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PhD Course in Basic and Developmental Neuroscience

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"Eating disorders in childhood and adolescence in the light of clinical and neurobiological findings, typical traits in anorexia nervosa and a brain morphometry study"

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Come sei grato ai miei occhi o cibo che sazi la mia voglia d’amore.
Ti lasci mangiare e io non mi vergogno
della mia preda che è un grande bisogno d’amore.
Alda Merini

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Rational and summary

Research in childhood and adolescence clinical population allows the analysis of the phenomenon in the very beginning of the disturbance in a population in which the effects of the disordered eating have not interfered in a stable manner the neuroendocrine circuits underlying the disease. The nature of eating disorders (EDs) is a controversial issue. A first approach considers EDs as the outcome of dysfunctions in the neuronal processes related to appetite and emotionality (Kaye et al., 2009, 2013). A second approach explains EDs as the outcome of the interaction between cognitive, socio-emotional, and interpersonal elements (Schmidt and Treasure, 2006; Cooper and Fairburn, 2011; Treasure and Schmidt, 2013). The transdiagnostic cognitive-behavioural model proposes that a dysfunctional system of self-evaluation is central to the maintenance of eating disorders (Fairburn, Cooper & Shafran, 2008). Moreover some authors proposed recently an 'impulse control' spectrum model of eating behaviour. Notablely, despite its apparent appeal, body weight may not be the most accurate measure to indicate one's position on the spectrum (Brooks, Rask-Andersen, Benedict, Schiöth, 2012). Neuroimaging techniques have been useful tools for accurate investigation of brain structure and function in EDs.

Specific findings have been a reduction in total gray and white matter volumes in anorexia nervosa (AN) patients compared with healthy controls or the persistence of the gray matter volume changes when weight is restored. A number of regions in the brain help regulate food and weight and previous studies have reported regional brain abnormalities in patients with EDs (Brooks et al., 2011; Joos et al., 2010; McCormick et al., 2008; Suchan et al., 2010). However, the results from these studies are inconsistent, and there is no agreement upon which regions of the brain are most affected. New studies point to the ways only higher human brain regions like the frontal cortex and insula are implicated in the ongoing starvation of AN. These higher brain regions play a crucial role in emotions, personality, and rewards, all of which are thought to be important in anorexia nervosa. It's important to remember also that the temperament and personality traits that might create a vulnerability for developing AN should be taken into account (e.g. attention to detail, concern about consequences, and a drive to accomplish and succeed) (Kaye & Bailer, 2011; Lask, 2000).

This thesis contains doctoral studies about Eating Disorders (EDs) in childhood and adolescence carried out in the past 3 years and has been organized in an introduction and in five different studies.

The aim of the first study was to investigate the prevalence risk for developing AN in a very wide sample of adolescents 15-19 years (17 866 adolescents; 47.8% males; data extracted from ESPAD-Italia®2005 database), obtaining a psychological profile of these at risk subjects, as assessed by the Italian Offer Self-Image Questionnaire (OSIQ). The study also evaluated gender, age, weight, height and eating attitude.

The second, third and fourth Chapters described a multicenter national study carried out in 2012-2013 in Italy aimed to investigate a sample of patients 7-18 years old with an eating disorder to determine if the relationships between Eating Disorders (EDs) diagnosis in childhood and adolescence key factors and core eating disorder mechanisms are transdiagnostic. A comparison to distinguish overlapping and specific factors between the various EDs in children and adolescents was performed using principal component analysis. A mixture of transdiagnostic and disorder-specific processes was implicated in the phenomenology of eating disorders in childhood and adolescence; to evaluate more deeply the model, in Chapters three and four – the subtypes of the classical diagnosis of Eating Disorders were taken in account. These sections are aimed to underline the utility of sub typing analysis in the cognitive-behavioral maintaining factors model of Eating Disorders in childhood and adolescence with a focus on Anorexia Nervosa restricting subtype.

The fifth and last chapter describes a study that stems from the collaboration with the the National Institute of Nuclear Physics (INFN) and concerns a MRI investigation of brain structure in anorexia nervosa. As findings support the utility of the examination on personality subtypes in EDs research, the section described the preliminary steps towards a study of structural magnetic resonance focusing on restricting-type Anorexia Nervosa adolescent patients. The purpose of this section was to undertake an investigation on whole brain volumes of a sample of 24 AN restrictive type (AN-R) adolescent patients using voxel - based morphometry and compare them with a same age and gender sample of 24 healthy control subjects. Moreover we aimed to relate the exploratory results of whole brain volumes and region of interest (ROI) analysis with measures of key features of AN-R adolescent patients.

Introduction

Eating disorders (EDs) which, by definition in the Diagnostic and Statistical Manual of Mental Disorders version 4 (DSM-IV- American Psychiatric Association, APA, 2010) constitute anorexia nervosa (AN) and bulimia nervosa (BN) are typically female adolescent-onset psychiatric conditions. A third type, binge eating disorder (BED) is informally mentioned in the Appendix of DSM-IV, but is included as a third ED in the DSM-V.

Despite obvious physical and behavioral signs, many referrals for eating disorders (ED), are not given a specific diagnosis, but instead labeled with Eating Disorder Not Otherwise Specified (EDNOS) (Fairburn & Cooper, 2011).

Anorexia Nervosa (AN) and Bulimia Nervosa (BN) are recognizable by severe emaciation and uncontrolled eating patterns respectively and the intertwining of the primary behaviors with the psychological and physical consequences of starvation/disregulation represent the core symptomatology of ED. However these indicators are not enough for diagnosis following the current criteria (Becker, Eddy & Perloe, 2009).

Although many of the biological findings in eating disorders can be best understood as results of starvation and disturbed eating behaviors, some are causally linked as risk or maintaining factors. Most eating disorders emerge during adolescence—a vulnerable period of brain reorganization—and malnutrition during this crucial period can negatively affect illness trajectories. Starvation shrinks the brain, and is associated with many behavioral and psychosocial problems such as rigidity, emotional dysregulation, body image disturbance, and social difficulties. Many symptoms resolve with weight gain and when brain mass is restored (Ribases et al., 2005).

Notwithstanding the presence of neuropsychological disturbances in people with ED being known (e.g. ruminations and obsessions about weight, shape and eating), and of personality traits as perfectionism and alessitymia (Bento et al., 2010; Taylor, Parker, Bagby & Bourke, 1996), they are merely eluded to in the diagnostic criteria (Wildes et al, 2011). Diagnosing a specific ED is further complicated by other major psychiatric conditions that share similar clinical symptoms, such as anxiety and depression (Hughes, 2012; Hildebrandt, Bacow, Markella & Loeb, 2012; Spindler & Milos, 2007).

The diagnostic machinery and treatment responses that rely heavily on the DSM-IV EDs criteria to assess improvement in symptoms was re-organized in the last years following the publication of the DSM-V which would be in line with a more transdiagnostic view approach (Keel, Brown, Holland & Bodell 2012; Hebebrand & Bulik , 2011; Birgegard, 2012) but this approach is still widely debated.

DSM-IV subtypes anorexia nervosa by the presence or absence of bulimic symptoms. In the DSM-5, feeding disorders and eating disorders have been integrated into one single category. The criteria for anorexia nervosa have been reworded and the amenorrhea criterion has been removed. The threshold for the diagnosis of bulimia nervosa has been lowered so that once-a-week binge eating and complementary behaviors are now sufficient for a patient to be diagnosed as having bulimia nervosa. Subtyping of bulimia nervosa has been removed. Two new official feeding and eating disorders have been introduced into DSM-5: avoidant/restrictive food intake disorder and binge eating disorder. The definition of and the criteria for feeding and eating disorders given in DSM-5 are an improvement on those used in DSM-4 and should help to reduce the eating disorders not otherwise specified (EDNOS).

The etiology of ED is a controversial issue. A first approach considers ED as the outcome of dysfunctions in the neuronal processes related to appetite and emotionality (Kaye et al., 2009, 2013). A second approach explains ED as the outcome of the interaction between cognitive, socio-emotional, and interpersonal elements (Schmidt and Treasure, 2006; Fairburn, Cooper & Shafran, 2008; Cooper and Fairburn, 2011; Treasure and Schmidt, 2013). Moreover some authors proposed recently an ‘impulse control' spectrum model of eating behaviour. They suggested that it is temperamental dominance that dictates which behaviour is more frequently observed (restrictive vs. impulsive), for example, a person with AN who is generally restrictive, but with bouts of binging and purging. Notably, despite its apparent appeal, body weight may not be the most accurate measure to indicate one's position on the spectrum (Brooks, Rask-Andersen, Benedict, Schiöth, 2012).

The transdiagnostic cognitive-behavioural model proposes that a dysfunctional system of self-evaluation is central to the maintenance of eating disorders. The model suggests that self-worth is largely defined in terms of control over eating, weight or shape, and this overvaluation of the importance of weight and shape maintains efforts of dietary restraint. Inflexible dietary rules are difficult to maintain, and binge eating occurs for some patients as a cognitive control over eating is disrupted. In addition to this core model, additional

mechanisms that include clinical perfectionism and mood intolerance were proposed by Fairburn and Harrison (2003) to maintain eating disorders. The cognitive-behavioral model of eating disorders informs enhanced cognitive-behavioral therapy for eating disorders (CBT-E; Fairburn, Cooper & Shafran, 2008), and early results appear promising for the utility of this transdiagnostic treatment (Byrne, Fursland, Allen, & Watson, 2011; Fairburn et al., 2009).

The transdiagnostic theory suggests that not all maintaining mechanisms operate in all eating disorder patients; some maintaining mechanisms may be more important for some individuals than others. Importantly, whereas maintaining mechanisms may differ at the individual level, the transdiagnostic theory implies that maintaining mechanisms do not differ at the diagnostic level.

This paradigm shift has been undoubtedly buoyed by the continuing advances in our understanding of the underlying neurobiological mechanisms of disordered eating, through genetic studies, and illustrated using technologies that measure brain structure and function.

Neuroimaging data of people with eating disorders could provide evidence that supports a spectrum model of eating disorders. Specifically, the reduced, or at least the dysregulation of striatal dopaminergic circuits, combined with varying degrees of prefrontal-cortex-related cognitive control could contribute to the differential pathologies observed in AN, BN and BED (Kaye & Bailer, 2011; Berridge, 2009; Berthoud & Morrison , 2008).

Contemporary genetic findings may help to explain how these patterns of brain activation occur in people with ED. The proposed candidate genes might in part contribute to better understand the phenotypic expression of ED, but their effects are quite difficult to explore because of the complex gene-environment interactions (Campbell, Mill, Uher & Schmidt, 2011; Bulik et al., 2006).

The most potent risk factor is female gender. How much this association can be attributed to biological rather than social factors is uncertain. Sexual divergence is less pronounced in binge eating disorder (Nazar et al., 2008) and in prepubertal anorexia nervosa (Olivry & Corcos, 1999). Twin and family studies suggest that anorexia nervosa, bulimia nervosa, and binge eating disorder are complex genetic diseases, and for each disorder the estimated heritableility ranges between 50% and 83% (Javaras et al., 2008; Bulik et al., 2007; Bulik et al., 2004). Linkage studies have identified loci for anorexia and bulimia nervosa and for associated behavioral traits such as compulsivity (Bacanu et al., 2005; Bergen et al., 2003; Bulik et al., 2003). About a

third of genetic risk for eating disorders and depression (Wade, Bulik, Neale & Kendler, 2000), anxiety disorders (Keel, Klump, Miller, McGue, & Iacono, 2005) and addictive disorders (Baker, Mazzeo & Kendler, 2007) is shared. Compelling evidence has suggested a role for serotonin system dysfunction in the pathogenesis of eating disorders (EDs), including anorexia nervosa (AN) and bulimia nervosa (BN). Studies have examined the association between EDs and a functional polymorphism of the serotonin transporter gene promoter (5-HTTLPR).

Numerous interrelated risk factors that include also social and familial influences (Krug et al., 2013) have been implicated in the development of eating disorders (EDs). Some epidemiological studies have identified risk and protective factors common to these diseases. A comparison to distinguish overlapping and specific risk factors between the various ED can be difficult because of discrepancies across study designs, samples, diagnostic procedures and risk measures. Some of these shortcomings could be tackled by assessing risk and protective factors for different eating disorders related conditions within the same study. Such an approach is important also for the development of integral prevention and intervention programs, which might result effective for a spectrum of eating disorder problems. At the same time, considering the reported high between-study heterogeneity, future studies should focus on more homogeneous endophenotype.

To this matter two different subtypes of anorexia nervosa are specified, the binge-eating/purging type (AN-BP), in which binge eating is usually associated with purging through self-induced vomiting or misuse of laxatives and diuretics or enemas during the previous 3 months – and - the restricting type (AN-R), in which weight loss is accomplished exclusively through a massive reduction in food intake and excessive exercise over the previous 3 months. AN-R subjects are characterized by starvation and associated internalizing psychopathology that can impact cognitive abilities. The multifactorial etiopathogenesis of AN comprises biological, psychological, and environmental factors (Herpertz-Dahlmann, Seitz, & Konrad, 2011), which are all supposed to be involved in the onset and maintenance of the condition. In particular, the possible role of specific neurobiological alterations has been suggested (for a recent review, see Brewerton, Frampton, & Lask, 2009), as also supported by the evaluation of AN patients' neuropsychological performance (Tchanturia, Campbell, Morris, & Treasure, 2005).

Neuropsychological investigations have found that AN patients are impaired in different cognitive domains, such as visuospatial abilities (Gillberg, Gillberg, Rastam, & Johansson, 1996; Jones, Duncan, Brouwers, &

Mirsky, 1991; Kingston, Szmukler, Andrewes, Tress, & Desmond, 1996; Szmukler et al., 1992), empathic abilities (Gillberg et al., 2009; Russell, Schmidt, Doherty, Young, & Tchanturia, 2009; Tchanturia, Anderluh, et al., 2004), executive functioning (Cavedini et al., 2004; Green, Elliman, Wakeling & Rogers, 1996, Lauer, Gorzewski, Gerlinghoff, Backmund & Zihl, 1999; Tchanturia, Anderluh, et al., 2004), and central coherence (Lopez, Tchanturia, Stahl, & Treasure, 2009). Among executive functioning, a specific weakness in set shifting or cognitive flexibility has been consistently reported in AN patients (for a systematic review, see Roberts, Tchanturia, Stahl, Southgate, & Treasure, 2007). Impaired behavioral response shifting has been related to abnormalities in the fronto-striato-thalamic circuitry of AN patients (Zastrow et al., 2009). Whereas several studies have provided evidence that cognitive alterations in AN patients are present during starvation, empirical support that documents these deficits outside the AN acute phase of malnutrition is more elusive. Reduced set shifting and weak central coherence are thought to be part of the eating disorder endophenotype (Holliday, Tchanturia, Landau, Collier & Treasure, 2005; Lopez, Tchanturia, Stahl & Treasure, 2009), since a selective impairment on these abilities is shared by AN patients, their unaffected sisters, and recovered AN subjects (Tenconi et al., 2010). It has been proposed that these neuropsychological dysfunctions may have specific links with the core clinical characteristics of AN. In particular, impaired set shifting may be linked with the cognitive and behavioral pattern of inflexibility (Roberts, Tchanturia, Stahl, Southgate & Treasure, 2007); weak central coherence may be linked with the excessive preoccupation with detail of body parts, weight, and food composition (Lopez, Tchanturia, Stahl & Treasure, 2008); visuospatial deficits may be related to the distortion of body image (Lena, Fiocco, & Leyenaar, 2004). It has been shown that restrictive or purging subtypes of AN may have different cognitive profiles, with the first characterized by reflective cognitive style and the latter, in keeping with bulimia nervosa, by impulsivity (Kaye, Bastiani, & Moss, 1995; Lena et al., 2004). Previous studies have documented in particular an inaccuracy in the estimation of one's own body parts in patients with anorexia nervosa suggesting that disordered body perception may be a central aspect of AN. However, the neuropsychological bases of such alterations are still unclear.

Neuroimaging techniques have been useful tools for accurate investigation of brain structure and function in eating disorders. Computed tomography, magnetic resonance imaging, positron emission tomography, single photon emission computed tomography, magnetic resonance spectroscopy, and voxel-based morphometry

have been the most relevant technologies in this regard. Specific findings have been a reduction in total gray and white matter volumes compared with healthy controls or the persistence of the gray matter volume changes when weight is restored. Some of these findings suggest that the changes are most likely to be due to neuronal damage secondary to malnutrition, with possible regeneration of myelin accounting for the general reversibility (Lask, 2000). A number of regions in the brain help regulate food and weight. In the hypothalamus, for instance, chemicals like insulin and leptin send messages about hunger and energy balance. With weight loss, the levels of these chemicals become abnormal, signaling that the body doesn't have enough fuel and that the person needs to eat. The evidence suggests that such changes are driven by starvation and serve to conserve energy or stimulate hunger and feeding; they likely do not cause AN. But people with AN seem able to override or ignore signals from lower brain regions like the hypothalamus. New studies point to the ways uniquely human higher brain regions like the frontal cortex and insula are implicated in the ongoing starvation of AN. These higher brain regions play a crucial role in emotions, personality, and rewards, all of which are thought to be important in AN. It's important to remember also that the temperament and personality traits that might create a vulnerability for developing AN should be taken into account (e.g. attention to detail, concern about consequences, and a drive to accomplish and succeed) (Kaye & Bailer, 2011; Lask, 2000).

Research in childhood and adolescence clinical population allows in this context analyzing the phenomenon in the very beginning of the disturbance. Our research can be subdivided into tree main domains: epidemiological studies on Anorexia Nervosa in adolescence (Chapter 1); mantaining factors clinical studies on early EDs diagnosis by means a multicenter national study (Chapter 2, 3 and 4); construction of studies on MRI research on brain volumes data to get further inside in the structural changes of AN restrictive subtype adolescents (Chapters 5).

Chapter 1

Developing Anorexia Nervosa in adolescence. The role of Self-Image as a risk factor in a national prevalence study

1.1 Abstract

Objective: The aim of the present study was to investigate the prevalence risk for developing anorexia nervosa (AN) in a very wide sample of adolescents aged 15–19 years, obtaining a psychological profile of these at-risk subjects, as assessed by the Italian Offer Self-Image Questionnaire (OSIQ).

Method: Data were extracted from ESPAD-Italia®2005 database (European School Survey Project on Alcohol and Other Drugs). The study (17,866 adolescents, 15–19 years old; 47.8% males), also evaluated gender, age, weight, height and Eating Attitude Test-26 (EAT-26). The OSIQ psychometric qualities were evaluated. Multinomial analysis assessed self-image risk of AN association.

Results: Adolescents at risk approached 1.4% (2.2% of girls and 0.5% of boys); 19- and 17-year-old females exhibited a higher prevalence. Overall adolescent risk included: impulse control, family relationships and psychopathology. Critical areas in the AN developing showed age and gender differences: body image for younger females, impulse control for the older, psychopathology for young males and sexual attitudes for the older represented the poorer adjustment dimensions.

Discussion: Results support screening procedures and tailored school-based prevention.

Keywords: Adolescents, School Survey, Self-image, Anorexia Nervosa

1.2 Introduction

Anorexia nervosa (AN) is a condition that primarily impacts adolescents, which may have extremely destructive results. Its morbidity and mortality rates are among the highest and they are associated with significant functional impairment. AN is more frequent in females and it has been traditionally considered as a condition that contributes equally to psychological, biological and sociological dysfunctions (Hasan & Hasan, 2011). A recent review on epidemiological data about eating disorders (EDs) (Smink, van Hoeken, & Hoek, 2012) highlighted girls aged 15–19 as a high-risk group. In fact, the post-pubertal years are a crucial

time of vulnerability. Developmental changes during puberty, stressful events and challenges can elicit EDs (Treasure, Claudino, & Zucker, 2010).

The lifetime prevalence of DSM-IV AN in adults is about 0.6% (0.9% in females and 0.3% in males), and many cases stay undetected in the health-care system (Treasure et al., 2010). Lifetime prevalence among adolescents is higher as compared to adults, especially among girls. Furthermore, these rates significantly increase when cases of broad AN (4.2–5.3%), in which diagnostic criteria for AN are not fully satisfied, are included (Isomaa, Isomaa, Marttunen, Kaltiala-Heino, & Bjorkqvist, 2009; Keski-Rahkonen et al., 2007; Stice, Marti, Shaw, & Jaconis, 2009). Yet, findings from the literature reports vary depending on the sample analysed. The lifetime prevalence rates for the entire population of adolescents range from 0.3% to 0.6% (Stice et al., 2009; Swanson, Crow, Le Grange, Swendsen, & Merikangas, 2011), while for female adolescents rates range from 1.8% to 2.2% (Isomaa et al., 2009; Keski-Rahkonen et al., 2007). Data about male adolescents are poorer and discordant. The lifetime prevalence rates for young men range from 0% (Bulik et al., 2006) to 0.24% (Raevuori et al., 2009); in contrast, another study states that there is no significant difference between males and females (0.3% for both genders); the lack of a female preponderance of EDs could be due in this case to the large female to male ratio for subthreshold AN (lifetime prevalence ratios: male 0.1%; female 1.5%) (Swanson et al., 2011). Although there are some Italian studies on general population (Favaro, Ferrara, & Santonastaso, 2003; Preti et al., 2009), to our knowledge none has been designed specifically for adolescents (Gigantesco, Lega, & Picardi, 2012) except for a study by Cotrufo, Gnisci, and Caputo (2005) that screened a sample of female students aged 17–20 years old, identifying the risk for an ED.

Several environmental risk and maintaining factors have commonly been described among ED subtypes, including low self-esteem, high self-standards, negative social evaluation and social and parental pressure; various authors have suggested assessing the association of several risk factors when analysing those associated with AN (Casper & Offer, 1990; Casper, Offer, & Ostrov, 1981; Gunnard et al., 2012). A very important one is self-image, as highlighted by many authors (Bruch, 1974; Iniewicz,2005; Selvini Palazzoli, 1974). It has been speculated that deficits in self-image (particularly low self-esteem) are possible predictors of the onset of AN and other EDs. It is possible that the focus on weight and eating control is an attempt to

strengthen self-esteem in a period characterised by developmental issues regarding interpersonal relationships and creating an identity.

Several case–control studies of risk factors for AN contributed to building a knowledge base regarding risk for AN. Negative self-evaluation and personal vulnerability traits (Fairburn, Cooper, Doll, & Welch, 1999; Karwautz et al., 2001), negative affectivity, family discord and higher parental demands (Karwautz et al., 2001; Pike et al., 2008) appear to be particularly common and characteristic antecedents of AN.

EDs in childhood and adolescence represent a clinical burden for paediatric and mental health services, and efforts to improve early diagnoses are needed (Nicholls, Lynn, & Viner, 2011; Treasure & Russel, 2011), such as the development and application of instruments able to detect risk factors. The Offer Self-Image Questionnaire (OSIQ; Offer, Ostrov, & Howard, 1981) was found appropriate for profiling adolescents at risk of AN; it was originally designed and validated for the evaluation of adolescents aged between 13 and 19 years old. OSIQ is a self-rating tool that contains evaluative statements referred to a full range of the adolescent's psychological experiences (Offer & Howard, 1972). The tool has the strength to avoid observer bias and research conducted using the OSIQ (Laukkanen, Halonen, Aivio, Viinamäki, & Lehtonen, 2000; Lindfors, Elovainio, Sinkkonen, Aalberg, & Vuorinen, 2005; Patton & Noller, 1994), including Italian studies (Bacchini & Magliulo, 2003), has provided support for the psychometric validity and reliability of this instrument.

Moreover, literature reports that the constructs measured by the OSIQ overlap those measured by other traditional clinical inventories (Coché & Taylor, 1974; Dudley, Craig, & Mason, 1981) and when evaluating adolescents with different psychological problems, the OSIQ results reported different relationships between specific disorders and specific self-image deficits (Casper et al., 1981; Koenig, Howard, Offer, & Cremerius, 1984; Offer, Ostrov, & Howard, 1982; Teri, 1982). The instrument has also been used to measure self-image components in adolescent anorexic subjects (Casper et al., 1981; Erkolahti, Saarijärvi, Ilonen, & Hagman, 2002; Iniewicz, 2005; Steinhausen, 1985; Steinhausen & Vollrath, 1993) and an OSIQ study on EDs have been carried out in Italy as well (Bacchini, Duval, Valerio, & Pasanisi, 2005). Literature reports that, when evaluated with the OSIQ, anorexic subjects showed negative scores in the dimensions of emotional tone, sexual attitudes and social relationships (Casper et al.,1981; Erkolahti et al., 2002); particularly, older

patients showed maladjustment in impulse control, body image and psychopathology (Casper et al., 1981; Steinhausen & Vollrath, 1993).

The aim of the present study was to investigate the prevalence risk for developing AN in a very wide sample of adolescents age 15–19 years, comparing males and females and obtaining a psychological profile of these at-risk subjects, as assessed by the OSIQ. We hypothesise that self-image in anorexic subjects will be much more perturbed than in healthy adolescents and that gender and age will be the main variables involved in the risk for developing AN; we speculate the importance of considering gender and the developmental stages of adolescence, when interpreting the scores of the OSIQ.

1.3 Methods

Recruitment

Data collection was performed by the standardised methodology; participation was voluntary and the target population comprised Italian high-school students aged 15–19 years. The Italian National Research Council (CNR) in the performance of its function and, in particular, in order to achieve the ESPAD-Italia® survey goals, requires the authorisation of the school head, to fill in the ESPAD-Italia® questionnaire by the students. The survey is included in the Scholastic Plan for Education (Decree of the President of the Italian Republic n.275/1999, Art. 8), edited, decided and approved by Collegial Bodies, including teachers, parents and students (Legislative Decree n.297/1994). Data collection was performed by standardised methodology using anonymous self-administered questionnaires completed in the classroom, participation was completely voluntary. None of the students refused to participate in the study. The survey is anonymous and there is no way for any student identification; the students are asked not to put their name on the questionnaire and on the envelope to return the questionnaire. After compiling each student puts the questionnaire into an envelope; soon after envelops are collected by the teacher in charge for the administration and sent in a single shipment to CNR. Given the evidence of the impossibility of any student identification and to trace data collected by each student there is no need for privacy. Sampling and data collection procedures are available in the 2007 European School Survey Project on Alcohol and Other Drugs (ESPAD) Report (Hibell et al., 2009). After completing the standard ESPAD-Italia®2005 questionnaire (41,365 participants; 48.1% males; mean age 17 years, SD = 1.6) (Molinaro et al., 2011), a subsample of students (21,000 subjects) was

asked to complete an additional module composed of the Eating Attitude Test-26 (EAT-26) questionnaire (Dotti & Lazzari, 1998; Garner, Olmsted, Bohr, & Garfinkel, 1982), and the OSIQ (Offer & Howard, 1972). The subsample was randomly chosen from the original sample of ESPAD-Italia®2005 questionnaire and there were no significant differences between this subsample and the original larger sample. Of 21,000 ESPAD subsample students, 17,866 fully responded to the additional modules and there were no significant differences between individuals who fully responded to the additional questionnaires versus those who did not. For Methodological issue of ESPAD-Italia® surveys see also Molinaro, Siciliano, Curzio, Denoth & Mariani, 2012; Siciliano et al., 2012; Bastiani et al.,2013; Scalese et al, 2014.

Dependent variable: risk of developing AN

Adolescents within the 10th percentile of the Body Mass Index (BMI) distribution according to age and gender were defined as underweight (UW). BMI was calculated using the standard formula weight/height^2 (kg/m^2). This conforms with the Italian Society for Pediatric Endocrinology and Diabetes reference population, where subjects whose BMI were <10th percentile are considered as UW (Cacciari, Milani, Balsamo & SIEDP, 2002–03, 2006).

In this study, UW subjects with an EAT-26 score ≥20 were judged to be at risk for developing AN (high-risk group). EAT-26 is an abbreviated 26-item version of the EAT-40, created by Garner et al. (1982). Similar to the EAT-40, a cutoff of 20 was used to separate ED cases from non-cases. Originally developed to diagnose just AN, both the EAT-40 and the EAT-26 have been used as a screening method for non-clinical populations (Latzer & Tzischinsky, 2005) and it is characterised by good correlation between the emotional distress of the subject and his/her body image (Garner et al., 1982; Mintz & O'Halloran, 2000).

Independent variables: self-image

In order to evaluate self-image during adolescence, the Italian form (De Vito, Luzzati, Palazzi, & Guerrini, 1989) of the OSIQ was used. It consists of 130 items, grouped into 11 scales. According to the authors, five different aspects define self-image: the psychological self, the social self, the family self, the sexual self and the coping self (Bacchini & Magliulo, 2003; Offer & Howard,1972).

