent–offspring regression model to estimate h^2 (Falconer and Mackay, 1996; Lynch and Walsh, 1998). Using this model, the slope of the regression line approximates the heritability of the neurocognitive traits when offspring values are regressed against the value in the mother.

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