OSIQ psychometric quality

-Stability of the test: A test-retest methodology was used for a subgroup of the previous national survey, ESPAD-Italia®2004 sample with a gap of 3 weeks between administrations. To estimate the reliability of the

OSIQ a correlation matrix (Pearson's r coefficient) between the two different survey administrations was computed and the mean row scores for each scale were compared with those in the retest (Laukkanen, Halonen, & Viinamaki, 1999). The total sample size in the reliability study comprised 271 students; -Internal validity: Descriptive statistics of the OSIQ measures were computed. To evaluate the psychometric properties of the OSIQ scales the Confirmatory Factor Analysis (CFA) was used. Dimensionality was assessed by γ-index, a proportion of the total variance of the indicators explained by the latent factor. Values > .20 are sufficient to consider the items of the scale as uni-dimensional (Reckase, 1979; Fornell & Larker, 1981). Reliability was assessed as internal consistency using McDonald's Omega (ω) (McDonald, 1999), values ≥ .7 are generally considered acceptable (Fayers & Machin 2000). To examine construct validity, the measure was expressed using the correlation scale-factor (Cor, y; f). A correlation scale-factor > .80 indicates good validity (Nunnally, 1972); -Correlation between scales: A correlation matrix (Pearson's r coefficient) between the various OSIQ scales and the EAT-26 total score was performed.

Exploring the psychometric properties of the OSIQ (De Vito et al., 1989), all the subscales were examined in our research. Results of this study showed a good test–retest reproducibility of OSIQ after a 3 weeks re-administration interval. According to previous studies, internal consistency was good except for morals, sexual attitudes and superior adjustment factors (Laukkanen et al., 1999; Patton & Noller, 1994) which are confirmed as the weaker subscales. Moreover, we consolidated the assumption of unidimensionality in each OSIQ scale using confirmatory factor analysis (CFA) (data not published).

Statistical analyses

Categorical variables are expressed as percentages. Comparisons between groups were made using a chi-square test. Multivariate logistic regression analyses were adopted to assess the association between self-image characteristics, age and sex and risk of developing AN. Data were analysed using SPSS version 17.

1.4 Results

Sample features

The sample analysed comprised 17,860 individuals aged 15–19 years (mean age 17.2 years, SD = 1.42; 47.8% males) who fully completed the questionnaire (data on gender, age, weight and height, EAT-26 and

OSIQ). Characteristics of the sample and of the subjects at risk for developing AN (UW and EAT-26 score ≥20) are reported in Table 1.1.

Table 1.1 Sample features and description of subjects at risk of developing anorexia nervosa (UW and with an EAT-26 score ≥ 20)

		All Sample			UW and EAT-26 ≥ 20		
		Male	Female	All	Male	Female	All
		n = 8530	n = 9330	n = 17860	n = 43	n = 210	n = 253
		%	%	%	%	%	%
Age	15 years	17.3%	16.6%	16.9%	20.9%	11.4%	13.0%
	16 years	18.2%	18.3%	18.3%	9.3%	15.7%	14.6%
	17 years	19.5%	20.0%	19.8%	27.9%	21.4%	22.5%
	18 years	20.0%	20.7%	20.4%	7.0%	18.1%	16.2%
	19 years	25.0%	24.3%	24.6%	34.9%	33.3%	33.6%
Area	North West	28.1%	29.8%	29.0%	20.9%	30.5%	28.9%
	North East	21.0%	24.2%	22.7%	18.6%	23.3%	22.5%
	Centre	19.6%	16.0%	17.7%	20.9%	13.3%	14.6%
	South and Islands	31.30%	29.90%	30.60%	39.60%	32.90%	34.00%

Of the entire sample, 1.4% of adolescents seem to be at risk for developing AN, 2.2% of girls and 0.5% of boys: the group at risk significantly differs from other adolescents regarding gender ($\chi 2 = 97.4$, $p < 0.0001$). Of the females at risk for AN, the 19- and 17-year-olds present the higher prevalence (3.1% and 2.4% respectively). There are no significant prevalence differences in the geographic area of residence ($\chi 2 = 2.419$, $p = 0.490$) between the high-risk and the no-risk group (Table 1.2).

Table 1.2 Prevalence of subjects at risk of developing anorexia nervosa (UW and with an EAT-26 score ≥ 20) within the entire sample, characterized by the main socio-demographic variables

	Boys		Girls		All	
	n	**%**	**n**	**%**	**N**	**%**
15 years	9	0.6	24	1.5	33	1.1
16 years	4	0.3	33	1.9	37	1.1
17 years	12	0.7	45	2.4	57	1.6
18 years	3	0.2	38	2.0	41	1.1
19 years	15	0.7	70	3.1	85	1.9
North West	9	0.4	64	2.3	73	1.4
North East	8	0.4	49	2.2	57	1.4
Central	9	0.5	28	1.9	37	1.2
South and Islands	17	0.6	69	2.5	86	1.6
All Samples	43	0.5	210	2.2	253	1.4

Multinomial analysis

Probability for developing AN is four times higher among females than males (odds ratio [OR] = 3.91, confidence interval [CI] 95%, 2.80–5.46) and increases by 16% (OR = 1.16, CI 95%, 1.06–1.27) with each year in this age group. OSIQ scales positively associated with the risk of developing AN are impulse control (OR = 1.03, CI 95%, 1.01–1.06), family relationships (OR = 1.01, CI 95%, 1.01–1.02) and psychopathology (OR = 1.03, CI 95%, 1.01–1.05). Finally, a poorer adjustment in the Mastery of External World seems to be a protective factor (OR = 0.98, CI 95%, 0.95–0.99) (Table 1.3).

Table 1.3 Multivariate Logistic Model for risk to develop AN, all sample

OSIQ scales	All sample OR (95% CI)*
PS-1 Impulse Control	1.03 (1,01-1,06)
PS-2 Emotional Tone	-
PS-3 Body Image	-
SS-1 Social Relationships	-
SS-2 Morals	-
CS-1 Mastery of External World	0,98 (0,95-0,99)
CS-2 Psychopathology	1,03 (1,01-1,05)
CS-3 Superior Adjustment	-
FS Family Relationship	1,01 (1,01-1,02)
SX Sexual Attitudes	-
Age in years**	1,16 (1,06-1,27)
Gender: famale vs male	3,91 (2,80-5,46)

***** OR value of OSIQ scale must be interpreted for each unit change; ** Continuous variable

Logistic model for risk of developing AN, stratified for gender and age

Stratifying for age and gender, more OSIQ scales become significant when comparing adolescents at risk for developing AN with healthy subjects.

Table 1.4 shows that younger females at risk of developing AN show more issues in body image (OR = 1.05, CI 95%, 1.01–1.08), morals (OR = 1.06, CI 95%, 1.02–1.09) and family relationships (OR = 1.02, CI 95%, 1.01–1.03).

Older females at risk of developing AN have more issues in impulse control compared to other adolescents (OR = 1.06, CI 95%, 1.03–1.10).

Comparing young male adolescents at risk for developing AN versus healthy subjects, poor adjustment appear in the area of psychopathology (OR = 1.12, CI 95%, 1.06–1.18). For the older adolescents, family relationships is a critical aspect of the self-image (OR = 1.06, CI 95%, 1.01–1.12) and a poorer adjustment in the sexual attitudes area is observed in this subgroup (OR = 1.11, CI 95%, 1.03–1.19). Also in this case the OR value of the OSIQ scale must be interpreted for each unit change (Table 1.4).

Table 1.4 Multivariate Logistic Model for risk to develop AN, all sample and stratified for age and gender

OSIQ scales	Girls 15-17 years OR (95% CI)*	Girls 18-19 years OR (95%CI)*	Boys 15-17 years OR (95% CI)*	Boys 18-19 years OR (95% CI)*
PS-1 Impulse Control	-	1.06 (1.03-1.10)	-	-
PS-2 Emotional Tone	-	-	-	-
PS-3 Body Image	1.05 (1.01-1.08)	-	-	-
SS-1 Social Relationships	-	-	-	-
SS-2 Morals	1.06 (1.02-1.09)	-	-	-
CS-1 Mastery of External World	-	-	-	-
CS-2 Psychopathology	-	-	1.12 (1.06-1.18)	-
CS-3 Superior Adjustment	-	-	-	-
FS Family Relationship	1.02 (1.01-1.03)	-	-	1.06 (1.01-1.12)
SX Sexual Attitudes	-	-	-	1.11 (1.03-1.19)
Age in years**	-	-	-	-
Gender: famale vs male	-	-	-	-

***** OR value of OSIQ scale must be interpreted for each unit change

** Continuous variable

1.5 Discussion

This study highlights the possibility of early detection of adolescents at risk of developing AN, and contributes to recent studies on the epidemiology of 'broad phenotype', defined by UW plus a concurrent problematic EAT-26 score, among adolescents. Deficits in self-image specific dimension were associated with the possible onset of AN. The use of a self-reporting questionnaire to analyse a sample of 17,866 students was valuable both for its ease of administration and the reliability of its assessment (Keel, Crow, Davis, & Mitchell, 2002).

Age and gender

Our research was conducted during the peak age of AN occurrence. The age of onset is usually mid-adolescence (Hasan & Hasan, 2011) and in particular among those aged 15–19 years (Smink et al., 2012). Table 1.2 shows that in our sample, the prevalence of adolescents at risk of developing AN is 1.4%. Furthermore, 17- and 19-year-olds females are at greater risk (2.4% and 3.1% respectively). Among males the 17- and the 19-year-old subjects are at a greater risk too (0.7% and 0.7% respectively). These data are consistent with other studies (Isomaa et al., 2009; Keski-Rahkonenet et al., 2007; Stice et al., 2009).

Data from this study show a probability of developing AN, which is four times higher for females. Although these results confirm that anorexia is a female-predominant disease, its impact on men should not be underestimated. In fact, the prevalence of risk in males is about 0.5%. It should also be considered that the diagnostic criteria of anorexia have so far been focused on women. In a recent review, Wooldridge and Lytle (2012) argued that while AN can be considered as a female problem, as much as 25% of the clinical population is male, but research on AN in males is limited.

Macro socio-demographic characteristics

Our results do not show any significant differences in the prevalence of risk of developing AN by geographic location. In Italy, the number of epidemiological studies on EDs at a national level is still limited. Previous studies hypothesised that the degree of urbanisation may have a significant impact on the prevalence on AN in Italy (Cotrufo et al., 2005; Favaro et al., 2003) suggesting that AN would be more common among high degree of urbanisation regions (i.e. North West and Centre). Gigantesco et al. (2010, 2012) reported differences in geographical areas regarding incidence rates within the Italian population. The higher number of specialist services as well as the improvement of quality of care in some regions may have influenced the detection of AN. Yet the link between degree of urbanisation and AN is not establelished and recent studies have demonstrated that urban life is a potential environmental risk factor for bulimia nervosa but not for AN (van Son, van Hoeken, Bartelds, van Furth, & Hoek,2006).

Multinomial analysis

Many studies have shown that self-image in anorexic girls is much more perturbed than in healthy girls (Erkolahti et al., 2002; Iniewicz, 2005; Steinhausen & Vollrath, 1993). Comparing adolescents at risk for developing AN with healthy subjects, the main differences involve age and sex. The likelihood of developing AN for females is four times greater than for males and the risk tends to increase with increasing age. Furthermore, adolescents at risk reported higher scores in impulse control and psychopathology. In detail, among adolescents, the probability of developing AN increases by about 30% for each 10 points of each scale. Moreover, family relationships represent a discriminating feature in the groups of adolescents at-risk. On the other hand, impairment in Mastery of External World dimension seems to be a protective factor. The likelihood of developing AN is 40% lower for each increase of 10 points of the Mastery scale. To our knowledge, no other studies have previously provided such finding and this result is counterintuitive. We

speculate that it could be related to the feeling of competence that develops in the behaviour of control and restriction, typical of the disease.

AN has been associated in some clinical researches with impulse regulation problems. Empirical studies of impulsivity have used both self-report questionnaire and more objective behavioural measures (e.g. reaction time tasks) as indices of different aspects of the multi-dimensional impulsivity construct: women with AN make more errors of commission, indicating impulsivity, than controls. Moreover, some authors proposed recently an ‘impulse control' spectrum model of eating behaviour. They suggested that it is temperamental dominance that dictates which behaviour is more frequently observed (restrictive vs. impulsive), for example, a person with AN who is generally restrictive, but with bouts of binging and purging. Notablely, despite its apparent appeal, body weight may not be the most accurate measure to indicate one's position on the spectrum (Brooks, Rask-Andersen, Benedict, Schiöth, 2012).

Stratified multinomial analysis

As highlighted above, gender and age are the main variables involved in the risk for developing AN. According to this, the second step was to explore differences in the OSIQ aspects among younger, older, male and female adolescents. Authors have suggested the importance of considering gender and the developmental stages of adolescence, when interpreting the scores of the OSIQ (Laukkanen et al., 2000). Previous studies reported that older adolescents at risk of developing AN have more perturbation in impulse control, self-perception and body image, and more general in psychopathology, when compared with other adolescents (Casper et al., 1981). In our study, impulse control is the most impaired dimension for AN at risk older girls (18–19 years), which seems to be the subgroup with a higher risk prevalence (5.1%). It is possible that the characteristics of specific dimensions of self-image in anorexics subjects might change with age for phenomena related to the chronicity of the disease and to the hormonal changes that follow. As the impulse control dimension is usually associated with binge eating/purging behaviours, we could speculate that it would be the expression of the frequent later evolution of AN restrictive type to binge/purging type. The well-known transdiagnostic migration supports the idea that subjects good in controlling their behaviours could, along with age increasing, lose this control. Levels of self control and impulsivity can change over time and this might have important implications for treatment strategies.

Data of this study point out that the risk for developing AN among younger females is associated with the body self-image. Particularly, the likelihood of developing AN is 50% higher for each increase of 10 points in the Self-Iimage scale. A greater impairment in body image is linked to the younger ones due to the recent changes brought about by puberty and may be due to the fear of growing up. These data seem to confirm body distortion and dissatisfaction having a key role in the development of AN among early adolescents (Castellini et al., 2012; Riva & Gaudio, 2012; Sala et al., 2012). Moreover, a weakness in OSIQ Morals dimension among younger females could be attributed to a more general immaturity in the development of the person.

To our data, family relationships represent a risk factor in younger female and in older males. The family problems are more prevalent among these subgroups because of a possible greater dependence on the family. People with AN report less healthy levels of family affective involvement and behaviour control when compared with families of controls subjects and a number of different perspectives have been developed (Bruch, 1974; Maine, 1991; Strober & Yager, 1985). Theorisations of family functioning in this field have focused on the importance of the whole family interactions (Minuchin, Rosman, & Baker, 1978; Selvini Palazzoli, 1974). Family features need to be considered as one of the factors in a multifactorial system for the development of the EDs (Lask, 2000). Research in the value of adding family therapy for adolescent patients with AN has shown promising results (Lock et al., 2010; Smith & Cook-Cottone, 2011).

AN in males is hypnotised to be a more malignant form of illness, requiring a greater loading of biological and environmental factors for its expression compared with that in females (Strober, Freeman, Lampert, Diamond, & Kaye, 2001). To our data for young male adolescents, the impaired area is psychopathology: for each point of increase of the scale, the likelihood for developing AN increases by 12%. Regarding older adolescents, the main risk scale is sexual attitudes followed by the family relationships. Decreased interest in sex, fears concerning sex, conflict over gender identity or sexual orientation could actually be emotional and mental characteristics of AN in males. The markedly higher prevalence of AN among females has encouraged speculation that causative influences may differ between genders. Qualitative observations suggest that, when compared with females, males with AN have more general atypical features such as psychosis or psychotic regression, personality disorder and sexual uncertainty (Ewan, Middleman, & Feldmann, 2014; Fichter & Daser, 1987); for these patients, Strober et al. (2006) reported less concern about

actual weight. Fichter and Daser (1987) observed that 80% of the males in their study grew up in families that regarded sex as a taboo subject. In general, the males with anorexia appeared to identify more closely with their mothers than with their fathers. Moreover, Kearney-Cooke and Steichen-Asch (1990) found that men with EDs tend to have dependent, avoidant and passive–aggressive personality styles. It remains for future study to carry out clinical and biological research to shed additional light on gender effects in the expression of AN.

This study represents a large, school-based sample, in Italy. As such, it expands the existing descriptive knowledge base regarding eating pathology and offers a contribution to understand the prevalence of EDs. In particular, the data comparing risk correlates for males and females of different age class, represents a significant addition to the field of EDs research.

Limits

Several limitations of the study deserve note. The findings that eating and shape concerns, as measured by the EAT, are more common among females than males is not new. Also, it is not new that eating disturbances are associated with self-image.

As a cross-sectional study, this research was able to determine the relationship between OSIQ self-perception aspects and risk for developing AN, but not the causal relationship. A cross-sectional study is like a photograph of a phenomenon and it does not identify the temporal trends of the phenomenon itself and its evolution (as is the case of a follow-up study). The significance of the study results from access to large surveys of Italian high-school students. However, another consideration is that sampling school-based surveys capture only those adolescents belonging to the school environment: thus it may underestimate or overestimate the prevalence within this age cohort. Although self-reported height and weight to obtain BMI has been shown to be a reasonable approximation (Jeffery, 1996), participants self-reported weight and height is considered as a critical issue by some authors because individuals tend to report fake or wrong values regarding weight and BMI (Gorber, Tremblay, Moher, & Gorber, 2007). More generally we can say that self-report based studies tend to measure the self-awareness of the participants and that this kind of measures display the vulnerability to self-reporter bias.

Moreover, this is a screening study and not a clinical analysis. The categorisation criteria for UW are coherent with that stipulated by diagnostic criteria for AN; being UW and having a problematic EAT-26

score profile would represent two central features in the definition of AN, however, there may be factors beyond the ED that affect the condition of UW but also the EAT-26 score, such as particular medical conditions. Analysing subjects by referring to the concept of broad AN phenotype makes it difficult to attain the quality of a clinical investigation and this study could be considered as an assessment of premorbid traits as well. Nevertheless, this issue should also represent strength in the context of the many cases that go undetected in the health-care system (Treasure et al., 2010) and our study could detect the ‘under-threshold disease' population too.

How do the findings reflect on practice and on policy formulation?

Adolescents are disproportionately afflicted by EDs. Since these pathological attitudes are fraught with stigma and secrecy, adolescents have many difficulties in seeking appropriate health care. Young people with AN rarely self-identify, thus help to recognise their problems and increase their motivation for treatment is strongly needed. Due to the unawareness and the lack of confidence of the parents and teachers in the approach of EDs (Rees & Clark-Stone, 2006), more understanding and experience are needed to ensure early detection and intervention (Isomaa et al., 2009; Williams, Goodie, & Motsinger, 2008). School-based intervention could be valuable to screen subjects at risk and to improve prevention programmes (Canetti, Bachar, Gur, & Steind, 2009). Community strategies are also needed to reach those adolescents not attending school.

Our data underline that an effective plan for prevention should consider the specific characteristics of the targeted population. For instance, younger adolescents could present risk factors which are not the same for older ones (in this study: body image, morals and family relationship for females and psychopathology for males). Depending on the target population, it is therefore possible to prioritise the most appropriate variables for intervention. Establelishing the most significant issues, both of high and low influence, is the first step towards a successful intervention: the mismatch between males and females and the analysis of risk factors could be a valuable focus for further research.

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Chapter 2

An evaluation of the cognitive-behavioral maintaining factors model of Eating Disorders in childhood and adolescence: findings from a multicenter national study

2.1 Abstract

Objective: To determine if the relationships between Eating Disorders (EDs) diagnosis in childhood and adolescence, key factors and core eating disorder mechanisms are transdiagnostic.

Method: Young patients (n = 419; mean age 14.7±2.14; age range 7-18 years; males 13.8%) diagnosed with an eating disorder (ED) on the base of DSM-IV adapted to childhood were assessed through standardized instruments (EDI-3, Eating Disorder Inventory-3; EDE 12.0D, Eating Disorder Examination, 12th edition; CBCL, Child Behavior Checklist; CAPS, Child Adolescent Perfectionism Scale; BUT, Body Uneasiness Test) to evaluate key EDs features as low self-esteem, self-oriented perfectionism, interpersonal difficulties, mood intolerance, overevaluation of weight and shape, dietary restraint and binge eating, prior to entering treatment in six Italian clinical centers for EDs in childhood and adolescence. Descriptive statistics to compare mean values of eating disorder factors and mechanism, multiple comparisons between diagnosis, correlation analysis and principal component analysis (PCA) were performed.

Results: Of the entire young patients' collective, 51.5% were diagnosed with Anorexia Nervosa (AN), 12.3% were diagnosed with Bulimia Nervosa (BN) and 36.2% were diagnosed with Eating Disorder Not Otherwise Specified (EDNOS). All the demographic, physical and indicator variables showed significant differences by diagnosis (Kruskall Wallis non parametric test $p<.05$; Pearson chi square $p<.05$). For all the combination comparisons, affective problems, body dissatisfaction, body image concern and shape concern presented no significant between diagnosis differences in their mean values ($p<.05$). Correlation analysis results suggested that low self-esteem, perfectionism, interpersonal difficulties, mood intolerance and overvaluation of weight and shape processes were all strongly related to the core eating disorder maintaining factor in EDs (bulimia and restraint) for all the disorders taken together ($p<.01$). In PCA the first principal component is strongly and positively correlated with six of the original variables: bulimia (0.684), perfectionism (0.709), body dissatisfaction (0.802), low self esteem (0.803), interpersonal problems (0.823) and affective problems

(0.854) scores; the second principal component is strongly and positively correlated with restraint (0.677), shape concern (0.731), body image concern (0.684), self oriented perfectionism (0.635), anxious-depressed (0.612).

Discussion: For young patients the transdiagnostic characteristics of the disorders appear less pronounced than what literature reported for adult patients. To evaluate more deeply the model would be necessary to take in account also subtypes of the classical diagnosis of Eating Disorders.

Keywords: Transdiagnostic; Cognitive-Behavioral Model; Eating Disorders; Childhood and Adolescence

2.2 Background

Transdiagnostic conceptualizations aim to identify processes or maintaining factors that are common across psychological disorders, with the intent to improve clinical treatments (Mansell, Harvey, Watkins, & Shafran, 2009). Fairburn and colleagues have proposed a model which suggests that common mechanisms operate across all eating disorder diagnostic categories, including anorexia nervosa (AN), bulimia nervosa (BN) and eating disorder not otherwise specified (EDNOS) (Fairburn, Cooper, & Shafran, 2008; Fairburn, Cooper, & Shafran, 2003).

Although over the past decade, research efforts led to several evidence for the validity of a transdiagnostic cognitive-behavioral model of eating disorders only a few studies examined the model in children and adolescents patients' population in wich the effects of the disorder have not interfered in a stable manner the neuroendocrine circuits underlying the disorder.

Eating Disorders (EDs) are now one of the most troubling diseases in the Western Hemisphere: they are spreading with remarkable rapidity, affecting an ever larger part of the population in terms of socio-demographic characteristics with a greater economic impact on the national health services (Robergeau, Jill & Silber, 2006). The age of onset of the disease has lowered, with a worsening of the prognosis and the need for differential treatments. International epidemiological studies revealed an increased incidence of EDs in women between 12 and 25 years old, and estimated in western countries, including Italy, the prevalence of Anorexia Nervosa (AN) at 0.2-0.8%, of Bulimia Nervosa (BN) at 3%, and of Eating Disorder not Otherwise Specified (ED-NOS) between 3.7 and 6.4 %. It also appears that the incidence of AN is 4-8 new cases per

year per 100,000 people, and 9-12 for the BN and that the age of onset falls between 10 and 30 years, with a mean age onset of 17 years. The disease is therefore continuing to rise, especially as regards the bulimia and binge eating disorder or BED (Binge Eating Disorder). The male / female ratio has changed and it is estimated to be 1: 9, but the number of males is growing, associated with the delineation of new disorders typical of males (bigoressia or reverse anorexia). Male pathology is in particular increasing in pre-adolescent and adolescent. In recent years, we are seeing a lowering of the age at onset of these disorders that are starting to spread substantially even among children (Lask & Bryant-Waugh, 1993) and self-destructive behavior, often very intense and harmful can be present in this age group. Although the bulimic behaviors and mechanisms of elimination have a very low prevalence (Fisher, Schneider & Burns, 2001; Gowers, Crisp, Joughin & Bhat, 1991) exists in these young patients a "continuum" between bulimia and anorexia and the frequent transition from one disorder to another (Eddy et al., 2008). Some authors (Lask, 1993; Rosen, 2003; Peebles, Wilson, & Lock, 2006) agree in reporting, among children suffering from eating disorders, an increased incidence of other psychiatric conditions such as depression, anxiety or obsessive compulsive disorder.

Although many of the biological findings in eating disorders can be best understood as results of starvation and disturbed eating behaviors, some are causally linked as risk or maintaining factors. Most eating disorders emerge during adolescence—a vulnerable period of brain reorganization—and malnutrition, in particular during this crucial period, can negatively affect illness trajectories.

Despite the presence of neuropsychological disturbances in people with EDs being known (e.g. ruminations and obsessions about weight, shape and eating), and personality traits as perfectionism (Bento et al., 2010), they are merely eluded in the diagnostic criteria (e.g. fear of weight gain and a sense of lacking control) (Wildes, 2011). Diagnosing a specific ED is further complicated by other major psychiatric conditions that share similar clinical symptoms (Hughes, 2012; Hildebrandt, Bacow, Markella & Loeb, 2012; Spindler & Milos, 2007).

Several studies have identified risk, protective and maintaining factors common to these diseases. A comparison to distinguish overlapping and specific factors between the various EDs can be difficult considering the high between-study heterogeneity (discrepancies across study designs, samples, and

diagnostic procedures and factors measures). Some of these shortcomings could be tackled by assessing maintaining factors for different eating disorders related conditions within the same study.

The transdiagnostic cognitive-behavioral core model proposes that a dysfunctional system of self-evaluation is fundamental to the maintenance of eating disorders. Self-worth is largely defined in terms of control over eating, weight or shape, and this over evaluation of the importance of weight and shape maintains exertion of dietary restraint. Uncompromising dietary rules are difficult to maintain, and binge eating behavior happen when cognitive control over eating is wasted.

In addition to this core model, four other mechanisms were proposed by Fairburn and colleagues (2003) to maintain eating disorders. 1) Low self-esteem is proposed to motivate individuals to pursue achievement in the valued domain of weight and shape control to increase feelings of self-worth, thereby maintaining overevaluation of weight and shape. 2) For those with clinical perfectionism, the self is evaluated in terms of achievement in the valued domain of eating, weight and shape, thereby increasing efforts of dietary restraint and overevaluation of the importance of weight and shape. 3) Interpersonal problems may lead to increased efforts of dietary restraint in an effort to control weight and shape and achieve the perceived socially valued ideal. 4) Mood intolerance may encourage binge eating and purging as a way to cope with the experience of intense mood states.

The cognitive-behavioral model of eating disorders informs enhanced cognitive-behavioral therapy for eating disorders and suggests that whereas maintaining mechanisms may differ at the individual level, the transdiagnostic theory implies that maintaining mechanisms do not differ at the diagnostic level (Fairburn, 2008; Byrne, Fursland, Allen, & Watson, 2011; Fairburn et al., 2009).

In the present research evidences from a multicenter national study were used to describe a population of young patients. The analysis of socio-demographic, behavioral and psychological traits related to the core and additional maintaining factors aimed to evaluate a possible preliminary model of "spectrum disorder" of EDs in childhood and adolescence in relation to a possible continuum in characteristics measure. A transdiagnostic approach to the maintenance of eating disorders will be supported if relationships in the model are found to be equivalent in those diagnosed with AN, BN and EDNOS.

2.3 Methods

Methodological aspects of the multicentre study and preliminary descriptive results were published in two project reports of the "Multicenter study on psychopathological features of eating disorders in childhood and adolescence" by Curzio et al. (2013 and 2014).

Study design and subjects

This research was based on a cross-sectional study of 419 children and adolescences subjects at first admission or rehospitalizations in 6 Italian Neuropsychiatry Units with diagnosis of AN, BN, EDNOS, according to the criteria of the DSM-IV adapted to childhood (Bravender et al., 2010). The recruitment period was 18 months.

Clinical units

The National Coordinator Reference Center of the project was the Mediterranean Foundation Stella Maris, Potenza (Italy). The clinical centers were selected considering a geographical criterion and the level of integration of provided services (outpatient, day hospital, residential care units, and hospitalization services) that have given excellent results for organizational requirements and performance.

The Clinical Centers were:

-Childhood and adolescent EDs Care Center Unit of the Division of Child Neurology and Psychiatry, Stella Maris Scientific Institute (IRCSS), University of Pisa – Calambrone (Pisa)

-EDs Care Center "G. Gioia" of the Mediterranean Foundation Stella Maris - Chiaromonte (Potenza)

-EDs Care Center - San Paolo Hospital, Milano

-EDs Care Center "Villa Miralago" - Cuasso al Monte (Varese)

-EDs Care Center "Residenza Palazzo Francisci" – Umbria Sanitary Local Agency 2 (ASL 2) – Todi (Perugia)

-Childhood and adolescent EDs Care Center of Regional importance, Child Neuropsychiatry Unit of Policlinic General Hospital "St. Orsola Malpighi", Bologna

Ethical issues

The study was carried out according to the standards for good ethical practice of the Health Units involved, and was approved by the regional ethical committee board of each clinical centre. Written informed consent from a parent or guardian of each patient was obtained. Patients and their parents completed all the

psychological tests during the first days of the clinical assessment. Data were collected by physicians and psychologists.

Variables

Data collected were related to demographic and physic characteristics and to the evaluation of behavioral and psychological traits related to self-evaluation, control over eating, weight or shape, clinical perfectionism, interpersonal problems and mood intolerance.

Standardized instruments

-EDI-3, Eating Disorder Inventory-3:

It is the latest revision to the Eating disorder inventory. Eating Disorder Inventory-three (EDI-3) was released in 2004. It contains the original items of the first EDI as well as EDI-2; it has been enhanced to reflect more modern theories related to the diagnosis of eating disorders. It was designed for use with subjects aged 13–53 years. It contains 91 items divided into twelve subscales rated on a 0-4 point scoring system. 3 items are specific to eating disorders and 9 are general psychological scales that while not specific are relevant to eating disorders. It yields six composites: Eating Disorder Risk, Ineffectiveness, Interpersonal Problems, Affective Problems, Overcontrol and General Psychological Maladjustment. It is a self report questionnaire administered in twenty minutes (Garner, 2004; Cumella, 2006; Clausen, Rosenvinge, Friborg & Rokkedal, 2011).

- EDE 12.0D, Eating Disorder Examination, 12th edition:

The EDE 12.0D is a semi-structured interview conducted by a trained clinician to assess the psychopathology associated with the diagnosis of an eating disorder. The EDE 12.0D is rated through the use of four subscales and a global score. The four subscales are: 1. Restrain, 2. Eating concern, 3. Shape concern, 4. Weight concern. The questions concern the frequency in which the patient engages in behaviors indicative of an eating disorder over a 28 day period. The test is scored on a 7 point scale from 0-6. With a zero score indicating not having engaged in the questioned behavior (Cooper & Fairburn, 1987; Cooper, Cooper & Fairburn, 1989; Beumont, Kopec-Schrader & Touyz, 1995; Berg, Peterson, Frazier & Crow, 2012).

-CBCL, Child Behavior Checklist:

The Child Behavior Checklist (CBCL) is a widely used method of identifying problem behavior in children. It is a component in the Achenbach System of Empirically Based Assessment developed by Thomas M.

Achenbach (Achenbach & Ruffle, 2000). Problems are identified by a respondent who knows the child well, usually a parent or other care giver. Alternative measures are available for teachers (the Teacher's Report Form) and the child (the Youth Self Report). There are two versions of the checklist. The preschool checklist (CBCL/1½-5) is intended for use with children aged 18 months to 5 years. The school-age version (CBCL/6-18) is for children aged 6 to 18 years. It is an important measure for children's emotional, behavioral and social aspects of life. It is used as a diagnostic tool for a variety of behavioral and emotional problems such as attention deficit hyperactive disorder, oppositional defiant disorder, conduct disorder, childhood depression, separation anxiety, childhood phobia, social phobia, specific phobia and a number of other childhood and adolescent issues. The checklist consists of a number of statements about the child's behavior, e.g. acts too young for his/her age. Responses are recorded on a Likert scale: 0 = Not True, 1 = somewhat or Sometimes True, 2 = Very True or Often True. The preschool checklist contains 100 questions and the school-age checklist contains 120 questions. Similar questions are grouped into a number of syndromes, e.g. Aggressive behavior and their scores are summed to produce a score for that syndrome. Some syndromes are further summed to provide scores for internalizing and externalizing problem scales. A total score from all questions is also derived. For each syndrome, problem scale and the total score, Tables are given that determine whether the score represents normal, borderline, or clinical behavior. These categorizations are based on quantiles from a normative sample (Achenbach & Ruffle, 2000; Adambegan et al., 2012).

-CAPS, Child Adolescent Perfectionism Scale:

The CAPS (Flett, Hewitt, Boucher, Davidson & Munro, 2000) is a 22-item measure based on the multidimensional conceptualization of perfectionism (Hewitt & Flett, 1991).The CAPS subscales measure levels of self-oriented and socially prescribed perfectionism. Participants provide 5-point ratings of their agreement with each item. Research indicates that the Self Oriented and Socially Prescribed Perfectionism subscale scores have test–retest correlations of 0 .74 and 0.66, respectively, and that the coefficient alpha values were 0.85 for the Self-Oriented subscale items and 0.81 for the Socially Prescribed subscale items (Flett et al., 2000). Correlations between the CAPS subscales and the Eating Disorder Inventory Perfectionism Subscale (Garner, Olmstead, & Polivy, 1983) provide evidence of the subscale interpretations of the CAPS scores (Flett, Hewitt, Boucher, Davidson & Munro, 2001).

-BUT, Body Uneasiness Test:

The BUT is a self-administered questionnaire specifically designed to explore several areas in clinical and non-clinical populations: body shape and/or weight dissatisfaction, avoidance, compulsive control behaviors, detachment and estrangement feelings towards one's own body, specific worries about particular body parts, shapes or functions. The BUT consists of two parts: BUT-A (34 items) and BUT-B (37 items). In keeping with previous validation studies the BUT-A scores were combined in a global severity index (GSI) and in 5 sub-scales resulting from factorial analysis: Weight phobia (WP - fear of being or becoming fat), body image concerns (BIC -worries related to physical appearance), Avoidance (A - body image related avoidance behavior), compulsive self monitoring (CSM - compulsive checking of physical appearance), and Depersonalization (D - detachment and estrangement feelings toward the body); BUT-B scores were combined in two global measures (positive symptom total, PST and positive symptom distress index, PSDI) and in eight factors that examine specific worries about particular sets of body parts or functions. Higher scores indicate greater body uneasiness (Cuzzolaro et al., 2006; De Panfilis, Rabbaglio, Rossi, Zita & Maggini, 2003).

Measures

The indicator variables used in the analysis, chosen by children and adolescents clinicians and researchers, were the following:

Low self-esteem was measured using "low self esteem" EDI-3 scale. The EDI-3 low self esteem scale assesses negative self-evaluation, cognitions of worthlessness, hopelessness and personal failure.

Self-oriented perfectionism was assessed using two scales: one from the EDI-3 perfectionism subscale and the other from the CAPS Self Oriented Perfectionism scale.

Interpersonal difficulties were measured using the EDI-3 "Interpersonal Problems" subscale, which assesses difficulty communicating feelings and developing intimate relationships with others and social apprehension.

Mood intolerance was assessed with the following: (i) EDI-3 "Affective problems" scale, which measures emotional dysregulation and interoceptive deficits) (ii) and YSR "Anxious depressed" subscale which measures rapid changes in mood and poor emotional control. The anxious-depressed subscale used in this study was selected because it contained items measuring aspects of both anxiety and depression in childhood and adolescence.

Overevaluation of weight and shape was assessed using three scales, one from the EDI-3, called "Body dissatisfaction", the second from the BUT, "Body image concern" and the third from EDE 12.0D "Shape concern". Dietary restraint was assessed using the EDE subscale "Restraint".

Binge eating was assessed using the EDE bulimia subscale that assesses ‘‘the tendency to think about, and engage in bouts of uncontrollable overeating (i.e., binge eating)’’ (Garner, 2004, p. 14).

Moreover, in order to better characterize the diagnostic groups, we created an index calculated through the relationship between the EDE subscale scores of bulimia and that of restraint (B/R Index=Bulimia+1/Restraint+1).

Data recording

Epidemiology Unit of the Institute of Clinical Physiology of the National Research Council (IFC-CNR) in Pisa (Italy) carried on collection, quality assessment and data analysis. The Unit of Epidemiology developed the software for recording data and the dedicated web interface. All data were collected on printed materials as clinical practice routine. The web based research database was constructed for the study and it remained available for clinicians that accessed it online after having required username and password (https://epid-prod.ifc.cnr.it/ccm). The database was structured as an Electronic Health Record system (EHR) and it is intended to record all anamnestic, clinical, psychosocial and behavioral information about the patient in order to offer a full view about patient’s condition and to allow for detailed analysis. Data were recorded anonymously in the data base with a single subjects identified by a unique number automatically generated; this number was recorded on the printed material for quality controls before statistical analysis. The database is intended to be useful for the present study but also for further research actions. It is indeed constructed following the standard definition of relational database with a set of tables all linkable trough the single subject key identifying. Each table is intended to record information regarding the same thematic area or the same functional/diagnostic evaluation.

Statistical analysis

Data cleaning, checking, and missing evaluation preceded statistical analysis. All categorical data were described as number of subjects and percentage while continuous variables were presented as mean ± standard deviation, median and minimum and maximum values. In the case of categorical variables the Pearson Chi-square test and the Fisher's exact test have been used. In the case of continuous variables (test

scores) the Kruskal Wallis nonparametric analysis of variance was used to evaluate significant differences among diagnosis. Multiple Comparisons between diagnoses were performed by the nonparametric Mann-Whitney U test for continuous variables and Fisher exact test for categorical variables. Correlations among continuous variables were investigated by the nonparametric Spearman's rank correlation coefficient (Spearman's rho), that is a nonparametric measure of statistical dependence between two variables. As the Pearson correlation coefficient the Spearman rho varies between -1 and +1, it occurs when two variables are perfectly negatively or positively correlated with each other. P values adjusted for multiplicity were obtained by the Bonferroni method. All tests were two tailed and a $P<.05$ was considered statistically significant.

A Principal Component Analysis (PCA), based on the correlation matrix and with rotated components by the Varimax method with Kaiser Normalization, was also performed. PCA is a descriptive exploratory technique designed to analyze the pattern of relationships among the variables included in the analysis. Principal component analysis PCA aims to produce a small set of independent principal components from a larger set of related original variables. It is a technique used to bring out strong patterns in a dataset. It's often used to make data easy to explore and visualize.

Principal component analysis (PCA) is a statistical procedure that uses an orthogonal transformation to convert a set of observations of possibly correlated variables into a set of linearly uncorrelated variables called principal components. The number of principal components is less than or equal to the number of original variables. This transformation is defined in such a way that the first principal component has the largest variance (that is, accounts for as much as possible of the variability in the data), and each succeeding component in turn has the highest variance possible under the constraint that it is orthogonal to (i.e., uncorrelated with) the preceding components. The method is mostly used as a tool in exploratory data analysis and also for making predictive models. PCA can be done by eigenvalue decomposition of a covariance or correlation matrix of a data matrix, usually after mean centering (and normalizing or using Z-scores) the data matrix for each attribute. Eigenvalues of the correlation matrix represents a partitioning of the total variation accounted for each principal component. The results of a PCA are usually discussed in terms of component scores, sometimes called factor scores (the transformed variable values corresponding to a particular data point), and factor loadings (the weight of each standardized original variable on each principal component). Factor loadings represent the correlation between the original variables and the

components, and are the key to understanding the underlying nature of a particular factor. PCA is a multivariate analysis (Maestro, Rossi, Curzio, Felloni, Grassi, Intorcia, Petrozzi, Salsedo & Muratori, 2014) able to revealing the internal structure of the data in a way that best explains the variance in the data. If a multivariate dataset is visualized as a set of coordinates in a high-dimensional data space, PCA can supply the user with a lower-dimensional picture, a projection or "shadow" of this object when viewed from its most informative viewpoint. This is done by using only few principal components, usually the first two components, so that the dimensionality of the transformed data is reduced. Variables are represented in terms of the distances between them in a low-dimensional space. The display of the variables in the final coordinate system, for example in the scatter plot of the first two components, provides an indication of the nature of the relationships between them. The interpretation in PCA is often based upon proximities between points in a low-dimensional map (i.e., two dimensions). The proximity between variables means that these tend to correlate together in the observations.

2.4 Results

The final sample comprised 419 children and adolescents (mean age 14.7±2.14; age range 7-18 years; males 13.8%). Of these enrolled patients, 48% is treated in outpatient ambulatory, 20% in day hospital, 18% in a residential or semi residential structures and 14% at hospital. The 73% of the collective was aged between 14 and 18 years. The percentage of males aged between 7 and 13 years is 34%, while females of this younger age class are 26%. Of the entire young patients' collective, 51.5% (n=215) were diagnosed with Anorexia Nervosa (AN) [mean age = 14.9 years (SD = 1.7); mean body mass index (BMI; kg/m2) = 16.0 (SD = 2.2)], 12.3% (n=51) were diagnosed with Bulimia Nervosa (BN) [mean age = 15.7 years (SD = 1.1); mean BMI = 21.6 (SD = 4.5)] and 36.2% (n=151) were diagnosed with Eating Disorder Not Otherwise Specified (EDNOS) [mean age = 13.9 years (SD = 2.6); mean BMI = 23.4 (SD = 8.1)]. Of those with AN, 87% met criteria for Anorexia Nervosa Restrictive type (AN-R) and of those with EDNOS 21.8% met criteria for Binge Eating Disorder (BED) (Table 2.1).

In Table 2.1 it is possible to observe that all the demographic, physical and indicator variables showed significant differences by diagnosis (Kruskal Wallis non parametric test $p<.05$; Pearson chi square $p<.05$).

Table 2.2 reports multiple comparisons by Mann-Whitney U test for continuous variables and Fisher exact test for categorical variables. These analysis revealed no gender differences only between AN and BN and no BMI differences only between BN and EDNOS ($p<.05$). Concerning the areas of interest indicator variables, for all the combination comparisons, affective problems (EDI-3), body dissatisfaction (EDI-3), body image concern (BUT) and shape concern (EDE 12.0D) presented no significant between diagnosis differences in their mean values ($p<.05$). Low self esteem (EDI-3) and interpersonal problems (EDI-3) average values are significantly different between EDNOS and the other two diagnosis ($p<.05$) resulting at the limit of statistical significance (p adjusted 0.051 and 0.054 respectively) and more impaired in BN compared to AN patients. Average levels of perfectionism (EDI-3), self oriented perfectionism (CAPS), anxious-depressed (YSR) and restraint are similar between AN and BN and higher than in EDNOS. Mean levels of bulimia (EDI-3) are different between AN (5.3±7.4) and BN (14.9±9.3) and between BN and EDNOS (5.9±7.5) (Table 2.2). To better characterize the diagnostic groups we analyzed the differences among AN, BN and EDNOS through an index calculated as the relationship between the EDE subscale scores of bulimia and that of restraint (B/R Index=Bulimia+1/Restraint+1): as Table 2.1 shows, the differences were significant among diagnostic groups (Kruskal Wallis nonparametric test p=0.000). In the multiple comparisons analysis the differences are significant in particular between AN and BN and between BN and EDNOS (p adjusted by Bonferroni Method=0.000 for both).

In Table 2.3 are reported the Spearman's rank correlation coefficient or Spearman's rho, denoted by the Greek letter ρ (rho). For the variables considered all the correlations were positive and highly significant ($p<0.01$, two tails). In particular, for all the EDs, affective problems were highly correlated with interpersonal problems (ρ=0.774), low self esteem (ρ=0.728), body dissatisfaction (ρ=0.709) and perfectionism (ρ=0.673); interpersonal problems were also linked to low self esteem (ρ=0.802), body dissatisfaction (ρ=0.716) and perfectionism (ρ=0.614) measures; low self esteem was related to body dissatisfaction (ρ=0.799) and perfectionism (ρ=0.572); perfectionism is highly correlated with body dissatisfaction (ρ=0.559) (Table 2.3).

In Table 2.4 are reported the correlations between core Eating Disorders maintaining mechanisms (binge eating and restraint) and the additional maintaining factors for all EDs and for each of the tree diagnosis considered. Correlation analysis results suggested that low self-esteem, perfectionism, interpersonal

difficulties, mood intolerance and overvaluation of weight and shape processes were all strongly related to the core eating disorder maintaining factor in EDs for all the disorders taken together (p<.01). In particular binge eating was mainly related to affective problems (ρ=0.672) and body dissatisfaction (ρ=0.606) and dietary restraint was mainly related to shape concern (ρ=0.449), and body dissatisfaction (ρ=0.372). It's worth of note that shape concern was more correlated with restraint than with binge eating while affective problems, body dissatisfaction, perfectionism, interpersonal problems and low self esteem variables were more correlated with binge eating.

Overevaluation of weight and shape, mood intolerance and interpersonal problems in particular are important areas of concern in the correlations with the central mechanisms of disorders also in the stratified analyzes by diagnosis. However, some differences between diagnostic groups were observed and the only indicator variable that resulted significantly correlated with the two core maintaining factor in all the tree different diagnosis was body image concerns (BUT subscale). This variable was significantly correlated (p<.01) with binge eating in BN (ρ=0.452) and in EDNOS (ρ=0.401); with restraint in BN (ρ=0.310, p<.05) and in AN with binge eating (ρ=0.294, p<.01) and restraint (ρ=0.251 p<.01); with restraint in EDNOS (ρ=0.302, p<.05).

In AN patients restraint was mainly correlated to shape concern (ρ=0.460, p<.01), body dissatisfaction (Cρ=0.306, p<.01) and affective problems (ρ=0.303, p<.01); binge eating was related mainly to affective problems (ρ=0.620, p<.01), body dissatisfaction (ρ=0.472, p<.01) and interpersonal problems (ρ=0.445, p<.01).

In BN patients binge eating was correlated mainly to body dissatisfaction (ρ=0.607, p<.01), interpersonal problems (ρ=0.550, p<.01) and low self esteem (ρ=0.503, p<.01) while restraint was related only to anxious-depressed (ρ=0.363, p<.01), shape concern (ρ=0.343, p<.05) and body image concerns (ρ=0.310, p<.05).

In EDNOS patients binge eating was correlated mainly to affective problems (ρ=0.781, p<.01), body dissatisfaction (ρ=0.729, p<.01) and perfectionism (ρ=0.702, p<.01) while restraint was related to body dissatisfaction (ρ=0.393, p<.01) and interpersonal problems (ρ=0.322, p<.01) (Table 2.4).

To explore the relationship among the core and additional maintaining factors in EDs a Principal component analysis (PCA), based on the correlation matrix shown in Table 2.5, was performed. Table 2.5 reveals

relationships between all used variables. A correlation value above 0.5 is deemed important and is in boldface.

The rotated principal components matrix of the first two components is observable in Table 2.6. This Table showed the rotated principal components matrix for the entire EDs sample and also for every diagnosis (AN, BN, EDNOS). The total variation accounted for the first two principal components is also shown.

On the whole, the first principal component was characterized by bulimia and the second one by restraint. The first principal component was strongly and positively correlated with six of the original variables: Bulimia (0.684), Perfectionism (0.709), Body dissatisfaction (0.802), Low self esteem (0.803), Interpersonal problems (0.823) and Affective problems (0.854) scores. This suggests that these six variables are strongly and positively correlated and vary together. If one increases, then the remaining five also increase. The second principal component is strongly and positively correlated with Restraint (0.677), Shape concern (0.731), Body image concern (0.684), Self Oriented Perfectionism (0.635), anxious depressed (0.612).

Table 2.6 shows that for each diagnosis the first two principal components were constituted by the same indicator variables as in the overall analysis: one is identified by bulimia and one by restraint. For each diagnosis the first principal component was strongly and positively correlated with Bulimia, Perfectionism, Body dissatisfaction, Low self esteem, Interpersonal problems and Affective problems scores; while the second principal component was strongly and positively correlated with Restraint, Shape concern, Body image concern, Self Oriented Perfectionism, anxious depressed dimensions. Figures 2.1, 2.2, 2.3 and 2.4 show the relationships among the examined variables in the subspace of the first two components for the entire EDs sample, and within each diagnosis (AN, BN, EDNOS). In the entire EDs sample two aggregations of variables were clearly distinguished: (1) Bulimia, Perfectionism, Body dissatisfaction, Low self esteem, Interpersonal problems and Affective problems, (2) Restraint, Shape concern, Body image concern, Self Oriented Perfectionism, anxious-depressed dimensions. Within each aggregation variables with the highest correlations are represented (Figure 2.1). The same aggregations were substantially observed also in AN patients (Figure 2.2) and BN patients (Figure 2.3) and to a lesser extent in ENDOS patients (Figure 2.4).

To complete the analysis we produced a principal component analysis including also the diagnosis variable (AN, BN and EDNOS). The scatter plot of the first two components is shown in Figure 2.5. Figure 2.5 includes and highlights the position of the 3 diagnosis respect to all the maintaining factors indicator

variables. AN group was particularly linked to restraint and BN group was particularly related to bulimia. EDNOS group appeared to be opposed to AN group.

2.5 Discussion

The transdiagnostic cognitive-behavioural model proposes that a dysfunctional system of self-evaluation is central to the maintenance of eating disorders. Core low self-esteem is proposed to motivate individuals to pursue achievement in the valued domain of weight and shape control to increase feelings of self-worth, thereby maintaining overevaluation of weight and shape. Self-esteem can be described as a favourable or unfavourable attitude towards oneself. Low self-esteem is a lack of respect for oneself, with feelings of unworthiness, inadequacies and deficiencies; body dissatisfaction is often associated with low self-esteem (Mäkinen, Puukko-Viertomies, Lindberg, Siime & Aalberg, 2012). For those with clinical perfectionism, the self is evaluated in terms of achievement in the valued domain of eating, weight and shape, thereby increasing efforts of dietary restraint and overevaluation of the importance of weight and shape. Interpersonal problems may lead to increased efforts of dietary restraint in an effort to control weight and shape and achieve the perceived socially valued ideal. Mood intolerance may encourage binge eating and purging as a way to cope with the experience of intense mood states.

Evidences from a multicenter national study were used in the present research to describe a population of young patients to verify the possibility of a spectrum model of disordered eating behavior (EDs).

In the present study, in a sample of 419 children and adolescents (mean age 14.7±2.14) diagnosed with AN (51.5%), BN (12.3%) and EDNOS (36.2%) all the demographic, physical and indicator variables showed significant differences by diagnosis ($p<.05$, Table 2.1). Also the multiple comparisons analyses (Table 2.2) revealed significant between diagnosis differences in their values ($p<.05$) with some exceptions: between AN and BN gender presents no significant differences and, for the indicator variables, perfectionism, self oriented perfectionism, anxious-depressed and restraint were similar in their mean values ($p<.05$). Between AN and EDNOS bulimia presented no significant differences and in the comparison of BN vs EDNOS mean values of BMI were not statistically different.

For all the EDs sample all the correlations among the variables considered (Spearman's rank correlation) were positive and highly significant ($p<0.01$). In particular, affective problems were highly correlated with

interpersonal problems (ρ=0.774), low self esteem (ρ=0.728), body dissatisfaction (ρ=0.709) and perfectionism (ρ=0.673). Interpersonal problems were also linked to low self esteem (ρ=0.802), body dissatisfaction (ρ=0.716) and perfectionism (ρ=0.614) measures. Low self esteem was related to body dissatisfaction (ρ=0.799) and perfectionism (ρ=0.572); perfectionism is highly correlated with body dissatisfaction (ρ=0.559) (Table 2.3).

Correlation analysis between core Eating Disorders maintaining mechanisms (bulimia and restraint) and the additional maintaining factors suggested that low self-esteem, perfectionism, interpersonal difficulties, mood intolerance and overvaluation of weight and shape processes were all strongly related to the core eating disorder maintaining factor in EDs. In particular binge eating was mainly related to affective problems (ρ=0.672) and body dissatisfaction (ρ=0.606) and dietary restraint was mainly related to shape concern (ρ=0.449), and body dissatisfaction (ρ=0.372). It's worth of note that shape concern was more correlated with restraint than with binge eating while affective problems, body dissatisfaction, perfectionism, interpersonal problems and low self esteem variables were more correlated with binge eating.

Overevaluation of weight and shape, mood intolerance and interpersonal problems in particular are important areas of concern in the correlations with the central mechanisms of disorders also in the stratified analyzes by diagnosis. However, several differences between diagnostic groups were observed and the only indicator variable that resulted significantly correlated with the two core maintaining factor in all the tree different diagnosis was body image concerns (BUT subscale).

Principal component analysis (PCA) revealed on the whole sample that the first principal component was characterized by bulimia and the second one by restraint.

Samantha Brooks and colleagues in a recent review outlined a novel evidence-based 'impulse control' spectrum model of eating disorders (Brooks, Rask-Andersen, Benedict & Schiöth, 2012). A model of eating disorders was proposed that will aid future diagnosis of symptoms, coinciding with contemporary suggestions by clinicians and the proposed changes due to be published in the DSM-V. The review summarized conclusions drawn from research involving brain imaging methods that provide some evidence to support a neural model of eating disorders across a spectrum of restricted versus impulsive eating behavior. They proposed that neuroimaging data of people with eating disorders provide convincing evidence that supports a single impulse control spectrum model of eating disorders. Specifically, that reduced, or at

least dysregulation of striatal dopaminergic circuits, combined with varying degrees of prefrontal cortex (PFC) related cognitive control contribute to the differential pathologies observed in AN, BN and BED. In addition, genetic data suggests potential polymorphisms for EDs in the genes encoding BDNF, COMT and 5HT2A, the interactions between which may contribute to a spectrum of disordered eating. Genetic data may compliment neuroimaging findings, in that brain-derived neurotrophic factor (BDNF) is linked to synaptic plasticity in the mesolimbic reward pathway, whereas catechol-O-methyl transferase gene (COMT) is involved in the breakdown and clearance of dopamine arriving at the PFC. Interactions between these two systems, rather than isolated polymorphisms at each gene, may contribute to ED phenotypes and the neural activation observed in neuroimaging studies. Brooks and collegues proposed that it is the interaction between COMT related PFC activity and BDNF-related mesolimbic activity that contributes to an ED phenotype along a spectrum of restrictive vs. impulsive eating behavior. An imbalance in these systems likely leads to a dysregulated orchestration of somatic and cognitive signals arriving at the insular cortex, which ultimately may cause upregulation of 5HT2A receptors and increased anxiety. Thus, it is not single polymorphisms, but complex genetic interactions (as well as gene-environment interactions and epigenetics) that likely underpins differential neural activation. It is plausible that increased anxiety is associated with activation of the amygdala and with ratelimiting defects in the insula. Alterations in feeding behaviour (e.g. applying more restraint over eating in response to environmental factors) could lead to gene environment interactions and epigenetic affects that contribute to differential functioning of these brain systems. However, despite the implications of the data reviewed by these authors, one must bear in mind that further neuroimaging studies are also needed to clarify the cognitive-emotion interactions underlying restraint vs. impulsive behaviors, e.g. by using fMRI paradigms that utilize cognitive tasks, and connectivity analysis. It is also of note that with increasing knowledge of structural differences among ED patients (e.g. using voxel-based morphometry, VBM) it will be vital to covary for structural brain differences in future brain imaging studies. Moreover, although genetic studies are convincing in this context, for ED, genetic data are still in their infancy and need further clarification.

For each diagnosis in our sample the first two principal components were constituted by the same indicator variables as in the overall analysis: the first principal component was strongly and positively correlated with bulimia (*impulsive eating behavior*), perfectionism, body dissatisfaction, low self esteem, interpersonal

problems and affective problems scores; while the second principal component was strongly and positively correlated with restraint (*restricted eating behavior*), shape concern, body image concern, self oriented perfectionism, anxious-depressed dimensions (Table 2.6). The PCA scatter plot that included the diagnosis variable (AN, BN and EDNOS) highlights the position of the three diagnosis respect to all the maintaining factors indicator variables. The AN group was particularly linked to restraint and the BN group was particularly related to bulimia. EDNOS group appeared to be opposed to AN group.

In sum a mixture of transdiagnostic and disorder-specific processes was implicated in the maintenance of eating disorders but the behavioral variables (restraint and binge eating) acted as poles of attraction of the other variables and configure a general design in which the diagnoses continue to have a role in discriminating the correlations between variables in different patients groups.

Some relationships resulted transdiagnostic and similar across diagnoses, including the relationships between low self-esteem and overevaluation of weight and shape (body dissatisfaction, shape concern, body image concerns) and affective problems and binge eating as in Lampard 2013 (Lampard, Tasca, Balfour & Bissada,2013). Overevaluation of weight and shape was associated with dietary restraint across diagnoses but not in BN patients and with different values of the correlation and this is not congruent with Lampard research.

Low self-esteem is particularly problematic in eating disordered adults individuals because it often persists after remission of the eating disorder (Daley, Jimerson, Heatherton, Metzger, & Wolfe, 2008). In the present analyses in children and adolescents population this issue could be less important in the maintaining of the eating disorder and it is particularly positively correlated with bulimia, perfectionism, body dissatisfaction, interpersonal problems and affective problems scores.

Therefore, it appears that difficulty regulating emotion is associated with binge eating. Treatment interventions to improve emotion regulation skills related to affective instability may be relevant for all eating disorder diagnoses, primarily when binge eating is present.

The cognitive-behavioural model proposes that dietary restraint maintains binge eating. This positive relationship was supported in EDNOS, but not for AN or BN. This result in BN is similar to previous studies, which failed to find a positive relationship between dietary restraint and binge eating in samples of patients

seeking treatment for BN or atypical BN (Lampard, Byrne, McLean & Fursland, 2011; Lowe, Gleaves, & Murphy-Eberenz,1998; Lowe, Thomas, Safer, & Butryn, 2007).

As the data reported in this study were cross-sectional, conclusions about the direction of relationships in the model cannot be drawn. Longitudinal research is needed to assess the maintenance relationships between additional maintaining factors and core eating disorder mechanisms in the considered cognitive-behavioural model. In addition, eating disorder diagnosis in this study was determined in accordance with current DSM-IV-TR criteria; however, these eating disorder diagnostic criteria will be revised in DSM-V. DSM-V will maintain a distinction between AN and BN but will alter the diagnostic criteria such that some patients currently diagnosed with EDNOS (particularly subthreshold AN and BN) will be classified AN or BN. It would therefore be informative to test the relationship between core eating disorder maintenance processes and additional maintaining factors in all EDNOS subgroups separately, including binge eating disorder, purging disorder, subthreshold AN and subthreshold BN. Further research is needed to determine whether maintaining mechanisms are consistent across all EDNOS subgroups and across the revised DSM-V diagnostic groups.

By providing the first test in children and adolescents population of the transdiagnostic nature of relationships between additional maintaining factors and each core eating disorder maintaining mechanism in the cognitive-behavioural model of EDs, this study identified several associations between eating disorder mechanisms that are common across all eating disorder diagnoses. However, the results of this study point also toward disorder-specific maintenance processes.

There may be important maintenance pathways specific to different eating disorder diagnoses that require different treatment interventions or treatment modules, but further research is needed to explore this possibility. Results suggest that the relationship between maintaining mechanisms and eating disorder symptoms may differ between eating disorder diagnoses. If this is the case, a distinction should be maintained between eating disorder diagnostic groups in diagnostic schemes, particularly AN and BN. Similarly, research should continue to investigate disorder-specific maintenance processes in eating disorders and subsequently whether disorder-specific approaches to eating disorder treatment support improved treatment outcomes. Disorder-specific maintenance mechanisms may also implicate disorder-specific etiological processes, and this remains an important area for further research. Finally, results may have

implications for the prevention of eating disorders. Low self-esteem, overevaluation of weight and shape, mood intolerance and perfectionism were associated with core eating disorder symptoms in all eating disorder diagnostic groups, indicating that these may be effective targets for eating disorder prevention programmes. In conclusion, it is important to note that transdiagnostic approaches and disorder-focused approaches need not to be mutually exclusive (Mansell, Harvey, Watkins, Shafran, 2009) and that a "spectrum model" based on an impulse-control paradigm of EDs has to be considered on the base of the suggestion of Samantha Brooks and collegues (2012): a neural model of eating disorders across a spectrum of restricted versus impulsive eating behavior. Clinical practice can be informed by an understanding of both transdiagnostic maintaining mechanisms and maintaining mechanisms specific to eating disorder diagnostic groups. The current study suggests that not all processes identified in the cognitive-behavioural model of eating disorders may be operating in the same manner across eating disorder diagnoses. However, the cognitive-behavioural model does provide guidance to clinicians on a range of factors that may be important (but with different intensity grade in the maintenance of any given eating disorder).

Assessing the diagnostic categorization of eating disorders is made difficult by their low diagnostic reliability, low stability of diagnosis over time, the frequency of concurrent disorders and the rigid use of the DSM-IV diagnosis (APA, 2004). Psychiatric diagnoses are not entirely reliable (Hiller, Dichtl, Hecht, Hundt, & von Zerssen, 1993) and several authors attributed this to the evolution of the illness, the instability of diagnosis to the clinical course of the disease, the emergence of new information and the unreliability of measurement (e.g. Schwartz, Porte, Jr. Seeley, & Baskin, 2000). This would tend to contaminate the experimental differentiation in favour of only one diagnosis of ED.

If the transdiagnostic theory of eating disorders is completely accepted, it will be impossible to draw historical comparisons, compare treatment efficacy to historical controls, or estimate sample size for clinical trials. Even small changes can yield large differences in rates, reduce comparability across data gathered with different systems, and incur changes in diagnostic interview schedules. Moreover, empirical data can have limited impact on the choices between the two systems because findings are either absent or equivocal, particularly for differences at the criterion level (Rounsaville, 2002).

The starvation of AN leads to binging followed by purging as a compensatory behavior and EDNOS is largely a hybrid, comprised mostly of patients who do not quite meet the diagnostic criteria for AN or BN.

The danger of grouping all eating disorder patients together would be that the morbidity and mortality will be homogenised, resulting in a reduction in the apparent significance of AN. This could lead to a reduction in treatment for eating disorders especially for those patients with AN.

Maintaining AN and BN as separate diagnosis allows us to compare epidemiology and treatment interventions over time. A change in categorization would render this impossible; it might be useful to consider whether other dichotomies, such as mild and severe or acute and chronic, might be a more practical way to classify eating disorders (Maguire, Le Grange, Surgenor, Marks, Lacey, & Touyz, 2008). Comparing males with females, different ages of onset or precipitating factors, or experimentally different groups may help reveal the causal pathways of eating disorders. Research may be aided by comparing subcategories within the present diagnoses.

Table 2.1 Demographic and maintaining factors characteristics by type of Eating Disorder

		EDs (n=419; 100%)			AN (n=215; 51.5%)			BN (n=51; 12.3%)			EDNOS (n=118; 36.2%)			p*
Subtypes%					AN-R 87.0			BN-BP 76.5			BED 21.8			
Female %		86.2			92.6			92.2			74.8			0.000
Male %		13.8			7.4			7.8			25.2			0.000
7-13 years %		27.0			23.3			3.9			39.1			0.000
14-18 years %		73.0			76.7			96.1			60.9			0.000
		M ± SD	**Median**	**Min and max**	**M ± SD**	**Median**	**Min and max**	**M ± SD**	**Median**	**Min and max**	**M ± SD**	**Median**	**Min and max**	**p****
Age		14.7±2.14	15	7-18	14.9±1.7	15	10-18	15.7±1.1	16	13-18	13.9±2.6	14	7-18	0.000
BMI		19.38±6.40	17.58	11.2-53.6	16.0±2.2	15.8	11.2-23.4	21.6±4.5	20.2	13.5-36.3	23.4±8.1	20.4	13.0-53.6	0.000
Area of interest	**Indicator scale**	**M ± SD**	**Median**	**Min and max**	**M ± SD**	**Median**	**Min and max**	**M ± SD**	**Median**	**Min and max**	**M ± SD**	**Median**	**Min and max**	**p****
Low Self-Esteem	Low self esteem (EDI-3)	9.4±7.5	9	0-24	10.3±7.4	10	0-24	13.1±7.5	15	0-24	6.7±6.7	5	0-24	0.000
Perfectionism	Perfectionism (EDI-3)	6.7±5.8	6	0-24	7.3±5.7	7	0-24	9.0±6.5	9	0-20	5.0±5.3	3	0-24	0.000
	Self-oriented Perfectionism (CAPS)	35.4±13.4	36	0-60	37.7±13.6	37	0-60	39.5±9.9	40	20-60	31.1±13.1	32	0-58	0.000
Interpersonal Difficulties	Interpersonal problems (EDI-3)	18.2±13.7	18	0-54	19.6±13.8	19	0-54	24.41±12.5	24	0-52	14.03±12.9	13	0-50	0.000
Mood Intolerance	Affective problems (EDI-3)	20.3±16.6	19	0-68	22.1±16.4	21	0-68	28.8±15.9	26	0-59	14.8±15.4	11	0-53	0.000
	Anxious-depressed (YSR)	8.2±7.0	7	0-26	9.0±7.1	8	0-26	10.9±7.2	13	0-25	5.9±6.1	5	0-22	0.000
Overevaluation of Weight and Shape	Body dissatisfaction (EDI-3)	18.3±13.2	18	0-40	18.6±12.5	18	0-40	26.6±12.6	32	0-40	14.8±13.0	15	0-40	0.000
	Body image concerns (BUT)	2.2±1.6	2.1	0-5	2.3±1.5	2.2	0-5	3.3±1.4	3.8	0-5	1.6±1.6	1.2	0-5	0.000
	Shape concern (EDE 12.0D)	4.0±1.4	4.2	1-6	4.2±1.4	4.4	1-6	5.0±1.0	5.2	2-6	3.5±1.5	3.3	1-6	0.000
Restraint	Restraint (EDE 12.0D)	3.2±1.8	3.2	0-6	3.6±1.7	3.8	0-6	3.9±1.6	4.4	0-6	2.4±1.6	2.2	0-6	0.000
Binge Eating	Bulimia (EDI-3)	6.7±8.3	3	0-32	5.3±7.4	2	0-32	14.9±9.3	16	0-31	5.9±7.5	2.5	0-30	0.000
B/R Index	Bulimia / Restraint	2.2±3.1	1.0	0.1-33.0	1.6±2.9	0.8	0.1-33.0	3.80±2.7	3.7	0.2-14.0	2.5±3.2	1.0	0.1-16.0	0.000

Note: EDs, eating disorders; AN, anorexia nervosa; BN, bulimia nervosa; EDNOS, eating disorder not otherwise specified; AN-R, anoressia nervosa restricting type; BN-BP, bulimia nervosa binge purging types; BED, binge eating disorder; BMI, Body Mass Index; EDI-3, Eating Disorder Inventory 3; CAPS, Child and Adolescent Perfectionism Scale; YSR, Youth Self Report; BUT, Body Uneasiness Test; EDE 12.0D, Eating Disorder Examination Questionnaire; B/R Index=Bulimia+1/Restraint+1; M, Mean; SD, standard deviation; Min and max, minimum and maximum; *, Pearson chi square p; **, Kruskal Wallis nonparametric test p.

Table 2.2 Multiple Comparisons by Mann-Whitney U test for continuous variables and Fisher exact test for categorical variables: unadjusted p and p adjusted for multiplicity by Bonferroni Method (italic font) are reported

		AN vs BN	AN vs EDNOS	BN vs EDNOS
Gender		-	0.000 ***0.000***	0.009 ***0.027***
Age class		0.001 ***0.003***	0.002 ***0.006***	0.000 ***0.000***
Age		0.011 ***0.033***	0.000 ***0.000***	0.000 ***0.000***
BMI		0.000 ***0.000***	0.000 ***0.000***	-
Area of interest	**Indicator variable**			
Low Self-Esteem	Low self esteem (EDI-3)	0.017 *0.051*	0.000 ***0.000***	0.000 ***0.000***
Perfectionism	Perfectionism (EDI-3)	-	0.000 ***0.000***	0.000 ***0.000***
	Self-oriented Perfectionism (CAPS)	-	0.000 ***0.000***	0.000 ***0.000***
Interpersonal Difficulties	Interpersonal problems (EDI-3)	0.018 *0.054*	0.000 ***0.000***	0.000 ***0.000***
Mood Intolerance	Affective problems (EDI-3)	0.013 ***0.039***	0.000 ***0.000***	0.000 ***0.000***
	Anxious-depressed (YSR)	-	0.000 ***0.000***	0.000 ***0.000***
Overevaluation of Weight and Shape	Body dissatisfaction (EDI-3)	0.000 ***0.000***	0.004 ***0.012***	0.000 ***0.000***
	Body image concerns (BUT)	0.000 ***0.000***	0.000 ***0.000***	0.000 ***0.000***
	Shape concern (EDE 12.0D)	0.000 ***0.000***	0.000 ***0.000***	0.000 ***0.000***
Restraint	Restraint (EDE 12.0D)	-	0.000 ***0.000***	0.000 ***0.000***
Binge Eating	Bulimia (EDI-3)	0.000 ***0.000***	-	0.000 ***0.000***
B/R Index	Bulimia / Restraint	0.000 ***0.000***	0.002 ***0.006***	0.000 ***0.000***

Note: AN, anorexia nervosa; BN, bulimia nervosa; EDNOS, eating disorder not otherwise specified; BMI, Body Mass Index; EDI-3, Eating Disorder Inventory 3; CAPS, Child and Adolescent Perfectionism Scale; YSR, Youth Self Report; BUT, Body Uneasiness Test; EDE 12.0D, Eating Disorder Examination Questionnaire; B/R Index=Bulimia+1/Restraint+1; M, Mean; P values adjusted for multiplicity by Bonferroni Method <0.05 are in italic bold font.

Table 2.3 Correlation Matrix between additional and core maintaining factors in Eating Disorders: Spearman ‘s Rho correlation coefficient

		Affective problems	Interpersonal problems	Low self esteem	Body dissatisfaction	Perfectionism	Bulimia	Restraint	Shape concern	Body image concerns	Anxious depressed	Self oriented perfectionism
Affective problems	ρ	1.000	0.774**	0.728**	0.709**	0.673**	0.672**	0.334**	0.368**	0.438**	0.432**	0.291**
	p		0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Interpersonal problems	ρ		1.000	0.802**	0.716**	0.614**	0.546**	0.327**	0.346**	0.416**	0.415**	0.287**
	p			0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Low self esteem	ρ			1.000	0.799**	0.572**	0.504**	0.333**	0.349**	0.484**	0.415**	0.263**
	p				0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Body dissatisfaction	ρ				1.000	0.559**	0.606**	0.372**	0.425**	0.496**	0.336**	0.230**
	p					0.000	0.000	0.000	0.000	0.000	0.000	0.000
Perfectionism	ρ					1.000	0.550**	0.230**	0.276**	0.325**	0.374**	0.477**
	p						0.000	0.000	0.000	0.000	0.000	0.000
Bulimia	ρ						1.000	0.217**	0.344**	0.377**	0.275**	0.239**
	p							0.000	0.000	0.000	0.000	0.000
Restraint	ρ							1.000	0.449**	0.309**	0.295**	0.252**
	p								0.000	0.000	0.000	0.000
Shape concern	ρ								1.000	0.513**	0.334**	0.284**
	p									0.000	0.000	0.000
Body image concerns	ρ									1.000	0.389**	0.323**
	p										0.000	0.000
Anxious depressed	ρ										1.000	0.375**
	p											0.000
Self oriented perfectionism	ρ											1.000
	p											

Note: ρ=Spearman ‘s Rho correlation coefficient; p, p value; ** significant correlations with p<0.01 (two tails) after adjustment for multiplicity by Bonferroni method

Table 2.4 Correlation between additional and core maintaining factors by type of Eating Disorder: Spearman 's Rho correlation coefficient

			Low Self Esteem	Perfectionism		Interpersonal Difficulties	Mood Intollerance		Overevaluation of Weight and Shape		
			Low self esteem (EDI-3)	Perfectionism (EDI-3)	Self oriented perfectionism (CAPS)	Interpersonal problems (EDI-3)	Affective problems (EDI-3)	Anxious depressed (YSR)	Body dissatisfaction (EDI-3)	Body image concerns (BUT)	Shape concern (EDE 12.0D)
EDs	Binge Eating (Bulimia, EDI-3)	ρ	0.504	0.550	0.239	0.546	0.672	0.275	0.606	0.377	0.344
		p	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
	Restraint (EDE 12.0D)	ρ	0.333	0.230	0.252	0.327	0.334	0.295	0.372	0.309	0.449
		p	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
AN	Binge Eating (Bulimia, EDI-3)	ρ	0.390	0.427	0.195	0.445	0.620	0.184	0.472	0.294	0.287
		p	0.000	0.000	0.004	0.000	0.000	0.007	0.000	0.000	0.000
	Restraint (EDE 12.0D)	ρ	.283	0.119	0.095	0.254	0.303	0.134	0.306	0.251	0.460
		p	0.000	0.082	0.166	0.000	0.000	0.050	0.000	0.000	0.000
BN	Binge Eating (Bulimia, EDI-3)	ρ	.503	0.468	0.284	0.550	0.477	0.236	0.607	0.452	0.162
		p	0.000	0.001	0.043	0.000	0.000	0.096	0.000	0.001	0.256
	Restraint (EDE 12.0D)	ρ	0.121	0.013	0.235	0.163	0.120	0.363	0.186	0.310	0.343
		p	0.397	0.927	0.097	0.254	0.400	0.009	0.191	0.027	0.014
EDNOS	Binge Eating (Bulimia, EDI-3)	ρ	0.639	0.702	0.342	0.662	0.781	0.416	0.729	0.401	0.380
		p	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
	Restraint (EDE 12.0D)	ρ	0.301	0.259	0.219	0.322	0.264	0.273	0.393	0.172	0.302
		p	0.000	0.001	0.007	0.000	0.001	0.001	0.000	0.035	0.000

Note: EDs, eating disorders; AN, anorexia nervosa; BN, bulimia nervosa and binge eating disorder; EDNOS, eating disorder not otherwise specified; EDI-3, Eating Disorder Inventory 3; CAPS, Child and Adolescent Perfectionism Scale; YSR, Youth Self Report; BUT, Body Uneasiness Test; EDE 12.0D, Eating Disorder Examination Questionnaire; B/R Index=Bulimia+1/Restraint+1; ρ, Spearman's Rho correlation coefficient; p, p value

Table 2.5 Correlation Matrix between additional and core maintaining factors

		Affective problems	Interpersonal problems	Low self esteem	Body dissatisfaction	Perfectionism	Bulimia	Restraint	Shape concern	Body image concerns	Anxious depressed	Self oriented perfectionism
	Affective problems	1.000	0.752	0.694	0.676	0.645	0.603	0.319	0.386	0.427	0.447	0.278
	Interpersonal problems		1.000	0.779	0.699	0.578	0.447	0.327	0.374	0.419	0.429	0.296
	Low self esteem			1.000	0.786	0.529	0.391	0.328	0.369	0.493	0.432	0.253
	Body dissatisfaction				1.000	0.521	0.515	0.358	0.438	0.500	0.343	0.225
	Perfectionism					1.000	0.488	0.199	0.293	0.318	0.388	0.443
C	**Bulimia**						1.000	0.164	0.329	0.365	0.238	0.214
	Restraint							1.000	0.442	0.319	0.304	0.241
	Shape concern								1.000	0.534	0.354	0.302
	Body image concerns									1.000	0.401	0.349
	Anxious depressed										1.000	0.410
	Self oriented perfectionism											1.000

Table 2.6 Principal component analysis for EDs, AN, BN, EDNOS: factor loadings for the first two rotated principal components

Mantaining factors	Components EDs VE=59.7%		Mantaining factors	Components AN VE=54.6%		Mantaining factors	Components BN VE=61.8%		Mantaining factors	Components EDNOS VE=59.5%	
	1	2		1	2		1	2		1	2
Affective problems	**0.854**	0.258	**Affective problems**	**0.847**	0.276	**Low self esteem**	**0.910**	0.109	**Affective problems**	**0.884**	0.178
Interpersonal problems	**0.823**	0.279	**Interpersonal problems**	**0.802**	0.308	**Body dissatisfaction**	**0.860**	0.060	**Interpersonal problems**	**0.840**	0.203
Low self esteem	**0.803**	0.299	**Perfectionism**	**0.737**	0.096	**Interpersonal problems**	**0.838**	0.260	**Low self esteem**	**0.827**	0.222
Body dissatisfaction	**0.802**	0.296	**Low self esteem**	**0.735**	0.378	**Affective problems**	**0.811**	0.185	**Body dissatisfaction**	**0.785**	0.361
Perfectionism	**0.709**	0.246	**Body dissatisfaction**	**0.731**	0.357	**Bulimia**	**0.713**	0.199	**Perfectionism**	**0.744**	0.256
Bulimia	**0.684**	0.128	**Bulimia**	**0.617**	0.021	**Perfectionism**	**0.664**	0.311	**Bulimia**	**0.728**	0.236
Shape concern	0.231	**0.731**	**Shape concern**	0.138	**0.787**	**Restraint**	0.002	**0.750**	**Shape concern**	0.147	**0.746**
Restraint	0.123	**0.677**	**Body image concerns**	0.214	**0.723**	**Self oriented perfectionism**	0.061	**0.718**	**Restraint**	0.144	**0.630**
Body image concerns	0.354	**0.684**	**Restraint**	0.040	**0.650**	**Anxious depressed**	0.272	**0.717**	**Self oriented perfectionism**	0.142	**0.628**
Self oriented perfectionism	0.146	**0.635**	**Anxious depressed**	0.315	**0.478**	**Body image concerns**	0.468	**0.618**	**Anxious depressed**	0.353	**0.575**
Anxious depressed	0.309	**0.612**	**Self oriented perfectionism**	0.216	**0.437**	**Shape concern**	0.279	**0.563**	**Body image concerns**	0.402	**0.525**

Note: principal component analysis based on correlation matrix; rotation method: Varimax with Kaiser normalization; VE= Variance Explained by the first two components

Figure 2.1 Principal Component Analysis for Eating Disorders (EDs): projection of variables on the subspace of the first two principal components. The horizontal line is the Principal Component 1 while the vertical line is the Principal Component 2

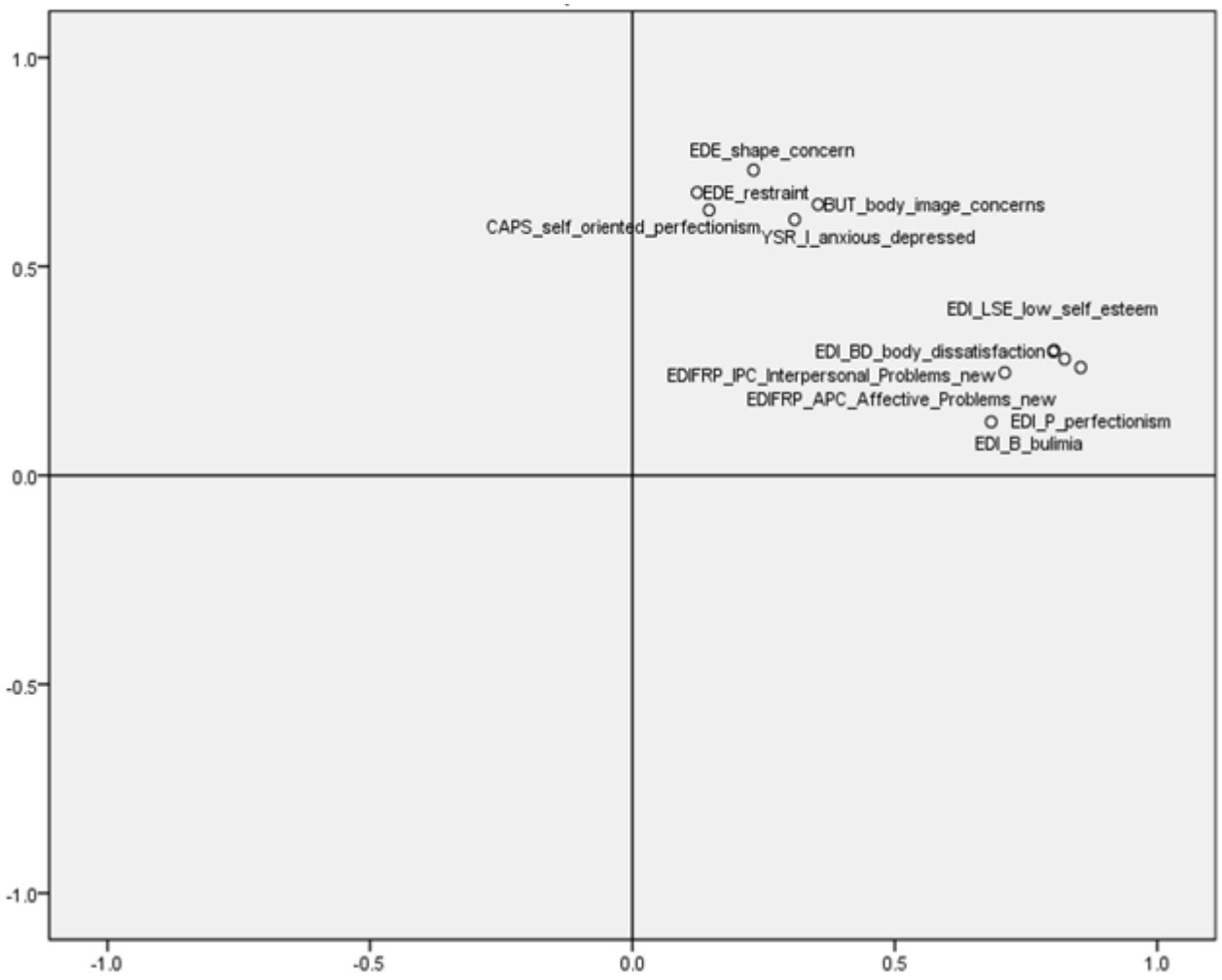


Figure 2.2 Principal Component Analysis for Anorexia Nervosa (AN) : projection of variables on the subspace of the first two principal components. The horizontal line is the Principal Component 1 while the vertical line is the Principal Component 2

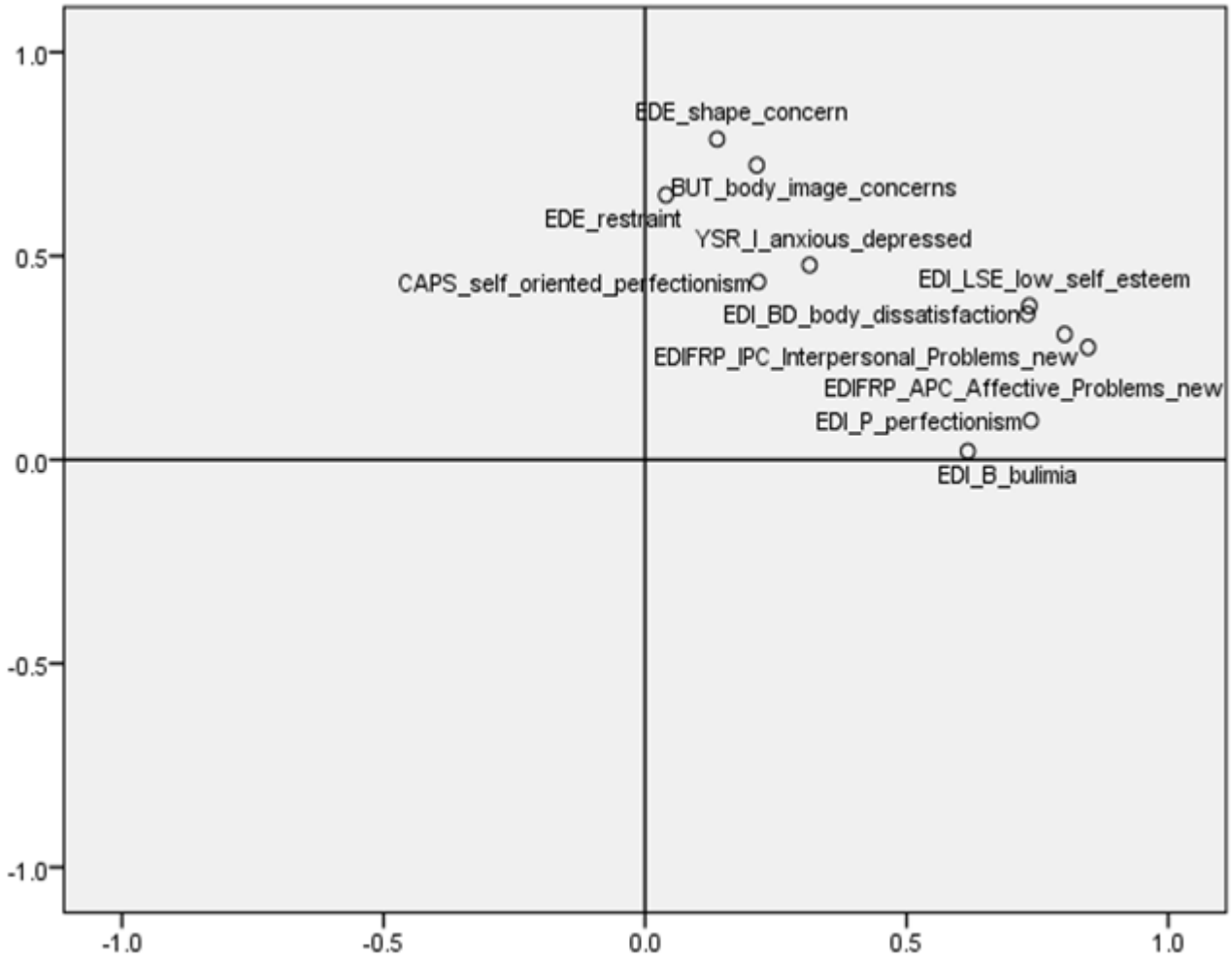


Figure 2.3 Principal Component Analysis for Bulimia Nervosa (BN): projection of variables on the subspace of the first two principal components. The horizontal line is the Principal Component 1 while the vertical line is the Principal Component 2

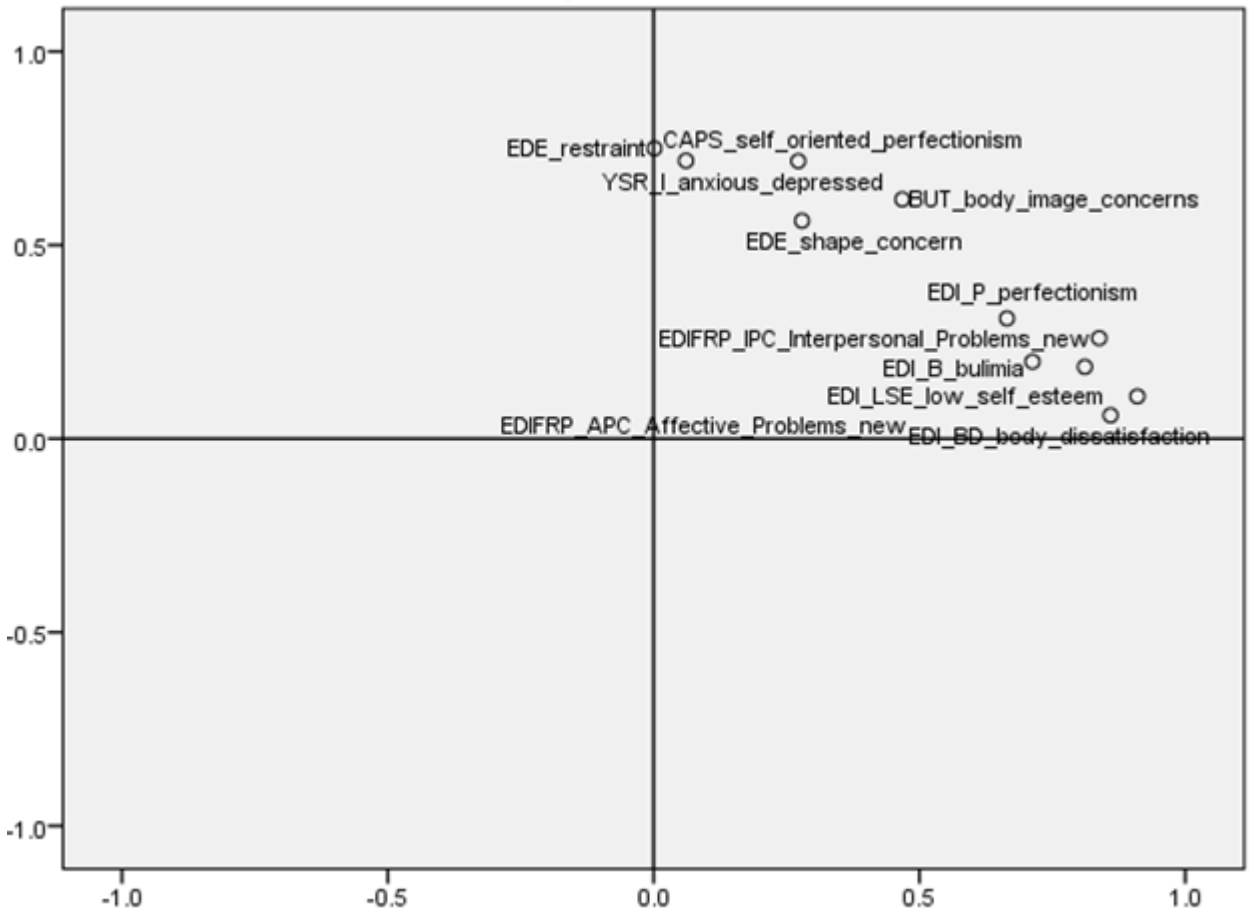


Figure 2.4 Principal Component Analysis for Eating Disorders Not Otherwise Specified (EDNOS): projection of variables on the subspace of the first two principal components. The horizontal line is the Principal Component 1 while the vertical line is the Principal Component 2.

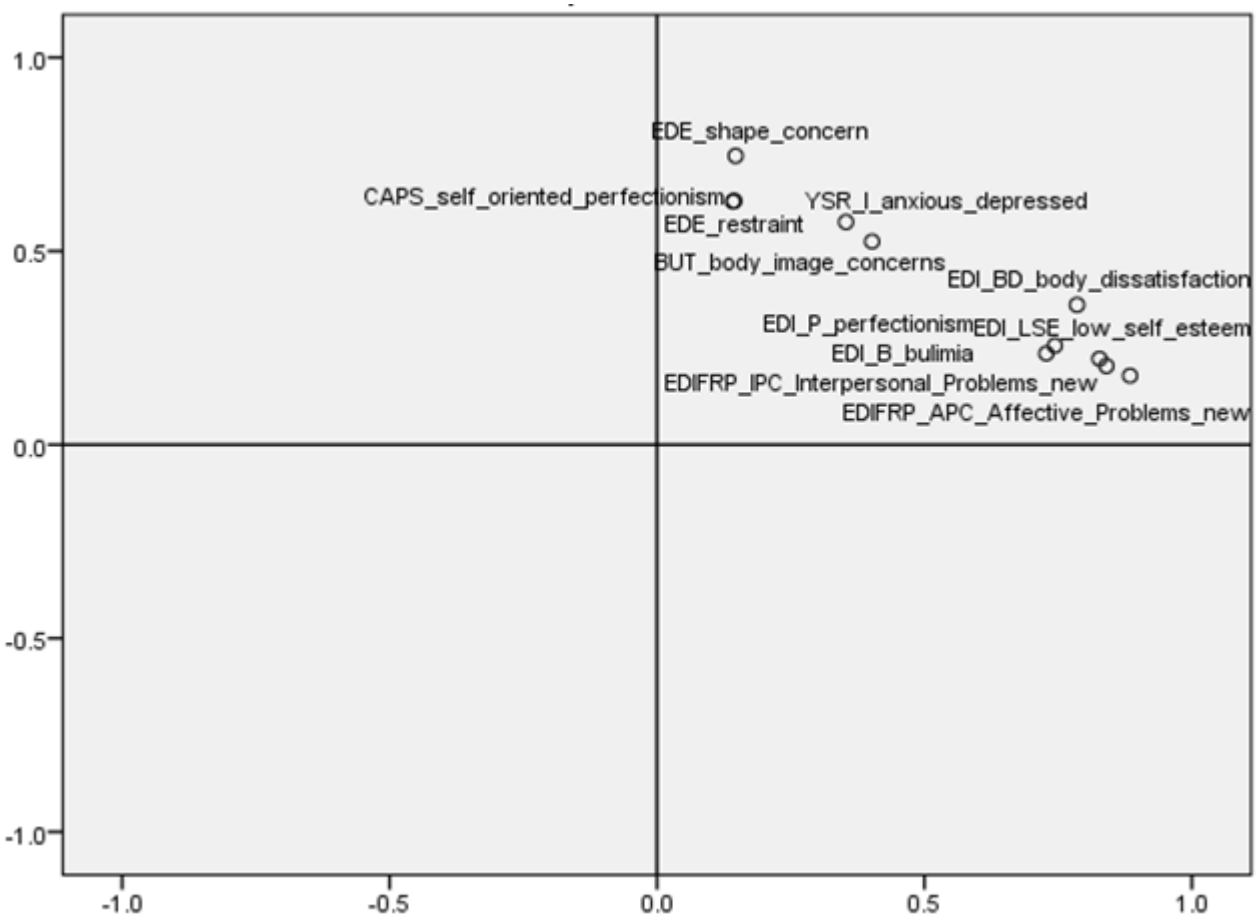
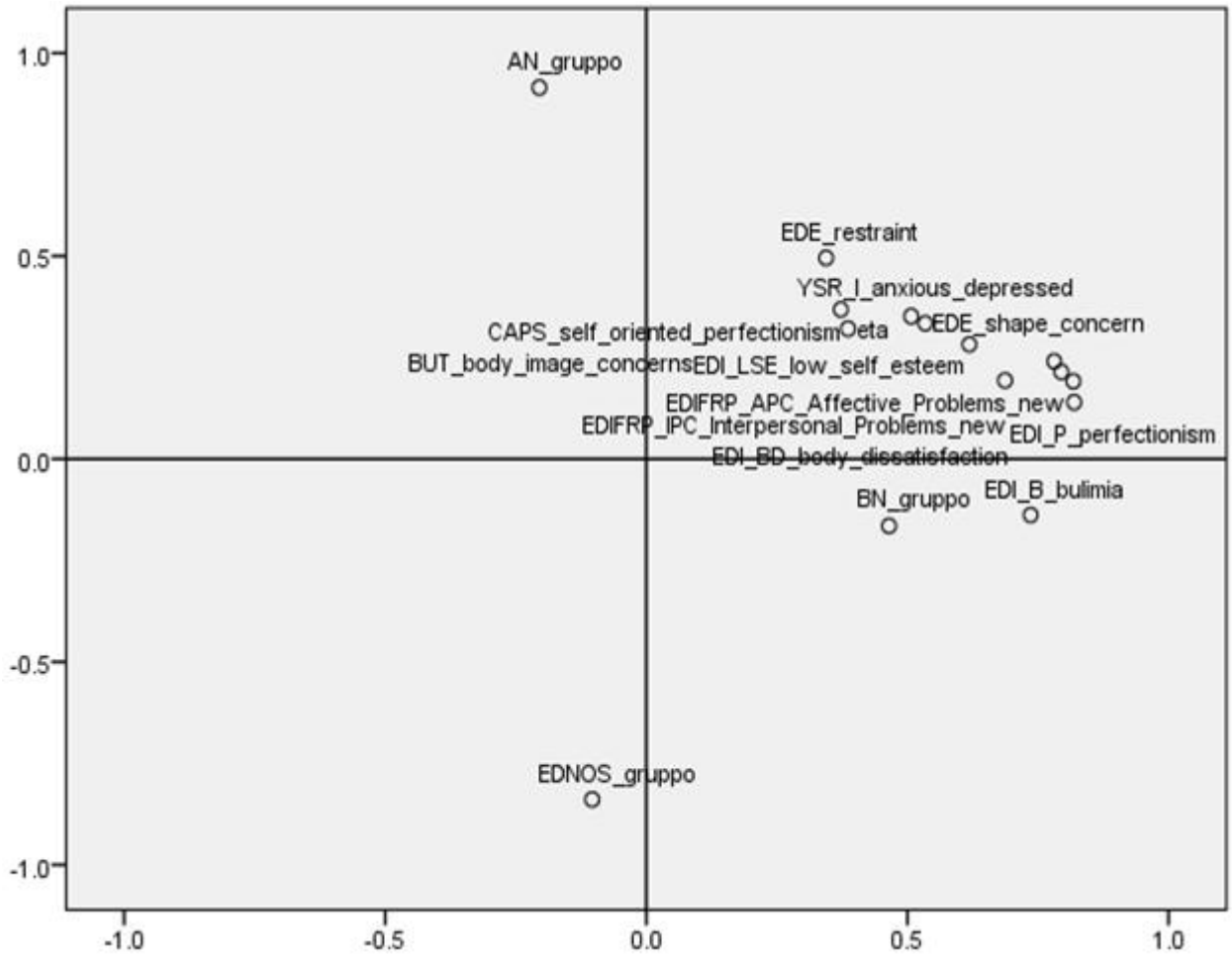


Figure 2.5 Principal Component Analysis with diagnosis of Eating Disorders (AN, BN, EDNOS): projection of variables on the subspace of the first two principal components. The horizontal line is the Principal Component 1 while the vertical line is the Principal Component 2.



Note: AN, anorexia nervosa; BN, bulimia nervosa; EDNOS, eating disorder not otherwise specified

Chapter 3

The utility of sub typing analyzing the cognitive-behavioral maintaining factors model of Eating Disorders in childhood and adolescence

3.1 Abstract

Objective: To determine if the relationships between Eating Disorders (EDs) diagnosis in childhood and adolescence, key factors and core eating disorder mechanisms are transdiagnostic considering subtypes of EDs.

Method: Young patients (n = 419; mean age 14.7±2.14; age range 7-18 years; males 13.8%) diagnosed with anorexia nervosa (51.5%), bulimia nervosa (12.3%), and eating disorder not otherwise specified (36.2%) on the base of DSM-IV adapted to childhood. The patients were assessed through Standardized Instruments (EDI-3, Eating Disorder Inventory-3: EDE 12.0D, Eating Disorder Examination, 12th edition; CBCL, Child Behavior Checklist; CAPS, Child Adolescent Perfectionism Scale; BUT, Body Uneasiness Test) to evaluate key EDs features as low self-esteem, self-oriented perfectionism, interpersonal difficulties, mood intolerance, overevaluation of weight and shape, dietary restraint and binge eating. Descriptive statistics to compare mean values of eating disorder factors and mechanism, multiple comparisons between diagnosis, correlation analysis and principal component analysis (PCA) were performed.

Results: Of the entire young patients' collective, 44.8% were diagnosed with Anorexia Nervosa Restricting type, 6.7% were diagnosed with Anorexia Nervosa Binge Purging type, 9.4% were diagnosed with Bulimia Nervosa Binge Purging type, 2.9% were diagnosed with Bulimia Nervosa, 7.9% were diagnosed with Binge Eating Disorder and 28.3% were diagnosed with Eating Disorder Not Otherwise Specified. In variables related to the maintaining factors, there were no significant differences between AN-BP vs BN-BP, between AN-BP vs BN and between BN-BP and BN. BED and EDNOS presented significant different values only for shape concern and body image concerns ($p<.05$). Significant differences for a large number of indicator variables were observed for BN-BP vs EDNOS, for AN-BP vs EDNOS, for BN vs EDNOS and for AN-R vs EDNOS. The indicator variables with less inter-diagnosis differences through multiple comparisons were anxious-depressed, perfectionism and self oriented perfectionism; on the contrary the variables with the

higher number of inter-diagnosis differences were body dissatisfaction, restraint and low self esteem. Principal component analysis (PCA) revealed that for almost all diagnoses the first principal component was related to bulimia and the second to restraint, showing the independence of the two variables. On the contrary, in BN restraint and bulimia were positively correlated in the second component, while in the AN-BP restraint was not clearly associated with any of the two principal components. For AN-R, BN-BP, BED and EDNOS, the first principal component was usually correlated with bulimia, perfectionism, body dissatisfaction, low self esteem, interpersonal problems and affective problems scores; while the second principal component was usually correlated with restraint, shape concern, body image concern, self oriented perfectionism, anxious-depressed dimensions.

Discussion: AN-R group, particularly related to restraint, shape concern and anxious-depressed, was not linked to AN-BP, BN-BP and BN groups that seemed to constitute an unique cluster, particularly related to bulimia, affective and interpersonal problems and perfectionism. EDNOS group appear to be opposed to AN group and also BED group seemed to be independent from the others. Results seemed to indicate an incomplete adherence to the trans-diagnostic model. In fact, the relationships among the several analyzed dimensions were not the same in every subgroup.

Keywords: Transdiagnostic; Cognitive-Behavioral Model; Eating Disorders; Childhood and Adolescence; EDs Subtypes

3.2 Background

Eating disorders (EDs) are syndromes characterized by significant disturbances in eating behavior and by distress or excessive concern about body shape or weight. Presentation varies, but eating disorders often occur with severe medical or psychiatric comorbidity. All dominant models of the eating disorders implicate personality variables in the emergence of weight concerns and the development of specific symptoms such as bingeing and purging. Standardized measures of personality traits and disorders generally confirm clinical descriptions of restricting anorexics (AN-R) as constricted, conforming, and obsessional individuals. A less consistent picture suggesting affective instability and impulsivity has emerged from the assessment of subjects with bulimia nervosa. Considerable heterogeneity exists within EDs subtypes, however, and a

number of special problems complicate the interpretation of personality data in this population. These include young age at onset, the influence of state variables such as depression and starvation sequelae, denial and distortion in self-report, the instability of subtype diagnoses, and the persistence of residual problems following symptom control (Vitousek, Kelly, Manke & Frederic, 1994).

Major eating disorders can be classified as anorexia nervosa (AN), bulimia nervosa (BN), and eating disorder not otherwise specified (EDNOS). Although criteria of the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision (DSM IV-TR), allow diagnosis of a specific eating disorder, many patients demonstrate a mixture of both anorexia and bulimia. Anorexia nervosa has two subtypes: restrictive eating (AN-R) and binge eating alternating with restrictive eating at different periods of the illness (AN-BP). Patients with bulimia nervosa can be subclassified into purging (BN-BP) and nonpurging (BN). Many patients have a combination of eating disorder symptoms that cannot be strictly categorized as either anorexia nervosa or bulimia nervosa and are technically diagnosed as eating disorder not otherwise specified. Listed in the DSM IV-TR appendix, binge eating disorder (BED) is defined as uncontrolled binge eating without emesis or laxative abuse. It is often, but not always, associated with obesity symptoms.

In the box above are shown DSM IV-TR Criteria for AN, BN and EDNOS and subtypes of them.

DSM IV-TR Criteria for Anorexia Nervosa

Refusal to maintain body weight at or above a minimally normal weight for age and height: Weight loss leading to maintenance of body weight <85% of that expected or failure to make expected weight gain during period of growth, leading to body weight less than 85% of that expected.

Intense fear of gaining weight or becoming fat, even though under weight.

Disturbance in the way one's body weight or shape are experienced, undue influence of body weight or shape on self evaluation, or denial of the seriousness of the current low body weight.

Amenorrhea (at least three consecutive cycles) in postmenarchal girls and women. Amenorrhea is defined as periods occurring only following hormone (e.g., estrogen) administration.

Types

Restricting type: During the current episode of anorexia nervosa, the person has not regularly engaged in binge-eating or purging behavior (self-induced vomiting or misuse of laxatives, diuretics, or enemas); Binge-eating–purging type: During the current episode of anorexia nervosa, the person has regularly engaged in binge-eating or purging behavior (self-induced vomiting or the misuse of laxatives, diuretics, or enemas).

DSM IV-TR Criteria for Bulimia Nervosa

Recurrent episodes of binge eating characterized by both:

Eating, in a discrete period of time (e.g., within any 2-hour period), an amount of food that is definitely larger than most people would eat during a similar period of time and under similar circumstances

A sense of lack of control over eating during the episode, defined by a feeling that one cannot stop eating or control what or how much one is eating

Recurrent inappropriate compensatory behavior to prevent weight gain

Self-induced vomiting

Misuse of laxatives, diuretics, enemas, or other medications

Fasting

Excessive exercise

The binge eating and inappropriate compensatory behavior both occur, on average, at least twice a week for 3 months.
Self evaluation is unduly influenced by body shape and weight.
The disturbance does not occur exclusively during episodes of anorexia nervosa.

Types
Purging type: During the current episode of bulimia nervosa, the person has regularly engaged in self-induced vomiting or the misuse of laxatives, diuretics, or enemas; Nonpurging type: During the current episode of bulimia nervosa, the person has used inappropriate compensatory behavior but has not regularly engaged in self-induced vomiting or misused laxatives, diuretics, or enemas.

DSM IV-TR Criteria for Eating Disorder Not Otherwise Specified
Eating disorder not otherwise specified includes disorders of eating that do not meet the criteria for any specific eating disorder.
For female patients, all of the criteria for anorexia nervosa are met except that the patient has regular menses.
All of the criteria for anorexia nervosa are met except that, despite significant weight loss, the patient's current weight is in the normal range.
All of the criteria for bulimia nervosa are met except that the binge eating and inappropriate compensatory mechanisms occur less than twice a week or for less than 3 months.
The patient has normal body weight and regularly uses inappropriate compensatory behavior after eating small amounts of food (e.g., self-induced vomiting after consuming two cookies).
Repeatedly chewing and spitting out, but not swallowing, large amounts of food.

Binge-eating disorder is recurrent episodes of binge eating in the absence if regular inappropriate compensatory behavior characteristic of bulimia nervosa (American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 4th ed, text rev. Washington, DC: American Psychiatric Association, 2000).

The modifications to eating disorders that appear in the 'Feeding and Eating Disorders' Chapter of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) include:

1. The addition of three disorders (avoidant/restrictive food intake disorder, rumination disorder, and pica) previously described in the DSM-IV-TR section 'Feeding and Eating Disorders of Infancy or Early Childhood'

2. Clarifications and modifications to anorexia nervosa and bulimia nervosa

3. The inclusion of binge eating disorder as a formal diagnosis

Research suggests that the majority of individuals seeking treatment for an eating disorder are classified as eating disorder not otherwise specified based on DSM-IV criteria. Using DSM-5 criteria, many of these individuals will be reassigned to a diagnosis with greater clinical utility. A large body of research also supports the inclusion of binge eating disorder as a formal diagnosis. The changes to eating disorders, recommended by the Eating Disorders Work Group, aim to clarify existing criteria and to decrease the frequency with which individuals are assigned to the heterogeneous residual category, eating disorder not otherwise specified (EDNOS), which provides little clinical utility.

Fairburn and colleagues have proposed a Cognitive-behavioral Maintaining Factors model, which suggests that common mechanisms operate across all eating disorder diagnostic categories, including anorexia nervosa (AN), bulimia nervosa (BN) and eating disorder not otherwise specified (EDNOS) (Fairburn, Cooper, & Shafran, 2008; Fairburn, Cooper, & Shafran, 2003). In the present research, using the sub typing of the DSM-IV diagnosis (AN-R, AN-BP, BN-BP, BN, BED and EDNOS), the analysis of socio-demographic, behavioral and psychological traits related to the core maintaining factors aimed to evaluate a possible preliminary model of "spectrum disorder" of EDs in childhood and adolescence in relation to a possible continuum in characteristics measure.

3.3 Method

For study design and subjects, clinical units, ethical issues, variables, standardized instruments, measures, data recording, statistical analysis see Chapter 2.

3.4 Results

The sample comprised 419 children and adolescents (mean age 14.7±2.14; age range 7-18 years; males 13.8%). The 73% of the collective was aged between 14 and 18 years. The percentage of males aged between 7 and 13 years is 34%, while females of this younger age class are 26%. Of the entire young patients' collective, 44.8% were diagnosed with Anorexia Nervosa Restricting type (AN-R, n=187) [mean age = 14.8 years (SD = 1.8); mean body mass index (BMI; kg/m2) = 15.9 (SD = 2.2)], 6.7% were diagnosed with Anorexia Nervosa Binge Purging type (AN-BP, n=28) [mean age = 15.8 years (SD = 1.2); mean BMI = 17.0 (SD = 2.1)], 9.4% were diagnosed with Bulimia Nervosa Binge Purging type (BN-BP, n=39) [mean age = 15.7 years (SD = 1.2); mean BMI = 21.2 (SD = 4.5)], 2.9% were diagnosed with Bulimia Nervosa (BN, n=12) [mean age = 15.7 years (SD = 1.1); mean BMI = 23.2 (SD = 4.7)], 7.9% were diagnosed with Binge Eating Disorder (BED, n=33) [mean age = 14.7 years (SD = 2.2); mean BMI = 33.3 (SD = 8.3)] and 28.3% were diagnosed with Eating Disorder Not Otherwise Specified (EDNOS, n=118) [mean age = 13.7 years (SD = 2.7); mean BMI = 20.5 (SD = 5.3)].

In Table 3.1 it is possible to observe that all the demographic, physical and indicator variables showed significant differences among diagnosis (Kruskal Wallis non parametric test $p<.05$; Pearson chi square $p<.05$).

Table 3.2 reports multiple comparisons by Mann-Whitney U test for continuous variables and Fisher exact test for categorical variables. These analyses revealed gender differences between AN-R and BED, between AN-BP and BED and between BN-BP and BED ($p<.05$). In fact in BED category there is the highest percentage of males than in all other groups (42.4%) and in AN-R, AN-BP and BN-BP the higher percentages of females (100% for AN-BP, 92.3% for BN-BP and 91.4% for AN-R). No differences in BMI were observed between AN-R and AN-BP ($p=0.150$), between BN-BP and BN, between BN-BP and EDNOS and between BN and EDNOS ($p>.05$). Concerning age multiple comparisons showed the following statistically significant differences ($p<.05$): AN-R vs EDNOS, AN-BP vs EDNOS and BN-BP vs EDNOS.

Concerning variables related to the considered maintaining factors, there were no significant differences between AN-BP vs BN-BP, between AN-BP vs BN and between BN-BP and BN. BED and EDNOS presented significant different values only for shape concern and body image concerns ($p<.05$). Significant differences for a large number of indicator variables were observed for BN-BP vs EDNOS, for AN-BP vs EDNOS, for BN vs EDNOS and for AN-R vs EDNOS (See Table 3.2 and 3.1). The indicator variables with less inter-diagnosis differences through multiple comparisons were anxious-depressed (YSR), perfectionism (EDI-3) and self oriented perfectionism (CAPS); on the contrary the variables with the higher number of inter-diagnosis differences were body dissatisfaction (EDI-3), restraint (EDE 12.0D) and low self esteem (Table 3.2).

To better characterize the six EDs subtypes an index calculated as rate between the bulimia and the restraint scores (B/R Index=Bulimia+1/Restraint+1) was used. A significant difference among the diagnostic groups was observed for this index (Kruskal Wallis nonparametric test $p=0.000$) (Table 3.1). Multiple comparisons showed significant differences between diagnostic subtypes (p adjusted by Bonferroni Method<0.05) with the exception of AN-BP vs BN-BP; AN-BP vs BN; AN-BP vs BED; BN-BP vs BN; BN-BP vs BED; BN vs BED, BED vs EDNOS. This analysis evidenced a gradient in the index values, with a minimum in AN-R (1.4±3.0) and a maximum in BN (4.6±3.4) and BED (4.1±4.5).

Area of interest	Indicator variable	AN-R		EDNOS		AN-BP		BN-BP		BED		BN		p**
		M ± SD, median		M ± SD, median		M ± SD, median		M ± SD, median		M ± SD, median		M ± SD, median		
Restraint	Restraint (EDE 12.0D)	3.5±1.8	3.7	2.5±1.7	2.4	4.4±1.4	4.9	3.9±1.7	4.4	1.9±1.6	1.5	3.9±2.0	4.1	0.000
Binge Eating	Bulimia (EDI-3)	4.1±6.8	1	4.8±6.5	2.0	12.4±7.1	13.0	14.3±9.2	15.3	9.0±5.0	9.8	17.8±9.3	18.5	0.000
Binge Eating B/R Index	Bulimia / Restraint	1.4±3.0	0.6	2.0±2.5	1.0	2.7±1.6	2.5	3.6±2.4	3.5	4.1±4.5	2.9	4.6±3.4	4.1	0.000

In Table 3.3 are reported the correlations between core EDs maintaining mechanisms (binge eating and restraint) and the additional maintaining factors for each of the six considered diagnoses. Differences in the correlations between indicator variables and the two core maintaining factors were observed among the six diagnoses. Correlation analysis results suggested that in AN-R the restraint indicator variable is related to shape concern (ρ=0.461, p<.01), affective problems (ρ=0.289, p<.01), body dissatisfaction (ρ=0.286, p<.01), low self esteem (ρ=0.278, p<.01), interpersonal problems (ρ=0.265, p<.01), body image concern (ρ=0.223, p<.01), and anxious-depressed (ρ=0.198, p<.01). In AN-BP the binge eating indicator variable is associated to body image concern (ρ=0.545, p<.01), body dissatisfaction (ρ=0.457, p<.01), and affective problems (ρ=0.444, p<.05). In BN-BP the binge eating indicator variable is linked to body dissatisfaction (ρ=0.606, p<.01), interpersonal problems (ρ=0.558, p<.01), affective problems (ρ=0.509, p<.01), low self esteem (ρ=0.482, p<.01), and perfectionism (ρ=0.468, p<.01). In the same group of patients restraint is correlated only with anxious-depressed indicator variable (ρ=0.336, p<.05). In BN binge eating is related to body image concern (ρ=0.768, p<.01), body dissatisfaction (ρ=0.722, p<.01), low self esteem (ρ=0.632, p<.05) and interpersonal problems (ρ=0.592, p<.05). In BED binge eating is strongly correlated with affective problems (ρ=0.931, p<.01), body dissatisfaction (ρ=0.852, p<.01), interpersonal difficulties (ρ=0.819, p<.01), perfectionism (ρ=0.785, p<.01), and low self esteem (ρ=0.759, p<.01). In EDNOS binge eating is particularly correlated with affective problems (ρ=0.727, p<.01) and restraint is mainly related to body dissatisfaction (ρ=0.408, p<.01), shape concern (ρ=0.374, p<.01) and interpersonal problems (ρ=0.370, p<.01).

To explore the relationship among the core and additional maintaining factors in EDs a principal component analysis (PCA) was performed. The rotated principal components matrix of the first two components is observable in Table 3.4. This Table shows the rotated principal components matrix for the each of the six diagnoses. The total variation accounted for the first two principal components is also shown. Figures 3.1,

3.2, 3.3, 3.4, 3.5, 3.6 showed the relationship among the examined variables in the subspace of the first two components within each subtype of diagnosis (AN-R, AN-BP, BN-BP, BN, BED and EDNOS). Table 3.4 showed for almost all diagnoses, with the exception of bulimia nervosa (BN) and anoressia nervosa binge purging subtype (AN-BP), that the first principal component was related to bulimia and the second to restraint, showing the independence of the two variables. On the contrary, in BN restraint and bulimia were positively correlated in the second component, while in the AN-BP restraint was not clearly associated with any of the two principal components. For AN-R, BN-BP, BED and EDNOS, the first principal component was usually correlated with bulimia, perfectionism, body dissatisfaction, low self esteem, interpersonal problems and affective problems scores; while the second principal component was usually correlated with restraint, shape concern, body image concern, self oriented perfectionism, anxious-depressed dimensions. However, anxious-depressed and body image concerns did not show a specific relationship with one of the two components in BED, because of their relationship with both components. A similar condition was observed for body image concerns in EDNOS. Results seemed to indicate an incomplete adherence to the trans-diagnostic model. In fact, the relationships among the several analyzed dimensions were not the same in every subgroup; however such differences were observed in particular in the two subgroups with the lower sample size (AN-BP =28 patients and BN = 12 patients).

To complete the analysis we produced a principal component analysis including also the diagnosis variable (AN-R, AN-BP, BN-BP, BN, BED and EDNOS). The scatter plot of the first two components is shown in Figure 3.7, which includes and highlights the position of the six diagnosis respect to all the maintaining factors indicator variables. AN-R group, particularly related to restraint, shape concern and anxious-depressed, was not linked to AN-BP, BN-BP and BN groups that seemed to constitute an unique cluster, particularly related to bulimia, affective and interpersonal problems and perfectionism. EDNOS group appear to be opposed to AN group and also BED group seemed to be independent from the others.

3.5 Discussion

Using the sub typing of the DSM-IV diagnoses (AN-R, AN-BP, BN-BP, BN, BED and EDNOS), the analysis of socio-demographic, behavioral and psychological traits related to the maintaining factors aimed to

evaluate the trandiagnostic cognitive behavioural model of EDs and elaborate a possible preliminary model of "spectrum disorder" of EDs in childhood and adolescence.

All dominant models of the eating disorders implicate personality and cognitive variables in the emergence of shape and weight concerns and the development of specific symptoms such as bingeing and purging.

Standardized measures of personality traits and disorders generally confirm clinical descriptions of restricting anorexics (AN-R) as constricted, conforming, and obsessional individuals (Calderoni, Fantozzi, et al., 2013; Calderoni, Muratori, et al., 2013). In our sample 44.8% were diagnosed with Anorexia Nervosa Restricting type and 6.7% were diagnosed with Anorexia Nervosa Binge Purging type.

A less consistent picture suggesting affective instability and impulsivity has emerged from the assessment of subjects with bulimia nervosa (Brooks, Rask-Andersen, Benedict & Schiöth, 2012). In the present study 9.4% were diagnosed with Bulimia Nervosa Binge Purging type and 2.9% were diagnosed with Bulimia Nervosa.

Considerable heterogeneity exists within EDs subtypes, however, and a number of special problems complicate the interpretation of psychological and behavioral data in this population.

Research suggests that the majority of individuals seeking treatment for an eating disorder are classified as eating disorder not otherwise specified based on DSM-IV criteria.

A large body of research supports the inclusion of binge eating disorder as a formal diagnosis. In our sample eating disorder not otherwise specified based on DSM-IV criteria were overall 151 (36.2%) but in the present analysis we extrapolate BED subjects that were 33 (7.9%) considering them as a distinct group from the EDNOS one (28.3%).The changes to EDs, recommended by the DSM-5, aim to clarify existing criteria and to decrease the frequency with which individuals are assigned to the heterogeneous category, eating disorder not otherwise specified (EDNOS), which provides little clinical utility.

Although over the past decade, research efforts led to several evidence for the validity of a transdiagnostic cognitive-behavioral model of eating disorders (e.g. Mansell, Harvey, Watkins, & Shafran, 2008), only a few studies examined the model (or the relative therapy) in children and adolescents patients' population (Wilfley, Kolko & Kass, 2011; Schmidt et al., 2007) and no studies examined the role of subtyping EDs in the analysis of a transdiagnostic approach.

All the demographic, physical and indicator variables showed significant differences among diagnosis (Kruskal Wallis non parametric test $p<.05$; Pearson chi square $p<.05$).

The analyses revealed gender differences between AN-R and BED, between AN-BP and BED and between BN-BP and BED ($p<.05$). In BED category there is the highest percentage of males than in all other groups (42.4%) and in AN-R, AN-BP and BN-BP the higher percentages of females (100% for AN-BP, 92.3% for BN-BP and 91.4% for AN-R). Concerning age multiple comparisons showed the following statistically significant differences ($p<.05$): AN-R vs EDNOS, AN-BP vs EDNOS and BN-BP vs EDNOS. No differences in BMI were observed between AN-R and AN-BP ($p=0.150$), between BN-BP and BN, between BN-BP and EDNOS and between BN and EDNOS ($p>.05$).

Concerning variables related to the considered maintaining factors, there were no significant differences between AN-BP vs BN-BP, between AN-BP vs BN and between BN-BP and BN, indicating these tree subtypes as a very homogeneous subgroup.

BED and EDNOS presented significant different values only for shape concern and body image concerns ($p<.05$).

The indicator variables with less inter-diagnosis differences through multiple comparisons were anxious-depressed (YSR), perfectionism (EDI-3) and self oriented perfectionism (CAPS); on the contrary the variables with the higher number of inter-diagnosis differences were body dissatisfaction (EDI-3), restraint (EDE 12.0D) and low self esteem (Table 3.2).

To better characterize the six EDs subtypes an index calculated as rate between the bulimia and the restraint scores (B/R Index=Bulimia+1/Restraint+1) was used. A significant difference among the diagnostic groups was observed for this index (Kruskal Wallis nonparametric test $p=0.000$) (Table 3.1). Multiple comparisons showed significant differences between diagnostic subtypes (p adjusted by Bonferroni Method<0.05) with the exception of AN-BP vs BN-BP; AN-BP vs BN; AN-BP vs BED; BN-BP vs BN; BN-BP vs BED; BN vs BED, BED vs EDNOS. This analysis evidenced a gradient in the index values, with a minimum in AN-R (1.4±3.0) and a maximum in BN (4.6±3.4) and BED (4.1±4.5): in this context it would be possible to argue in favor of a specific continuum in these behavioral characteristics that could be considered in agreement with Samantha Brooks and colleagues (2012) that outlined an ‘impulse control’ spectrum model of eating

disorders providing evidence to support a neural model across a continuum of restricted versus impulsive behavior.

In Table 3.3 are reported the correlations between core Eating Disorders maintaining mechanisms (binge eating and restraint) and the additional maintaining factors for each of the six considered diagnoses. Differences in the correlations between indicator variables and the two core maintaining factors were observed among the six diagnoses. In this case it is possible to observe the presence of a kind of gradient for which the relationships between preeminent behavioral factors for diagnosis and additional maintenance factors are overall very strong in BN and weaker in AN-R.

PCA indicated for all diagnoses, with the exception of bulimia nervosa (BN) and anoressia nervosa binge purging subtype (AN-BP), that the first principal component was related to bulimia and the second to restraint, showing the independence of the two variables. On the contrary, in BN restraint and bulimia were positively correlated in the second component, while in the AN-BP group, restraint was not clearly associated with any of the two principal components. Principal component analysis including also the diagnosis variable (AN-R, AN-BP, BN-BP, BN, BED and EDNOS) highlights the position of the six diagnosis respect to all the maintaining factors indicator variables. AN-R group, particularly related to restraint, shape concern and anxious-depressed, was not linked to AN-BP, BN-BP and BN groups that seemed to constitute a central and unique cluster, particularly related to bulimia, affective and interpersonal problems, low self esteem and Perfectionism. EDNOS group appear to be opposed to AN group and also BED group seemed to be independent from the others. The cluster constituted by AN-BP, BN and BN-BP is the one with the strongest correlations with all the variables considered. This could be due to the fact that this model was originally developed through the analysis of patients suffering from bulimia (Fairburn, C. G., 1981) and further extended to the entire EDs patients (Fairburn, Cooper & Shafran, 2003).

Elucidation of clinically relevant subtypes has been proposed as a means of advancing treatment research. Analysis of personality and cognitive traits has to be assessed at admission to classify participants into personality subtypes also to predict outcomes at discharge and risk of readmission.

One strategy for advancing treatment research in EDs is to determine whether there are any clinically relevant subtypes within the EDs population. This approach is based on the premise that a better understanding of variability within populations carrying the same categorical diagnosis offers hope for

maximizing the proportion of patients who achieve recovery (Angst & Cassano, 2005). Variations in treatment response among individuals with EDs may be due, in part, to within-group differences in behavioral or biological factors that could be targeted by novel, subtype-specific interventions (National Institute of Mental Health [NIMH], 2008). Conversely, a failure to recognize to clinically relevant subtypes in EDs may hinder treatment research if the interventions studied target a heterogeneous clinical population.

Another approach to identifying clinically relevant subtypes is to focus on comorbid psychopathology. For example, there is increasing interest in the utility of subtyping individuals with eating disorders based on patterns of within-group heterogeneity in personality psychopathology. With few exceptions (Thompson-Brenner et al., 2008; Wagner et al., 2006), studies have found three personality subtypes in patients with eating disorders:

1) an undercontrolled subtype characterized by impulsivity and behavioral or emotional dysregulation

2) an overcontrolled subtype characterized by inhibition and constraint

3) a low psychopathology subtype characterized by normative levels of personality functioning (for review, see Wonderlich, Joiner, Keel, Williamson, & Crosby, 2007).

Moreover, research has found differences among these subtypes in patterns of Axis I and II comorbidity, family history of psychopathology, rates of childhood abuse, and psychosocial functioning (Holliday, Tchanturia, Landau, Collier, & Treasure, 2005; Steiger et al., 2010; Westen & Harnden-Fischer, 2001).

Tailoring interventions to clinically relevant subtypes has been proposed as a strategy for improving treatment response in psychiatric populations (Angst & Cassano, 2005; NIMH, 2008). The current study contributes to and extends extant research documenting the validity of personality subtypes in individuals with eating disorders. Using PCA, we identified the following four subtype's clusters

1) AN-R
2) AN-BP, BN-BP, BN
3) BED
4) EDNOS

These clusters differed with respect to correlation among core and additional maintaining factors underlined by the cognitive behavioral transdiagnostic model of EDs.

Of note, our findings suggest that compared to AN-R patients, individuals with AN-BP, BN-BP and BN, characterized by emotion dysregulation and low self esteem, had stronger correlation with the variables included in the analysis.

These findings could converge with previous work, which suggests that a classification scheme based on comorbid personality psychopathology may have more clinical utility than current approaches to conceptualizing eating disorders (Westen & Harnden-Fischer, 2001).

Moreover, subtypes similar to those identified in this sample have been described in other psychiatric groups (e.g., Miller, Kaloupek, Dillon, & Keane, 2004), and a trait-based approach to conceptualizing personality psychopathology is consistent with proposed revisions to the classification of personality disorders in DSM-5 (Personality and Personality Disorders Work Group, 2010). BED category and EDNOS category revealed different and specific features in the analyzed areas. Thus, subtyping individuals may have utility across diagnostic categories as a means of identifying clinically relevant subgroups.

The findings of the current study need to be considered in light of several limitations. The first is the low sample size, in particular of some subtype: differences in PCA were observed mainly in the two subgroups with the lower sample size (AN-BP =28 patients and BN = 12 patients). Moreover this study did not evaluate maintaining factors prospectively.

A research by Janet Treasure of exploration of cerebral activity during presentation of food images has identified activations common to the whole eating disorders group and specific to subgroups with particular eating disorder diagnoses. An abnormal prefrontal reaction was specifically manifested in response to food stimuli, whereas differences in cerebellar, occipital, and parietal activity were present in reaction to both emotional and food images (Uher et al., 2004). Treasure concluded that clinical practice can be informed by an understanding of both transdiagnostic mechanisms and specific mechanisms to eating disorder diagnostic groups.

In conclusion, this study supports the clinical utility of personality subtypes in patients with EDs. Future research is needed to identify the mechanisms responsible for differential treatment response among personality subtypes in EDs. This work could help to increase the number of EDs patients who benefit from a good diagnostic classification and a tailored treatment and decrease the personal and societal costs of this debilitating illness.

Table 3.1 Demographic and clinical characteristics by type of eating disorder

		AN-R (44.8%)		**AN-BP** (6.7%)		**BN-BP** (9.4%)		**BN** (2.9%)		**BED** (7.9%)		**EDNOS** (28.3%)		**p***
Female %		91.4		100		92.3		91.7		57.6		79.7		0.000
Male %		8.6		0		7.7		8.3		42.4		20.3		0.000
7-13 years %		26.2		3.6		5.1		0		27.3		42.4		0.000
14-18 years %		73.8		96.4		94.9		100		72.7		57.6		0.000
		M ± SD	**Median**	**M ± SD**	**Median**	**M ± SD**	**Median**	**M ± SD**	**Median**	**M ± SD**	**Median**	**M ± SD**	**Median**	**p****
Age		14.8±1.8	15.0	15.8±1.2	16.0	15.7±1.2	16.0	15.7±1.1	16.0	14.7±2.2	15.0	13.7±2.7	14.0	0.000
BMI		15.9±2.2	15.6	17.0±2.1	16.9	21.2±4.5	20.1	23.2±4.7	24.5	33.3±8.3	32.4	20.5±5.3	19.5	0.000
Area of interest	**Indicator Scale**	**M ± SD**	**Median**	**M ± SD**	**Median**	**M ± SD**	**Median**	**M ± SD**	**Median**	**M ± SD**	**Median**	**M ± SD**	**Median**	**p****
Low Self-Esteem	Low self esteem (EDI-3)	9.6±7.3	10	13.1±7.2	12	12.4±7.5	15	15.3±6.8	17.0	6.8±7.1	5.00	6.8±6.6	5.5	0.000
Perfectionism	Perfectionism (EDI-3)	6.9±5.8	6	9.2±5.1	9.5	8.5±6.2	8.0	11.5±7.0	12.0	5.4±5.3	4.0	4.8±5.3	3.0	0.000
	Self-oriented Perfectionism (CAPS)	37.5±13.75	37	39.2±14.0	40.5	39.2±10.1	39.0	40.5±11.3	41.5	29.6±12.1	29.0	31.7±13.4	33.0	0.000
Interpersonal Difficulties	Interpersonal problems (EDI-3)	18.2±17.0	17	25.7±14.4	25.0	23.3±12.5	23.1	28.1±11.1	26.5	12.6±12.4	10.0	14.4±12.8	14.0	0.000
Mood Intolerance	Affective problems (EDI-3)	20.1±16.4	18	32.5±13.2	34.0	29.2±15.8	26.0	28.8±15.9	27.0	17.0±16.2	18.0	14.2±14.8	10.5	0.000
	Anxious-depressed (YSR)	9.2±6.8	9	7.8±8.2	5.5	11.1±7.9	14.0	10.9±5.1	11.5	6.4±6.8	5.0	5.7±5.8	4.8	0.000
Overevaluation of Weight and Shape	Body dissatisfaction (EDI-3)	16.9±12.2	16	27.3±11.6	32.5	25.7±13.6	32.0	28.8±7.5	31.0	15.4±13.8	14.0	14.5±12.7	14.5	0.000
	Body image concerns (BUT)	2.1±1.5	2.1	3.1±1.4	3.2	3.4±1.4	3.8	3.3±1.29	3.1	2.4±1.7	2.6	1.4±0.7	1.5	0.000
	Shape concern (EDE 12.0D)	4.0±1.4	4.3	4.2±1.1	4.8	5.0±1.2	5.2	5.2±0.8	5.2	4.3±1.5	4.6	3.2±1.4	3.0	0.000
Restraint	Restraint (EDE 12.0D)	3.5±1.8	3.7	4.4±1.4	4.9	3.9±1.7	4.4	3.9±2.0	4.1	1.9±1.6	1.5	2.5±1.7	2.4	0.000
Binge Eating	Bulimia (EDI-3)	4.1±6.8	1	12.4±7.1	13.0	14.3±9.2	15.3	17.8±9.3	18.5	9.0±5.0	9.8	4.8±6.5	2.0	0.000
B/R Index	Bulimia / Restraint	1.4±3.0	0.6	2.7±1.6	2.5	3.6±2.4	3.5	4.6±3.4	4.1	4.1±4.5	2.9	2.0±2.5	1.0	0.000

Note: AN, anorexia nervosa; BN, bulimia nervosa and binge eating disorder; EDNOS, eating disorder not otherwise specified; AN-R, Anoressia Nervosa Restrictive Type; BN-BP, Bulimia Nervosa Binge Purging Subtypes; BED, Binge Eating Disorder; BMI, Body Mass Index; EDI-3, Eating Disorder Inventory 3; CAPS, Child and Adolescent Perfectionism Scale; YSR, Youth Self Report; BUT, Body Uneasiness Test; EDE 12.0D, Eating Disorder Examination Questionnaire; M, Mean; SD, standard deviation; p*, Pearson chi square, p **, Kruskal Wallis nonparametric test p.

Table 3.2 Multiple Comparisons by Mann-Whitney U test for continuous variables and Fisher exact test for categorical variables: unadjusted p and p adjusted for multiplicity by Bonferroni Method (italic font) are reported

		AN-R vs AN-BP	AN-R vs BN-BP	AN-R vs BN	AN-R vs BED	AN-R vs EDNOS	AN-BP vs BN-BP	AN-BP vs BN	AN-BP vs BED	AN-BP vs EDNOS	BN-BP vs BN	BN-BP vs BED	BN-BP vs EDNOS	BN vs BED	BN vs EDNOS	BED vs EDNOS
Gender		-	-	-	0.000 ***0.000***	0.005 ***0.075***	-	-	0.000 ***0.000***	0.008 ***0.120***	-	0.001 ***0.015***	-	0.038 *0.570*	-	0.013 *0.195*
Age class		0.007 *0.105*	0.003 ***0.045***	0.041 *0.615*	-	0.004 ***0.06***	-	-	0.016 *0.240*	0.000 ***0.000***	-	0.018 *0.270*	0.000 ***0.000***	-	0.003 ***0.045***	-
Age		0.006 *0.090*	0.006 *0.090*	-	-	0.001 ***0.015***	-	-	0.039 *0.585*	0.000 ***0.000***	-	0.043 *0.645*	0.000 ***0.000***	-	0.013 *0.195*	-
BMI		0.010 *0.150*	0.000 ***0.000***	0.000 ***0.000***	0.000 ***0.000***	0.000 ***0.000***	0.000 ***0.000***	0.000 ***0.000***	0.000 ***0.000***	0.000 ***0.000***	-	0.000 ***0.000***	-	0.000 ***0.000***	-	0.000 ***0.000***
Area of interest	**Indicator variable**															
Low Self-Esteem	Low self esteem (EDI-3)	0.024 *0.360*	0.033 *0.495*	0.012 *0.180*	0.031 *0.465*	0.001 ***0.015***	-	-	0.001 ***0.015***	0.000 ***0.000***	-	0.003 ***0.045***	0.000 ***0.000***	0.001 ***0.015***	0.000 ***0.000***	-
Perfectionism	Perfectionism (EDI-3)	0.016 *0.240*	-	0.021 *0.315*	-	0.003 ***0.045***	-	-	0.004 *0.060*	0.000 ***0.000***	-	0.025 *0.375*	0.001 ***0.015***	0.006 *0.090*	0.001 ***0.015***	-
	Self-oriented Perfectionism (CAPS)	-	-	-	0.001 ***0.015***	0.000 ***0.000***	-	-	0.005 *0.075*	0.008 *0.120*	-	0.001 ***0.015***	0.003 ***0.045***	0.013 *0.195*	0.031 *0.465*	-
Interpersonal Difficulties	Interpersonal problems (EDI-3)	0.011 *0.165*	0.020 *0.300*	0.012 *0.180*	0.038 *0.579*	0.017 *0.255*	-	-	0.000 ***0.000***	0.000 ***0.000***	-	0.001 ***0.015***	0.000 ***0.000***	0.001 ***0.015***	0.001 ***0.015***	-
Mood Intolerance	Affective problems (EDI-3)	0.000 ***0.000***	0.002 ***0.030***	-	-	0.001 ***0.015***	-	-	0.000 ***0.000***	0.000 ***0.000***	-	0.005 *0.075*	0.000 ***0.000***	0.033 *0.495*	0.003 ***0.045***	-
	Anxious-depressed (YSR)	-	-	-	0.023 *0.345*	0.000 ***0.000***	-	-	-	-	-	0.010 *0.150*	0.000 ***0.000***	0.027 *0.405*	0.004 ***0.024***	-
	Body dissatisfaction (EDI-3)	0.000 ***0.000***	0.000 ***0.000***	0.001 ***0.015***	-	-	-	-	0.001 ***0.015***	0.000 ***0.000***	-	0.001 ***0.015***	0.000 ***0.000***	0.003 ***0.045***	0.000 ***0.000***	-
Overevaluation of Weight and Shape	Body image concerns (BUT)	0.002 ***0.030***	0.000 ***0.000***	0.011 *0.165*	-	0.000 ***0.000***	-	-	-	0.000 ***0.000***	-	0.016 *0.240*	0.000 ***0.000***	-	0.000 ***0.000***	0.003 ***0.045***
	Shape concern (EDE 12.0D)	0.006 *0.090*	0.000 ***0.000***	0.004 *0.060*	-	0.000 ***0.000***	-	-	-	0.000 ***0.000***	-	-	0.000 ***0.000***	-	0.000 ***0.000***	0.000 ***0.000***
Restraint	Restraint (EDE 12.0D)	0.017 *0.255*	-	-	0.000 ***0.000***	0.000 ***0.000***	-	-	0.000 ***0.000***	0.000 ***0.000***	-	0.000 ***0.000***	0.000 ***0.000***	0.002 ***0.030***	0.016 *0.240*	0.032 *0.480*
Binge Eating	Bulimia (EDI-3)	0.000 ***0.000***	0.000 ***0.000***	0.000 ***0.000***	0.023 *0.345*	-	-	-	-	0.000 ***0.000***	-	0.018 *0.270*	0.000 ***0.000***	0.009 *0.135*	0.000 ***0.000***	-
B/R Index	Bulimia / Restraint	0.000 ***0.000***	0.000 ***0.000***	0.000 ***0.000***	0.000 ***0.000***	0.003 ***0.045***	-	0.042 *0.630*	-	0.001 ***0.015***	-	-	0.000 ***0.000***	-	0.000 ***0.000***	0.005 *0.075*

Note: AN-R, anorexia nervosa restricting type; AN-BP, anorexia nervosa binge-purging type; BN-BP, bulimia nervosa binge-purging type; BN, bulimia nervosa; BED, binge eating disorder; EDNOS, eating disorder not otherwise specified; BMI, Body Mass Index; EDI-3, Eating Disorder Inventory 3; CAPS, Child and Adolescent Perfectionism Scale; YSR, Youth Self Report; BUT, Body Uneasiness Test; EDE 12.0D, Eating Disorder Examination Questionnaire; B/R Index=Bulimia+1/Restraint+1; M, Mean; P values adjusted for multiplicity by Bonferroni Method <0.05 are in italic bold font.

Table 3.3 Correlation between additional and core maintaining factors by type of Eating Disorder: Spearman's Rho correlation coefficient

			Low Self Esteem	Perfectionism		Interpersonal Difficulties	Mood Intollerance		Overevaluation of Weight and Shape		
			Low self esteem (EDI-3)	Perfectionism (EDI-3)	Self oriented perfectionism (CAPS)	Interpersonal problems (EDI-3)	Affective problems EDI-3	Anxious depressed (YSR)	Body dissatisfaction (EDI-3)	Body image concerns (BUT)	Shape concern (EDE 12.0D)
AN-R	**Binge Eating (Bulimia, EDI-3)**	ρ	0.392	0.419	0.215	0.423	0.579	0.269	0.419	0.207	0.249
		p	0.000	0.000	0.003	0.000	0.000	0.000	0.000	0.004	0.001
	Restraint (EDE 12.0D)	ρ	0.278	0.107	0.091	0.265	0.289	0.198	0.286	0.223	0.461
		P	0.000	0.144	0.215	0.000	0.000	0.006	0.000	0.002	0.000
AN-BP	**Binge Eating (Bulimia, EDI-3)**	ρ	0.103	0.235	0.040	0.353	0.444	-0.026	0.457	0.545	0.060
		p	0.603	0.230	0.841	0.065	0.018	0.896	0.015	0.003	0.763
	Restraint (EDE 12.0D)	ρ	0.162	-0.034	0.085	0.035	0.134	-0.150	0.191	0.233	0.287
		p	0.409	0.865	0.668	0.858	0.496	0.446	0.331	0.233	0.139
BN-BP	**Binge Eating (Bulimia, EDI-3)**	ρ	0.482	0.468	0.223	0.558	0.509	0.223	0.606	0.363	0.090
		p	0.002	0.003	0.172	0.000	0.001	0.173	0.000	0.023	0.585
	Restraint (EDE 12.0D)	ρ	-0.040	-0.083	0.288	-0.044	-0.030	0.336	0.071	0.179	0.378
		p	0.808	0.617	0.076	0.792	0.857	0.037	0.666	0.277	0.018
BN	**Binge Eating (Bulimia, EDI-3)**	ρ	0.632	0.491	0.466	0.592	0.509	0.288	0.722	0.768	0.350
		p	0.027	0.105	0.127	0.043	0.091	0.364	0.008	0.004	0.264
	Restraint (EDE 12.0D)	ρ	0.593	0.407	0.214	0.729	0.604	0.495	0.599	0.730	0.340
		p	0.042	0.189	0.505	0.007	0.038	0.102	0.040	0.007	0.280
BED	**Binge Eating (Bulimia, EDI-3)**	ρ	0.759	0.785	0.230	0.819	0.931	0.516	0.852	0.449	0.028
		p	0.000	0.000	0.198	0.000	0.000	0.002	0.000	0.009	0.879
	Restraint (EDE 12.0D)	ρ	0.267	-0.014	0.446	0.116	0.247	0.375	0.320	0.293	0.417
		p	0.134	0.939	0.009	0.520	0.165	0.032	0.069	0.099	0.016
EDNOS	**Binge Eating (Bulimia, EDI-3)**	ρ	0.597	0.679	0.387	0.622	0.727	0.385	0.693	0.349	0.442
		p	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
	Restraint (EDE 12.0D)	ρ	0.301	0.348	0.171	0.370	0.272	0.257	0.408	0.215	0.374
		p	0.001	0.000	0.064	0.000	0.003	0.005	0.000	0.019	0.000

Note: EDs, eating disorders; AN-R, anorexia nervosa restricting type; AN-BP, anorexia nervosa binge-purging type; BN-BP, bulimia nervosa binge-purging type; BN, bulimia nervosa; BED, binge eating disorder; EDNOS, eating disorder not otherwise specified; EDI-3, Eating Disorder Inventory 3; CAPS, Child and Adolescent Perfectionism Scale; YSR, Youth Self Report; BUT, Body Uneasiness Test; EDE 12.0D, Eating Disorder Examination Questionnaire; B/R Index=Bulimia+1/Restraint+1; ρ, Spearman's Rho correlation coefficient; p, p value

Table 3.4 Principal component analysis for AN-R, AN-BP, BN-BP, BN, BED, EDNOS: factor loadings for the first two rotated principal components

Mantaining factors	AN-R Components VE=55.4%		Mantaining factors	AN-BP Components VE=50.2%		Mantaining factors	BN-BP Components VE=62.4%		Mantaining factors	BN Components VE=71.7%		Mantaining factors	BED Components VE=67.2%		Mantaining factors	EDNOS Components VE=58.8%	
	1	2		1	2		1	2		1	2		1	2		1	2
Affective problems	**0.852**	0.270	**Body dissatisfaction**	**0.842**	0.078	**Low self esteem**	**0.909**	0.014	**Perfectionism**	**0.876**	0.181	**Affective problems**	**0.943**	0.160	**Affective problems**	**0.863**	0.169
Interpersonal problems	**0.779**	0.343	**Interpersonal problems**	**0.729**	0.439	**Body dissatisfaction**	**0.884**	0.047	**Anxious depressed**	**0.856**	0.203	**Interpersonal problems**	**0.884**	0.066	**Interpersonal problems**	**0.842**	0.233
Perfectionism	**0.752**	0.099	**Low self esteem**	**0.708**	0.364	**Interpersonal problems**	**0.852**	0.189	**Affective problems**	**0.822**	0.318	**Bulimia**	**0.846**	0.280	**Low self esteem**	**0.835**	0.221
Low self esteem	**0.700**	0.434	**Body image concerns**	**0.661**	-0.058	**Affective problems**	**0.838**	0.104	**Interpersonal problems**	**0.750**	0.499	**Perfectionism**	**0.841**	-0.040	**Body dissatisfaction**	**0.804**	0.352
Body dissatisfaction	**0.677**	0.419	**Affective problems**	**0.656**	0.499	**Bulimia**	**0.719**	0.152	**Self oriented perfectionism**	**0.750**	0.218	**Low self esteem**	**0.837**	0.158	**Bulimia**	**0.683**	0.217
Bulimia	**0.631**	-0.087	**Bulimia**	**0.651**	-0.005	**Perfectionism**	**0.661**	0.265	**Low self esteem**	**0.739**	0.575	**Body dissatisfaction**	**0.774**	0.323	**Perfectionism**	**0.678**	0.383
Shape concern	0.122	**0.777**	**Restraint**	0.393	-0.271	**Restraint**	-0.107	**0.754**	**Body image concerns**	0.347	**0.831**	**Restraint**	0.131	**0.786**	**Body image concerns**	0.455	0.424
Body image concerns	0.136	**0.762**	**Shape concern**	0.337	-0.206	**Self oriented perfectionism**	-0.024	**0.734**	**Restraint**	0.323	**0.781**	**Shape concern**	-0.097	**0.746**	**Shape concern**	0.272	**0.704**
Restraint	0.027	**0.609**	**Self oriented perfectionism**	-0.075	**0.710**	**Anxious depressed**	0.290	**0.708**	**Body dissatisfaction**	0.214	**0.773**	**Self oriented perfectionism**	0.161	**0.631**	**Self oriented perfectionism**	0.115	**0.701**
Anxious depressed	0.374	**0.544**	**Perfectionism**	0.300	**0.684**	**Body image concerns**	0.472	**0.620**	**Bulimia**	0.297	**0.725**	**Anxious depressed**	0.553	0.575	**Restraint**	0.176	**0.623**
Self oriented perfectionism	0.228	**0.451**	**Anxious depressed**	-0.056	**0.674**	**Shape concern**	0.291	**0.577**	**Shape concern**	0.111	**0.669**	**Body image concerns**	0.449	0.543	**Anxious depressed**	0.274	**0.581**

Note: principal component analysis based on correlation matrix; rotation method: Varimax with Kaiser normalization; VE= Variance Explained by the first two components; AN-R, anorexia nervosa restricting type; AN-BP, anorexia nervosa binge-purging type; BN-BP, bulimia nervosa binge-purging type; BN, bulimia nervosa; BED, binge eating disorder; EDNOS, eating disorder not otherwise specified

Figure 3.1 Principal Component Analysis for Anorexia Nervosa Restricting Type (AN-R): projection of variables on the subspace of the first two principal components. The horizontal line is the Principal Component 1 while the vertical line is the Principal Component 2.

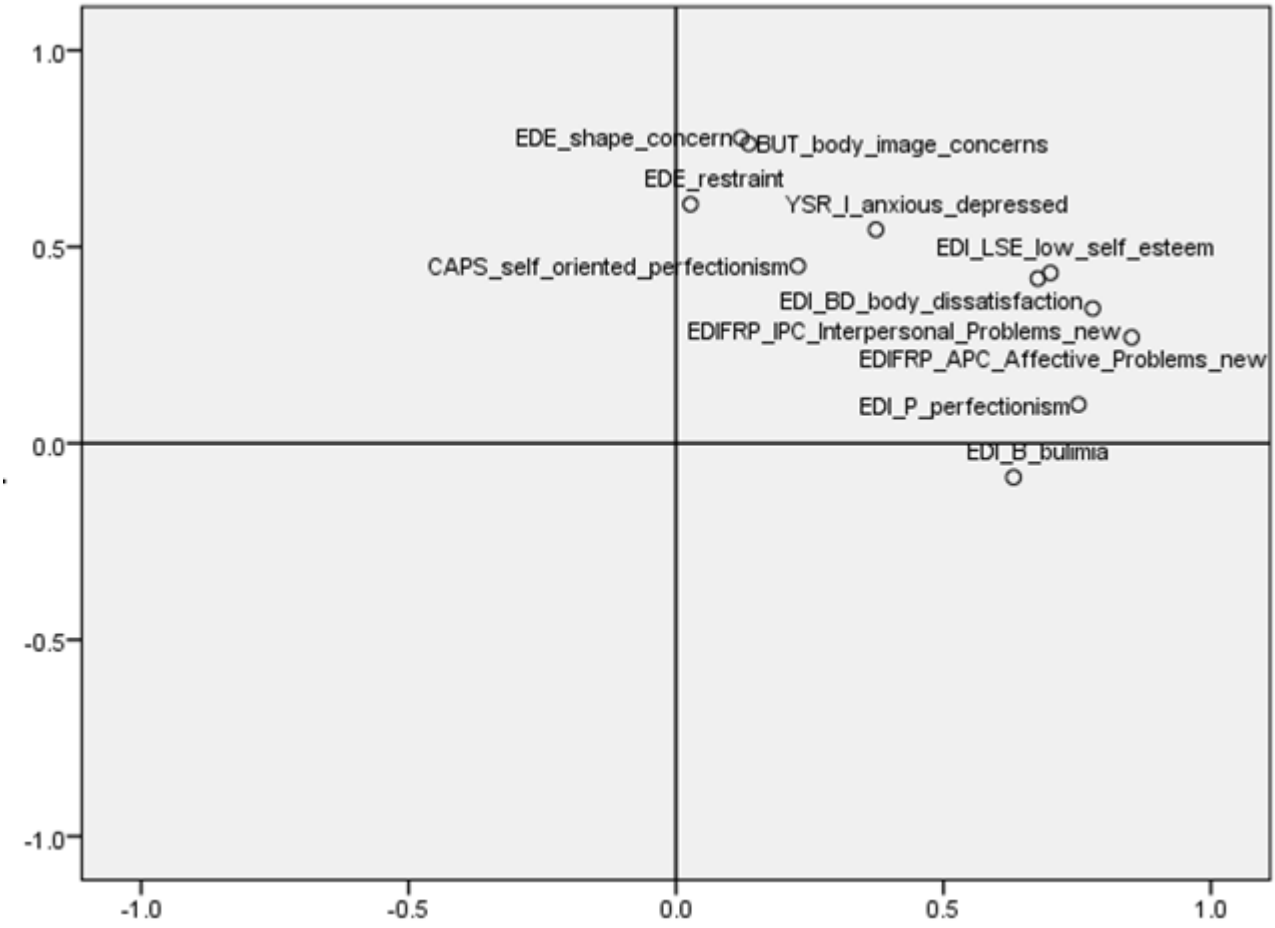


Figure 3.2 Principal Component Analysis for Anorexia Nervosa Binge-eating–purging type (AN-BP): projection of variables on the subspace of the first two principal components. The horizontal line is the Principal Component 1 while the vertical line is the Principal Component 2.

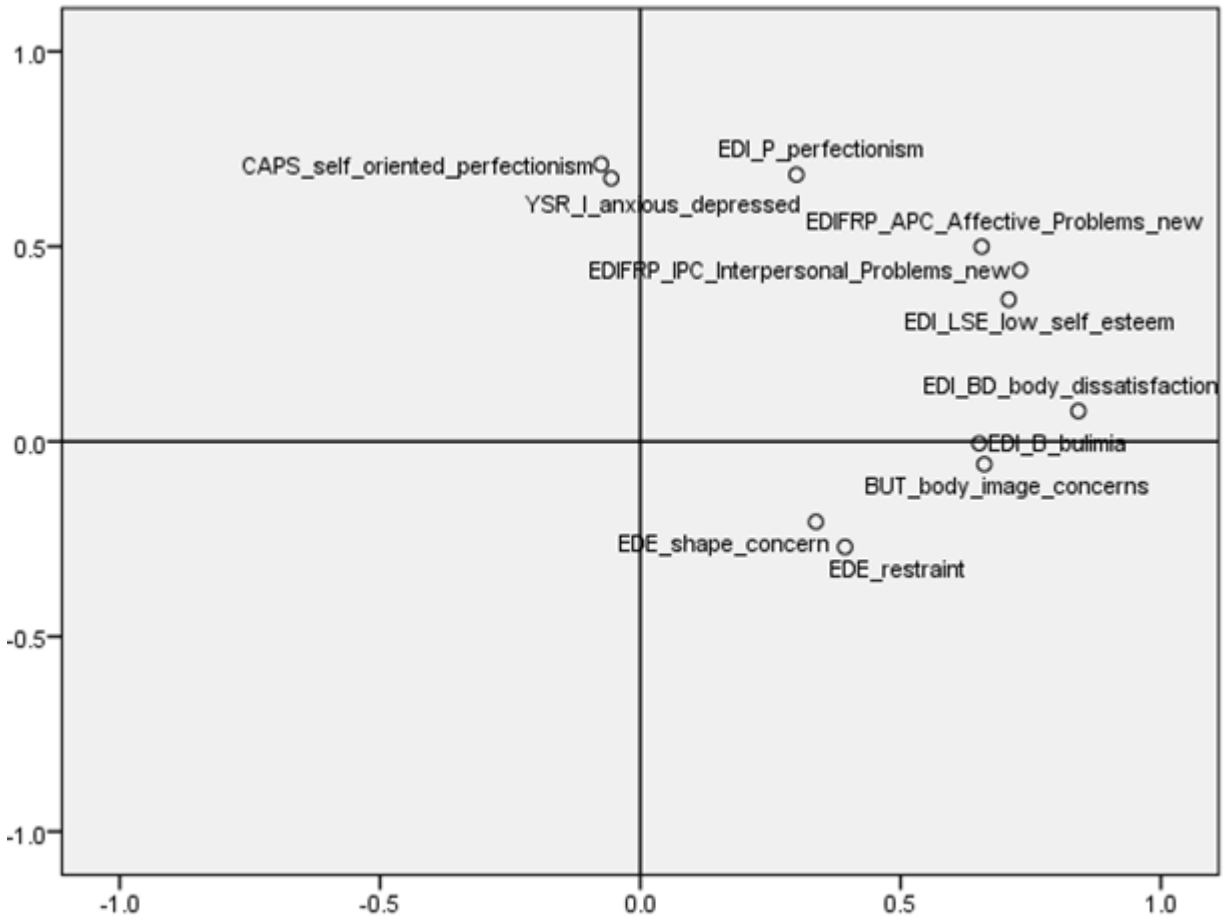


Figure 3.3 Principal Component Analysis for Bulimia Nervosa Binge-eating–purging type (BN-BP): projection of variables on the subspace of the first two principal components. The horizontal line is the Principal Component 1 while the vertical line is the Principal Component 2

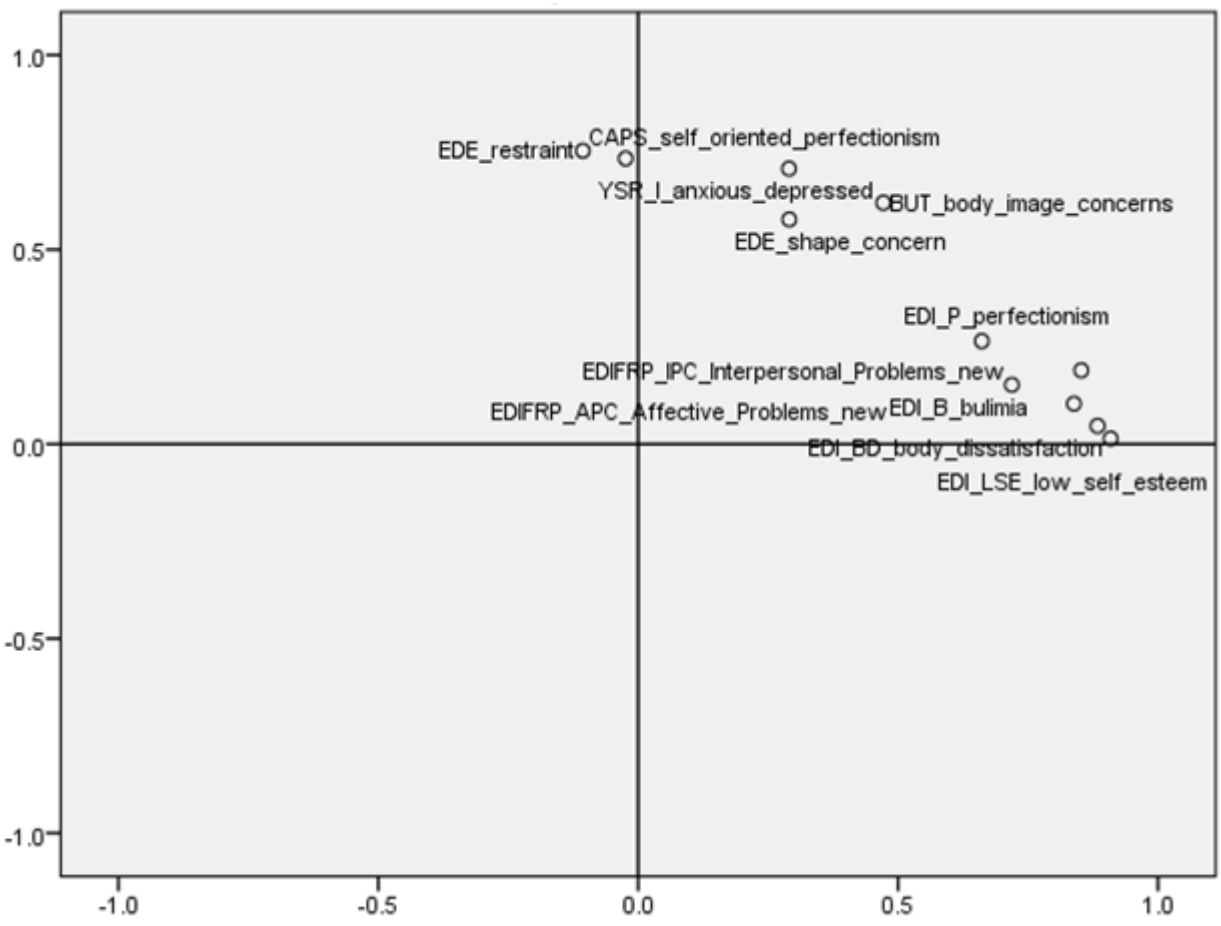


Figure 3.4 Principal Component Analysis for Bulimia Nervosa (BN): projection of variables on the subspace of the first two principal components. The horizontal line is the Principal Component 1 while the vertical line is the Principal Component 2

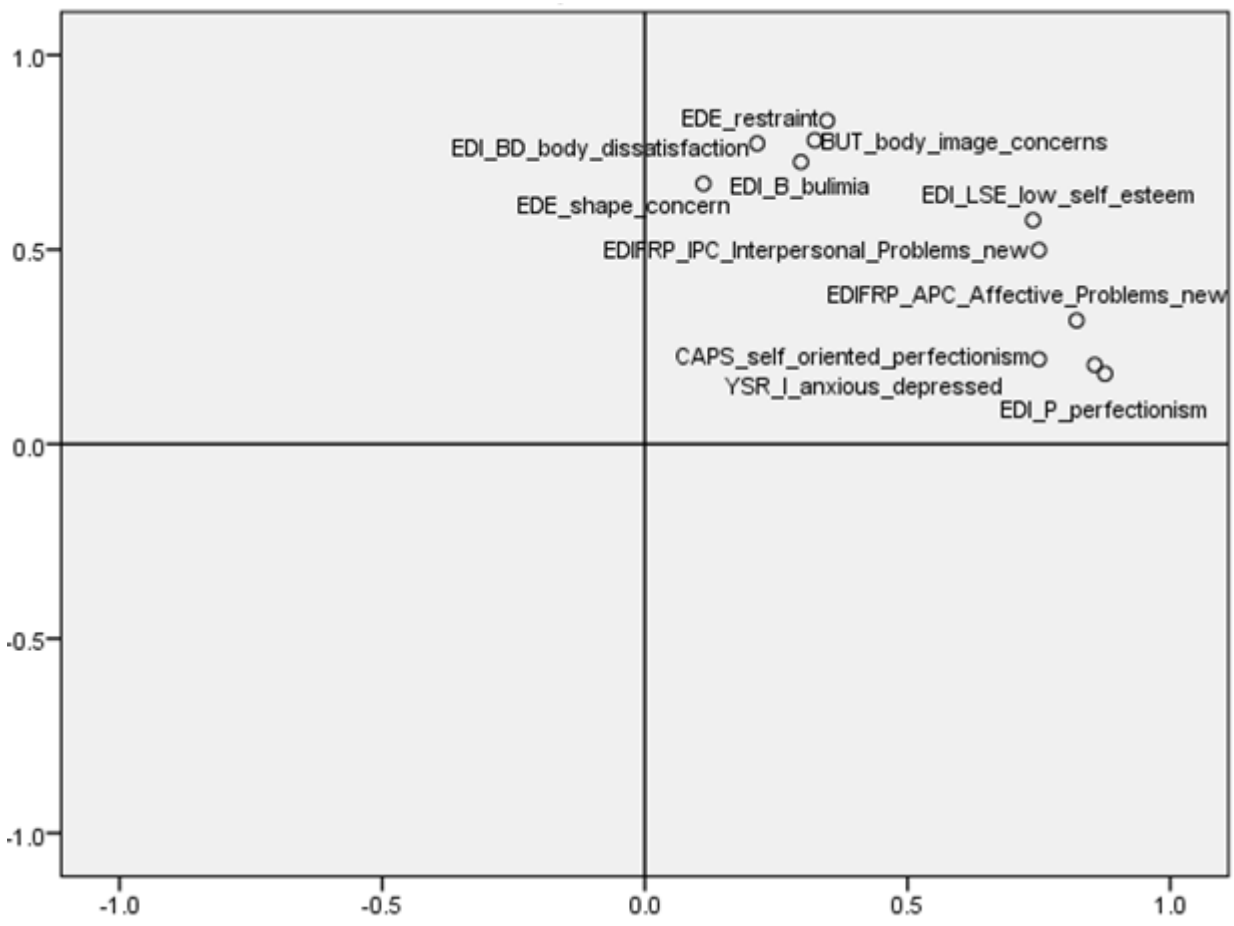


Figure 3.5 Principal Component Analysis for Binge Eating Disorder (BED): projection of variables on the subspace of the first two principal components. The horizontal line is the Principal Component 1 while the vertical line is the Principal Component 2

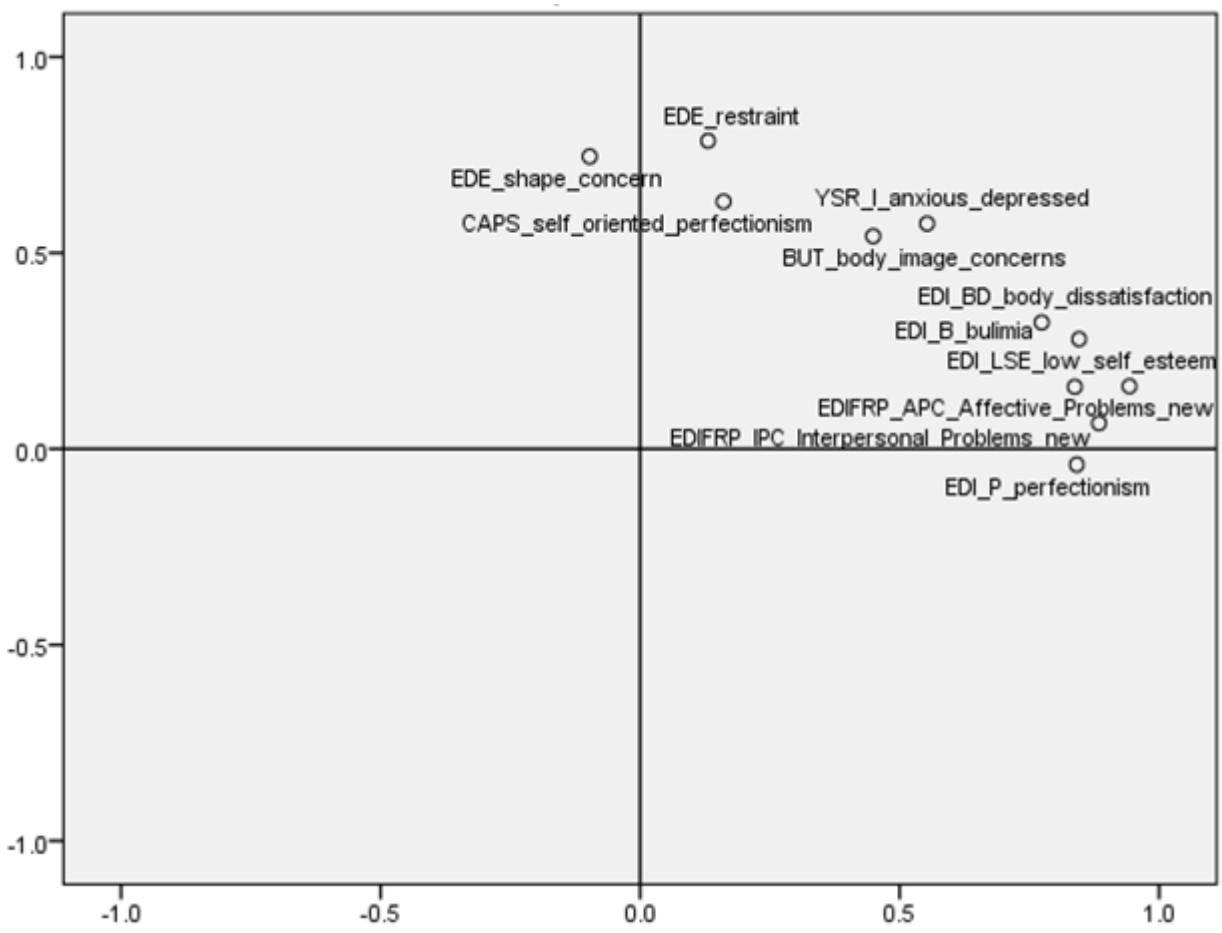


Figure 3.6 Principal Component Analysis for Eating Disorders not Otherwise Specified (EDNOS): projection of variables on the subspace of the first two principal components. The horizontal line is the Principal Component 1 while the vertical line is the Principal Component 2

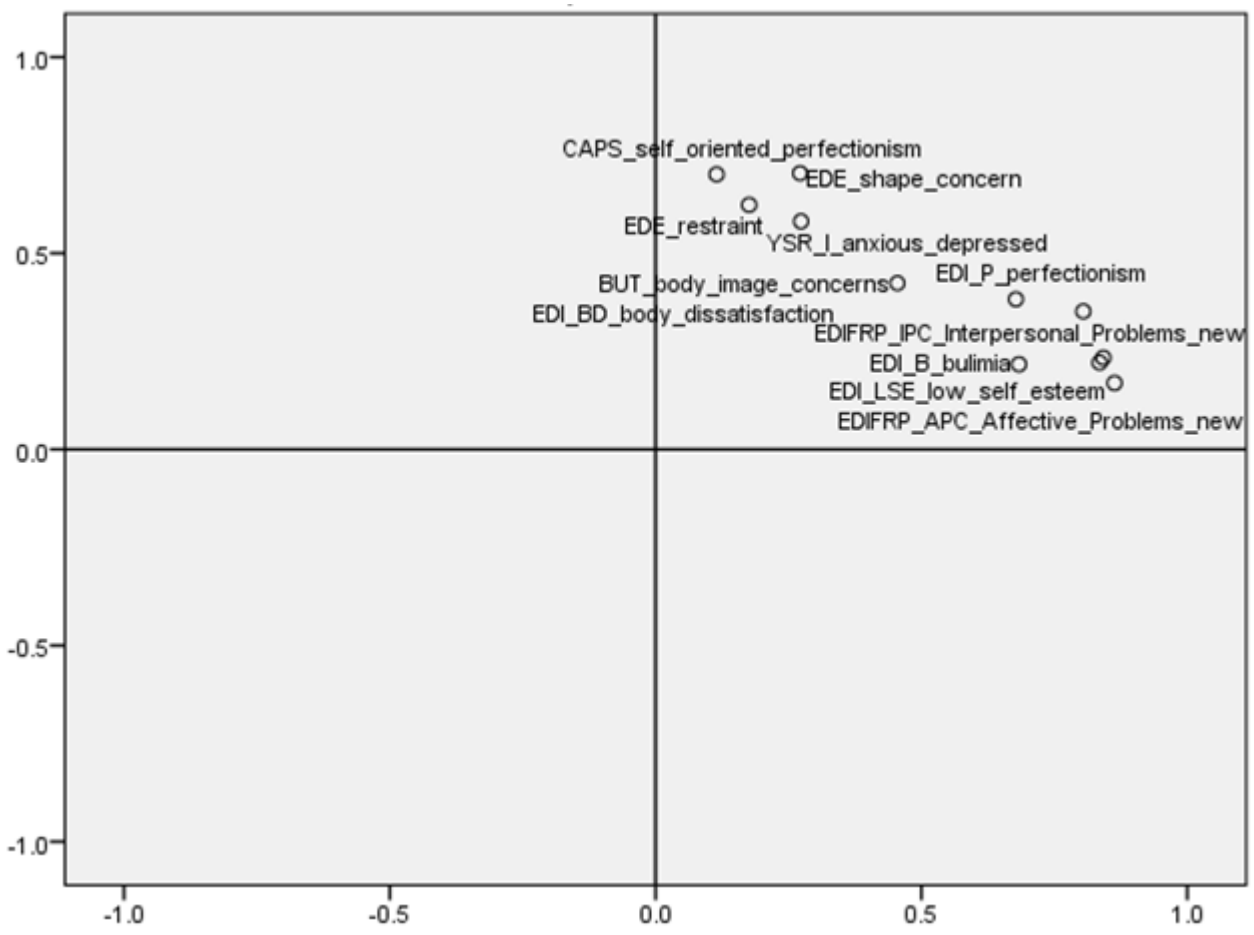
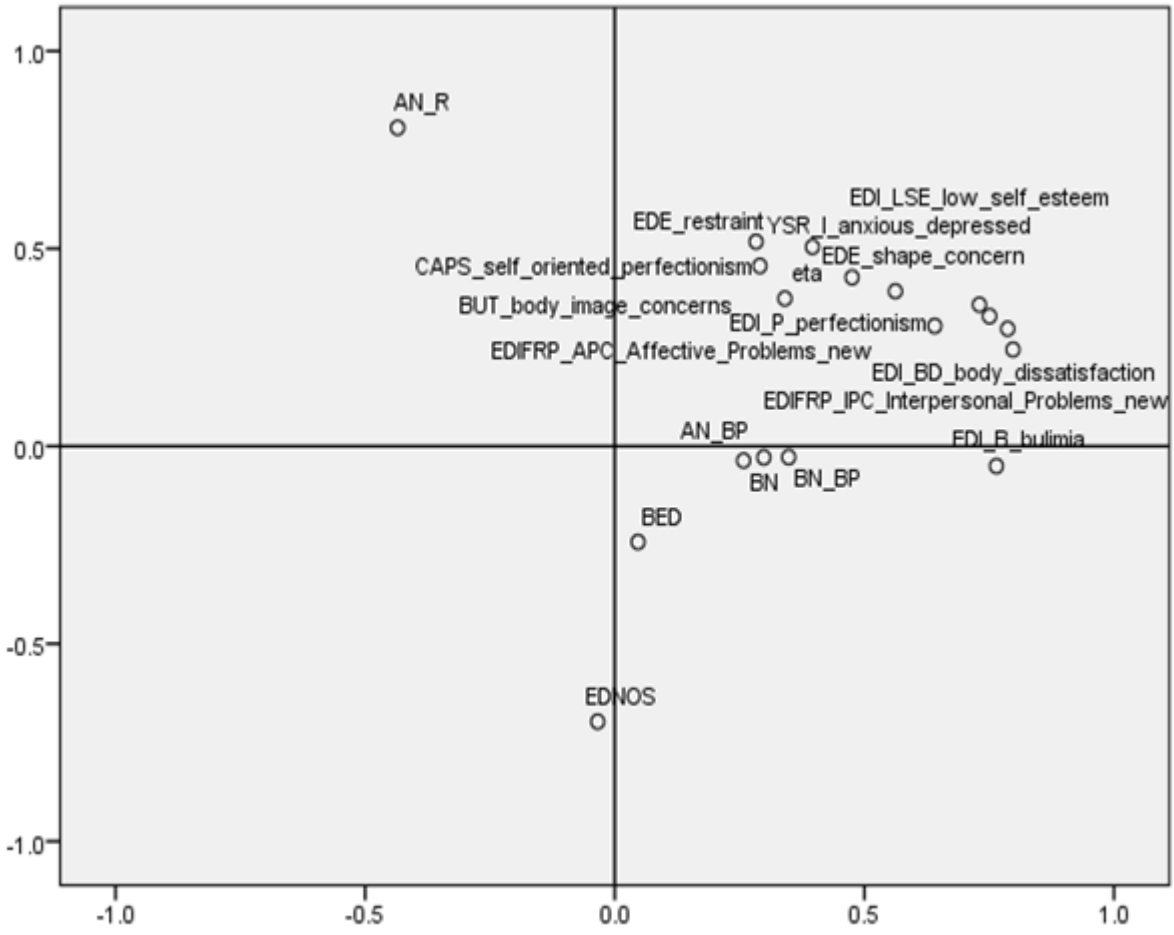


Figure 3.7 Principal Component Analysis with diagnosis of Eating Disorders (AN-R, AN-BP, BN-BP, BN, BED, EDNOS): projection of variables on the subspace of the first two principal components. The horizontal line is the Principal Component 1 while the vertical line is the Principal Component 2



Note: AN-R, anorexia nervosa restricting type; AN-BP, anorexia nervosa binge-purging type; BN-BP, bulimia nervosa binge-purging type; BN, bulimia nervosa; BED, binge eating disorder; EDNOS, eating disorder not otherwise specified

Chapter 4

Features of Anorexia Nervosa restricting type in childhood and adolescence on the base of the cognitive-behavioral maintaining factors model of Eating Disorders

4.1 Abstract

Objective: To determine specific features of Anorexia Nervosa Restricting Type in childhood and adolescence on the base of the Cognitive-behavioral Maintaining Factors model of Eating Disorders.

Method: The sample comprised 419 children and adolescents (mean age 14.7±2.14; age range 7-18 years; males 13.8). The patients were assessed through standardized instruments to evaluate key EDs features as low self-esteem, self-oriented perfectionism, interpersonal difficulties, mood intolerance, overevaluation of weight and shape, dietary restraint and binge eating. Multinomial logistic analysis was performed to outline AN-R characteristics in the comparison with other diagnostic subtypes.

Results: Of the entire young patients' collective, 44.8% were diagnosed with Anorexia Nervosa Restricting type (AN-R). Concerning anxious-depressed indicator variable, results indicated that having a high score in this domain is negatively associated with the risk of being diagnosed with AN-BP respect to AN-R. AN-R seem to be characterized by higher level not only of anxious-depressed scores respect to AN-BP but also of affective problems if compared with BN and EDNOS. Comparing young patients diagnosed with BED versus those with AN-R, emerged a critical aspect in the self oriented perfectionism scale in AN-R.

Discussion: Between all the indicator variables, probability for having a diagnosis of AN-R in our sample of children and adolescents with EDs is linked to variation in age, anxious-depressed, affective problems, shape concern, body dissatisfaction and self oriented perfectionism scores. The study suggests that some processes may be operating in particular way in AN-R group that seems to represent a phenotypically homogeneous subsample.

Keywords: Transdiagnostic; Cognitive-Behavioral Model; Eating Disorders; Childhood and Adolescence; EDs Subtypes; Anorexia Nervosa Restricting Type.

4.2 Background

Principal component analysis in Chapter three of the present doctoral report that included the diagnosis variable (AN-R, AN-BP, BN-BP, BN, BED and EDNOS) highlights the position of the six diagnosis respect to all the maintaining factors indicator variables. AN-R group, particularly related to restraint, shape concern and anxious-depressed, was not linked to AN-BP, BN-BP and BN groups that seemed to constitute a central and unique cluster, particularly related to bulimia, affective and interpersonal problems, low self esteem and Perfectionism. EDNOS group appear to be opposed to AN group and also BED group seemed to be independent from the others. The cluster constituted by AN-BP, BN and BN-BP is the one with the strongest correlations with all the variables considered. Elucidation of clinically relevant subtypes has been proposed as a means of advancing treatment research.

Prevalence rates of 0.3% indicate that anorexia nervosa (AN) is a relatively rare disorder (Hoek & van Hoeken, 2003). Its high relevance stems rather from its serious psychosocial and medical complications, which lead to death in approximately ten percent of cases (Mitchell & Crow, 2006). AN is characterized by a refusal to maintain body weight above a minimal normal weight, which is accompanied by an endocrine disorder resulting in amenorrhea. Although anorexic subjects are underweight, they experience an intense fear of gaining weight or becoming fat. Additionally, subjects with AN perceive their own body weight and shape in a distorted manner, which is linked with a denial of the severity of the actual low body weight. Whereas in the binge-eating purging subtype of AN, patients regularly engage in binge-eating attacks, followed by purging behavior (e.g., self-induced vomiting) in order to compensate food intake, persons diagnosed with the restricting subtype of AN predominantly use dieting as a method to lose weight (American Psychiatric Association, 2000). In general, fasting is accompanied by an aversion to “forbidden” food, particularly comprising food rich in proteins such as milk (Vaz, Alcaina, & Guisado, 1998). This avoidance of certain food has been labeled calorie phobia or food phobia, and results in the experience of negative consequences from eating, i.e., negative emotions like fear, and positive reinforcement from starvation (Ellison et al., 1998; Shafran et al., 1999). Hyperactivity is a salient clinical feature in a substantial subset of AN patients (Maestro, Scardigli, Brunori, Calderoni, Curzio, Denoth et al., 2014): the starvation induced hypoleptinemia contributes to this phenomenon. Higher levels of dietary restraint, depression and

the restricting subtype of AN were significantly associated with excessive exercise in the results of a study by Bewell-Weiss (Bewell-Weiss & Carter, 2010).

Individuals with Anorexia Nervosa (AN) typically fare worse than those with other eating disorders, and it is unclear why. Patients with AN are more likely to drop out of treatment prematurely and less likely to experience sustained symptom remission following treatment. They also face a risk of mortality that tends to be higher than that of every other psychiatric groups (Herzog et al., 1996; 2. Gowers et al., 2007; 3. Keel & Brown, 2010).

Anorexia nervosa is a complex psychiatric disorder with endocrinologic manifestations primarily affecting adolescent females. The classic triad of presenting symptoms is weight loss in excess of 15% of ideal body weight, behavioral changes and amenorrhea (secondary or primary). The menstrual irregularities may cause the patient or family to seek gynecologic consultation before the diagnosis of primary psychiatric disorder has been made. Hypoestrogenic hypothalamic amenorrhea may result in osteoporosis, stress fractures, and infertility.

Treasure (2006) reported that Anorexia nervosa (AN) is highly valued by people with the disorder. It is also a highly visible disorder, evoking intense emotional responses from others, particularly those closest to the person. Treasure proposed a maintenance model of restricting anorexia nervosa, combining intra- and interpersonal factors suggesting four main maintaining factors (perfectionism/cognitive rigidity, experiential avoidance, pro-anorectic beliefs, response of close others) to be integrated with what is known about starvation-related maintenance factors (Schmidt &Treasure, 2006).

Dysfunctional eating behavior is strongly associated with cognitive traits that may underpin the control of appetite. For example, people with AN are ascetic and extremely self-disciplined (Fassino et al., 2006), strive for perfection and are obsessional (Davies, Liao, Campbell, & Tchanturia, 2009), attend excessively to detail (Lopez, Tchanturia, Stahl, & Treasure, 2009), may have a genetic predisposition to be cognitively inflexible (Holliday, Tchanturia, Landau, Collier, & Treasure, 2005), are preoccupied with food and have anxiogenic concerns about shape, weight and eating (Fairburn & Harrison, 2003). Furthermore, obsessive–compulsive disorder (OCD) is commonly comorbid in people with AN, especially AN-R (Steinglass & Walsh, 2006).

It is unclear, however, how these traits are linked to brain processes, although these cognitive traits are likely to be associated with prefrontal cortex (PFC) functions underlying attention, planning, self-reference and

working memory. Subcortical activation interacts with executive functions (e.g. cognitive inhibition, working memory, and conflict monitoring) to regulate attention and modulate the saliency of a stimulus (Gazzaley et al., 2007). Dysregulation between the PFC, visual cortex and appetitive activation associated with the striatum may underlie dysfunctional cognitive traits in those with eating disorders and could modulate the reward value of a food stimulus. Additionally, excessive PFC function in people with AN-R may compensate for reduced or aberrant activation in mesolimbic appetite regions or conversely, the cognitive inhibition of an otherwise intact but anxiogenic subcortical response (Kaye, Fudge, & Paulus, 2009).

Whilst the anterior cingulate cortex (ACC), a monitor for conflict and prediction error, may be associated with eating disorders particularly in response to body dissatisfaction (Friederich et al., 2010), it is potentially the dorsolateral prefrontal cortex (DLPFC) that is most strongly implicated in aberrant appetitive responses in those with AN-R. For example, functional magnetic resonance imaging (fMRI) studies of women with eating disorders shows aberrant activation in the DLPFC (Brooks et al., 2011; Brooks et al., 2012b; Brooks et al., 2012a; Uher et al., 2003). Furthermore, activation of the DLPFC is associated with successful appetite suppression (Hollmann et al., 2011). Artificial stimulation of the DLPFC using repetitive Transcranial Magnetic Stimulation (rTMS) reduces food-induced craving (Van den Eynde et al., 2010), and improves working memory performance (Andrews, Hoy, Enticott, Daskalakis & Fitzgerald., 2011; Zanto, Rubens, Thangavel & Gazzaley, 2011). Thus, increased DLPFC activation in females with AN could reflect cognitive inhibition of appetitive responses, for example, associated with working memory ruminations about how to control one's eating.

Subliminal stimuli activate subcortical responses that are independent of PFC processes, and such stimuli can influence cognitive processes (Banse, Seise & Zerbes, 2001; Fazio & Olson, 2003; Gray, 2001; Hartikainen, Ogawa & Knight, 2000; Murphy & Zajonc, 1993). LeDoux (1996) suggests that a 'quick and dirty' neural pathway relays sensory information from the retina directly to the visual cortex and subcortical regions without engaging conscious processes associated with the PFC. Baars, in his Global Workspace Theory (GWT) suggests that unconscious processes, particularly derived from visual stimuli, interact with cognitive processes like working memory (Baars & Franklin, 2003) to set the context for a consciously-perceived self-relevant goal. This theory seems to fit well with the behavior of a person with AN-R, where

eating patterns and life events in general are rigidly controlled by self-imposed strategies that ultimately maintain a suppressing effect on appetitive processes, whereby the origin is largely unconsciously derived.

Also the trait of perfectionism, a multidimensional construct generally defined as the pursuit of extreme, unattainable standards of performance and intolerance of mistakes, has been implicated as a predisposing risk factor in eating disorders—anorexia nervosa (AN) in particular. Whereas the majority of the associations described are derived from cross sectional designs, some evidence supports the idea that higher than normative levels of perfectionism appear in advance of the onset of dieting and weight loss. A higher level of perfectionism has also been shown in parents of individuals with AN than in parents of non-AN controls, as well as in patients with AN compared to psychiatric controls. The relationship between perfectionism and both eating and related psychopathological features in individuals with AN has also been studied, revealing positive associations with obsessive compulsive disorder (OCD) and/or obsessive compulsive personality disorder (OCPD). Individuals with concurrent AN and perfectionistic tendencies show an increased severity of illness as reflected in lower BMI as well as an increased resistance to change and less favorable prognosis (Halmi et al., 2012).

Anorexia nervosa has two subtypes: restrictive eating and binge eating alternating with restrictive eating at different periods of the illness. Eating disorders before puberty include food avoidance emotional disorder, which is similar to anorexia; selective eating of only a few foods; pervasive refusal syndrome, with reduced intake and added behavioral problems; and functional dysphagia with no organic etiology. Unpleasant mealtimes and conflicts over eating can precede these conditions of childhood (Maestro, Cordella, Curzio, Intorcia, Roversi, Rossi, Scardigli, Silvestri, Muratori, 2015)

Anorexia Nervosa Subtiping in DSM IV-TR

-Restricting type: During the current episode of anorexia nervosa, the person has not regularly engaged in binge-eating or purging behavior (self-induced vomiting or misuse of laxatives, diuretics, or enemas).

-Binge-eating–purging type: During the current episode of anorexia nervosa, the person has regularly engaged in binge-eating or purging behavior (self-induced vomiting or the misuse of laxatives, diuretics, or enemas).

Behavioral phenotypes are defined by predominant restriction or bingeing/purging. All dominant models of the eating disorders implicate personality variables in the emergence of weight concerns and the

development of specific symptoms. Among women with anorexia nervosa, the anorexigenic hormones PYY, BDNF, and leptin are differentially regulated between the restricting and binge/purge types. Whether these hormone pathways play etiologic roles with regard to anorexia nervosa behavioral types or are compensatory merits further study (Eddy et al., 2015).

Girls with subclinical anorexia nervosa had a higher prevalence of separation anxiety diagnosis, and they reported significantly more major depressive and generalized anxiety symptoms compared with girls reporting no eating disorders. Girls with weight concerns reported significantly more major depressive, separation, and generalized anxiety symptoms compared with girls reporting no eating disorders (Touchettea et al., 2011). Data from a research of Harrison, Sullivan, Tchanturia and Treasure provide support for conceptualizations of EDs that emphasize the role of emotional functioning in the development and maintenance of EDs. Further research will concentrate on exploring whether these findings are state or trait features of EDs (Sullivan, S., Tchanturia, K. & Treasure, 2010). In a study by Adambegan, Treasure and colleagues the comparison of AN-R patients and their healthy sisters in regard to internalizing, externalizing and overall behavioural problems before onset of the ED showed significant differences in most aspects. Conditional logistic regression analyses showed a statistical significance in the total problem scale and in the internalizing scale. Girls with higher rates of behavioural problems, particularly 'internalizing behaviour problems', were significantly more likely to develop AN-R (Adambegan et al., 2012). A recent study underlined that AN restricting/type patients had lower Female Sexual Function Index (FSFI) total scores, compared with AN binge/purging type and BN patients and analysis showed that shape concern was associated with sexual dysfunction in AN restricting type patients (Castellini et al., 2012).

The present research is aimed to analyze Anorexia Nervosa Restricting type subjects on the base of the dimension of interest outlined by the transdiagnostic cognitive-behavioral core model of eating disorders, comparing them with all others subtypes of eating disorders in children and adolescents. We analyzed in particular patients with restrictive-type AN in order to evaluate a homogeneous subsample, as previous research demonstrated differences in several features between AN patients with and without binge-eating/purging behavior. Moreover we chose to examine the restricting subtype, considering this subgroup very specific and phenotypically homogenous, as it is regarded as the most aetiologically homogeneous of the eating disorders (Herzog et al., 1996).

4.3 Method

Methodological aspects of the multicentre study and preliminary descriptive results were described in Chapter 2 and 3 of the present document.

Statistical analysis

On the base of the analysis performed in Chapter 4, in the present Chapter, to evaluate the role of the maintaining factors indicator variables in discriminating the Anorexia Nervosa Restricting Type (AN-R) from other eating disorders (AN-BP, BN-BP, BN, BED; EDNOS), a multinomial logistic regression was performed using AN-R as reference category. Multinomial Logistic Regression is an extension of binary logistic regression to conduct when the dependent variable is nominal with more than two categories. As the binary logistic regression multinomial regression is used to describe data and to explain the relationship between dependent nominal variable and one or more independent variables. Odds ratio (OR) and 95% C.I. were reported. All statistical analysis was performed by SPSS 21.

4.4 Results

Of the entire young patients' collective (mean age 14.7±2.14; age range 7-18 years; males 13.8%), 44.8% were diagnosed with Anorexia Nervosa Restricting type (AN-R) [mean age = 14.8 years (SD = 1.8); mean body mass index (BMI; kg/m2) = 15.9 (SD = 2.2)], 6.7% were diagnosed with Anorexia Nervosa Binge Purging type (AN-BP) [mean age = 15.8 years (SD = 1.2); mean BMI = 17.0 (SD = 2.1)], 9.4% were diagnosed with Bulimia Nervosa Binge Purging type [mean age = 15.7 years (SD = 1.2); mean BMI = 21.2 (SD = 4.5)], 2.9% were diagnosed with Bulimia Nervosa [mean age = 15.7 years (SD = 1.1); mean BMI = 23.2 (SD = 4.7)], 7.9% were diagnosed with Binge Eating Disorder (BED) [mean age = 14.7 years (SD = 2.2); mean BMI = 33.3 (SD = 8.3)] and 28.3% were diagnosed with Eating Disorder Not Otherwise Specified (EDNOS) [mean age = 13.7 years (SD = 2.7); mean BMI = 20.5 (SD = 5.3)].

Multinomial analysis results are shown in Table 4.1. The AN-R subtype was chosen as reference category. Table 4.1 showed how the probability of being diagnosed as AN-BP, BN-BP, BN, BED and EDNOS respect to AN-R depended on variable scores of the areas of interest. Odds ratios were calculated in each subtype to obtain a measure of the degree to which the variables affects diagnosis. Odds Ratio values > 1 indicated that increasing the scores of the utilized scales increase the probability of not

belonging to the reference category (AN-R). Overall, the probability of having a diagnosis different from AN-R in our sample of children and adolescents with EDs is in some way linked to age, bulimia and restraint, anxious-depressed, affective problems, shape concern, body dissatisfaction and self oriented perfectionism ($p<0.05$). Age resulted a significant variable to discriminate AN-BP, BN-BP and EDNOS on AN-R. The probability of being AN-BP or BN-BP respect to AN-R increased with age (AN-BP: odds ratio [OR] = 1.407, confidence interval [CI] 95%, 1.007–1.967; BN-BP: odds ratio [OR] = 1.373, confidence interval [CI] 95%, 1.030–1.830). On the contrary the probability of being EDNOS respect to AN-R diminished with age (odds ratio [OR] = 0.863, confidence interval [CI] 95%, 0.762–0.978).

Having a high score in bulimia scale was positively associated with the risk of being diagnosed as BN-BP (odds ratio [OR] = 1.179, confidence interval [CI] 95%, 1.110–1.253), AN-BP (odds ratio [OR] = 1.128, confidence interval [CI] 95%, 1.057–1.203), BN (odds ratio [OR] = 1.276, confidence interval [CI] 95%, 1.152–1.412), BED (odds ratio [OR] = 1.209, confidence interval [CI] 95%, 1.116–1.300) and EDNOS (odds ratio [OR] = 1.085, confidence interval [CI] 95%, 1.030–1.142).

On the contrary, having a high score in restraint scale was negatively associated with the risk of being diagnosed as BED (odds ratio [OR] = 0.498, confidence interval [CI] 95%, 0.374–0.665) and EDNOS (odds ratio [OR] = 0.801, confidence interval [CI] 95%, 0.680–0.943).

Concerning anxious-depressed indicator variable, results indicated that having a high score in this domain was negatively associated with the risk of being diagnosed as AN-BP respect to AN-R (odds ratio [OR] = 0.917, confidence interval [CI] 95%, 0.859–0.980).

Further, AN-R seemed to be characterized by higher level not only of anxious-depressed level respect to AN-BP but also of affective problems if compared with BN and EDNOS. In fact, having a high score in this domain is negatively associated with the risk of being diagnosed as BN (odds ratio [OR] = 0.912, confidence interval [CI] 95%, 0.844–0.985) and with EDNOS (odds ratio [OR] = 0.966, confidence interval [CI] 95%, 0.936–0.997).

Table 4.1 showed that BED patients had more issues in shape concern (OR = 1.437, CI 95%, 1.016–2.032) and EDNOS patients had more issues in body dissatisfaction (OR = 1.049, CI 95%, 1.010–1.089) respect to AN-R. With a p-value near to the statistical significance ($p=0.05$) a more compromised shape concern dimension resulted in a lower probability to be EDNOS respect to AN-R (OR = 0.807, CI 95%, 0.648–

1.005, p=0.055) and in a higher probability to be BN-BP respect to AN-R (OR = 1.508, CI 95%, 1.001–2.274, p=0.050).

In this case A higher level of the self oriented perfectionism scale was a protective factor for the risk of having a diagnosis of BED respect to AN-R patients (odds ratio [OR] = 0.950, confidence interval [CI] 95%, 0.915–0.986).

4.5 Discussion

Specific personality traits feature are prominent in many models of the etiology and maintenance of anorexic symptoms (e.g., Schmidt & Treasure, 2006; Strober, 2004). Although the prototypical personality profile in AN emphasizes overcontrolled traits (Wonderlich, Lilenfeld, Riso, Engel, & Mitchell, 2005), many individuals with AN engage in behaviors that typically are associated with undercontrolled personality psychopathology (e.g., binge-eating or purging, self-injury, substance misuse) (Paul, Schroeter, Dahme, & Nutzinger, 2002; Peat, Mitchell, Hoek, & Wonderlich, 2009; Root et al., 2010; Krueger & Eaton, 2010). Several studies have documented personality subtypes in patients with AN (e.g. Strober, 1983; Holliday, Tchanturia, Landau, Collier & Treasure, 2005) and personality subtypes have conceptual appeal as a means of classifying subgroups of AN patients.

The present study is aimed to analyze Anorexia Nervosa Restricting type subjects (AN-R) on the base of the dimension of interest outlined by the transdiagnostic cognitive behavioral core model of eating disorders, comparing AN-R with all others subtypes of eating disorders (Herzog et al., 1996) in a sample of children and adolescents.

The sample comprised 419 children and adolescents. Of the entire young patients' collective, 44.8% were diagnosed with Anorexia Nervosa Restricting type (AN-R). Table 4.1 shows how the probability of being diagnosed as AN-BP, BN-BP, BN, BED and EDNOS respect to AN-R depended on variables scores of the areas of interest outlined by the transdiagnostic cognitive behavioural model.

Overall, the probability of having a diagnosis different from AN-R in our sample of children and adolescents with EDs is linked to age, bulimia and restraint, anxious-depressed, affective problems, shape concern, body dissatisfaction and self oriented perfectionism variables ($p<0.05$).

Age represented a significant variable to discriminate AN-BP, BN-BP and EDNOS versus AN-R. The probability of being AN-BP or BN-BP respect to AN-R increased with age. The age at disease onset has been used in the investigation of the clinical, neurobiological, and genetic heterogeneity of various mental disorders and pre-pubertal onset of BN is extremely rare. AN usually begins in the mid teen years after an episode of dietary restriction (Fairburn & Harrison, 2003). The resulting pathologic weight loss can be short lived and require little treatment or it can become entrenched and require more intensive treatment (Fairburn & Harrison, 2003). BN has a later age of onset (Mitchell, Hatsukami, Eckert, & Pyle, 1985) and may begin after dieting or may be preceded by AN (Sullivan, Bulik, Carter, Gendall, & Joyce, 1996). Some author stated that more than 50% of those with AN, characterized initially by restricting will develop bulimic symptoms and be classified as a binging and purging type of AN. It has been estimated that one-third of patients with BN have a history of AN (Bulik, Sullivan, Fear, & Pickering, 1997; Eckert, Halmi, Marchi, Grove, & Crosby, 1995; Eddy et al., 2008; Eddy et al., 2002; Strober, Freeman, & Morrell, 1997; Tozzi et al., 2005). Conversely, Santonastaso et al. reported that the rate of diagnostic crossover from BN to AN ranges from 0 to 7% (Santonastaso, Zanetti, De Antoni, Tenconi, & Favaro, 2006). Importantly, BN rarely occurs before AN and conversely, patients with severe BN rarely develop AN.

On the contrary the probability of being EDNOS respect to AN-R diminished with age. EDNOS is an especially prevalent category in populations that have received inadequate research attention such as very young children, males, ethnic minorities, and non-Western groups (Becker, Thomas & Pike, 2009). Disproportionately high rates of EDNOS among children have prompted criticism of the DSM-IV criteria for their presumed inability to capture clinically significant eating pathology in young people (Nicholls, Chater, & Lask, 2000). Indeed, investigators have described new eating disorders, such as selective eating disorder (Bryant-Waugh, 2000) and food avoidance emotional disorder (Higgs, Goodyer, & Birch, 1989), which may better encapsulate these unique presentations. In contrast, other theorists have proposed that adolescent EDNOS may signify a prodromal “disorder in evolution” (Le Grange, Loeb, Van Orman, & Jellar, 2004) which presages the ultimate development of full-blown AN or BN. Longitudinal investigations have provided some support for adolescent EDNOS as a risk factor for AN and BN (Chamay-Weber, Narring, & Michaud, 2005). Thus, differences between EDNOS and officially recognized disorders vary by age. More pronounced differences in younger age groups would provide support for the recognition of unique

childhood eating disorders, whereas smaller differences in younger age groups would bolster the conceptualization of EDNOS as a precursor to one of the estalished eating disorders. Participant age represented another demographic characteristic that influenced the magnitude of observed differences between EDNOS and officially recognized disorders. Younger samples demonstrated greater discrepancies in eating pathology between BN and EDNOS than older samples. In contrast, younger samples demonstrated greater similarities in general psychopathology between AN and EDNOS.

Differential age effects between AN and BN are to some extent consistent with epidemiological research indicating that BN may exhibit an older age of onset and a longer duration of illness (Hudson, Hiripi, Pope & Kessler, 2007) than AN. It is possible that EDNOS may develop among young people as a milder variant of psychopathology for which early, less intensive interventions would prevent the subsequent onset of full-blown BN. Indeed, to the extent that DSM-IV defined eating disorders do not adequately capture the differential clinical presentation of younger samples (Nicholls et al., 2000), childhood eating disorders typically focus on restricting (e.g., food avoidance emotional disorder, selective eating disorder) rather than purging behaviors (Bryant-Waugh, 2000).

Having a high score in bulimia scale was positively associated with the risk of being diagnosed as BN-BP, AN-BP, BN, BED and EDNOS. Analogously, having a high score in restraint scale was negatively associated with the risk of being diagnosed as BED and EDNOS. A recent study by De Young et al. compared the type and frequency of restrictive eating behaviors across the two subtypes of anorexia nervosa (restricting and binge eating/purging) in adult women (mean age, 25 years) to determine whether subtype differences in restrictive eating behaviors were attributable to severity of the disorder or to the frequency of binge eating. Results revealed that individuals with AN-BP generally reported more frequent restrictive eating behaviors than individuals with AN-R. These differences indicated that the presence and frequency of restrictive eating behaviors in AN may be nonweight-based markers of severity. Binge eating frequency did not account for these findings. The present findings are especially interesting in light of the weight-based severity rating in the DSM-5 (De Young et al., 2013)

Concerning anxious-depressed indicator variable, our results indicated that having a high score in this domain was negatively associated with the risk of being diagnosed as AN-BP respect to AN-R. Further, AN-R seemed to be characterized by higher level not only of anxious-depressed scores respect to AN-BP but also

of affective problems if compared with BN and EDNOS: having a high score in this domain is negatively associated with the risk of being diagnosed as BN and as EDNOS (vs AN-R). High levels of internalizing psychopathology (anxiety, depression, somatization) have been reported in people with EDs (García-Alba, 2004; McDermott, Forbes, Harris, McCormack, & Gibbon, 2006; Muratori, Viglione, Maestro, & Picchi, 2004), and this was associated with the severity of restriction [low body mass index (BMI); Dellava et al., 2010]. Some authors (e.g. Casper, 1990) suggested that a temperamental disposition toward emotional and behavioral restraint may be psychological risk factors for the development of the restricting type of anorexia nervosa. The personal qualities of behavioral restraint and reserve in combination with exacting standards and a sense of ineffectiveness might be risk factors for developing restricting anorexia nervosa. It is important to keep in mind that these traits cannot explain core psychopathological phenomena of anorexia nervosa, such as the denial of illness or body image distortions; they ought to be viewed instead as personality characteristics which might facilitate the development and perpetuate the process of anorexia nervosa. Moreover mood is intimately connected to feeding behavior, which in turn impacts mood. Chandler-Laney et al. investigated the neurochemistry and behavior of rats subjected to a regimen of periodic calorie restriction, and concluded that the treatment has a deleterious effect on the animals' mood. A history of caloric restriction induces neurochemical and behavioral changes in rats consistent with models of depression (Chandler-Laney et al., 2007). In Jahnget al. (2007), the authors subjected young rats to calorie restriction, and found 5-HT reductions and behavioral alterations. Five weeks of food restriction markedly increased plasma level of corticosterone, and significantly decreased 5-HT turnover rates in the hippocampus and the hypothalamus. 5-HTT mRNA expression decreased in the raphe nucleus of food restricted rats compared with free fed controls. These results suggest that chronic caloric restriction in young rats may lead to the development of depressive and/or anxiety disorders, likely, in relation with dysfunction of brain 5-HT system (Jahng et al., 2007).

The role of anxiety and affective problems has been emphasized in etiological/maintenance models of anorexia nervosa (e.g. Lavender et al., 2013). Negative affect is potentially a critical maintenance mechanism of some AN symptoms The relationship of affect and eating disorder behavior in anorexia nervosa (AN) was examine by Engel and colleagues that found that higher daily ratings of negative affect were associated with a greater likelihood of dietary restriction on subsequent days (Engel et al., 2013).

According to the DSM-IV, one of the diagnostic characteristics of AN is denial. These patients tend to view their low weight as an accomplishment rather than as an affliction and as a result have little motivation for change. Their drive for thinness is considered egosyntonic. Some refer to the denial of AN patients from a psychodynamic perspective, claiming that these patients play with the idea of death like a child in a game, pretending that they can disappear through death and return in a mystical way (Jackson & Davidson, 1986; Sours, 1980). Other authors relate to the dialogue of AN with life and death from an interpersonal theory perspective. According to this viewpoint, AN patients are not attracted to death so much as they are seeking control over their life and a sense of identity. The symptoms represent a latent suicidal act as a result of feeling depressed for not achieving such control and thereby serve as a way to achieve false control (Bruch, 1974; Bruch, 1979; Russell, Halasz & Beumont, 1989). Bachar and colleagues used the differentiation between the attraction to and repulsion by life and the attraction to and repulsion by death as independent factors in order to clarify the perceptions of life and death among ED patients. They found that AN patients are characterized by a rejection of life rather than a contemplation of death or an attraction to it (Bashar, Latzer, Gur & Bonne, 2002). This point of view is also in accordance with the attachment theory. According to this theory, AN patients do not dare express their interests or needs, but rather feel insecurely attached to others by dependency or avoidance. They lack confidence in the world and in the ability to cope with negative emotions. Rather than relying on human beings to fulfill their secure base needs, they resent food and in doing so fulfill those needs (Ward & Gowars, 2003).

In the present study BED patients seemed to have more issues in shape concern and EDNOS patients had more issues in body dissatisfaction respect to AN-R.

As publication of DSM-V draws near, research is needed to validate the diagnostic scheme for binge eating disorder (BED). Shape and weight overvaluation has stimulated considerable debate in this regard, given associations with psychosocial impairment and poor treatment outcome in BED. The study by Striegel and collegues (2010) suggested that shape and weight overvaluation is a useful diagnostic specifier in BED (Goldschmidt et al., 2010)

People with EDNOS commonly present with extremely disturbed eating habits, a distorted body image and an intense fear of gaining weight. DSM-5 improved on upon DSM-IV by providing more detail about eating disorders that do not meet criteria for anorexia nervosa, bulimia nervosa, or binge eating disorder. These

presentations were previously classified as Eating Disorder Not Otherwise Specified (EDNOS) in DSM-IV, but the category was renamed OSFED (Other Specified Feeding or Eating Disorder) in DSM-5. The advantage of the DSM-IV EDNOS category was that people could receive an eating disorder diagnosis without meeting the relatively narrow criteria for anorexia or bulimia. The disadvantage was that people with very different symptoms got lumped into the same category, which made accessing specialized care and conducting research pretty challenging. Unfortunately, the pervasive myth that EDNOS was somehow less severe than anorexia or bulimia sometimes prevented people who fit into this category from seeking help, or insurance companies from covering costs.

A more compromised shape concern dimension resulted in a lower probability to be EDNOS respect to AN-R and in a higher probability to be BN-BP respect to AN-R. A higher level of the self oriented perfectionism scale was a protective factor for the risk of having a diagnosis of BED respect to AN-R patients. Regarding shape concern results by Lavender (2013) supported the theorized association between body checking and overvaluation of shape and weight, and suggest that targeting such behaviors in treatment may have utility in reducing dietary restriction (Wonderlich et al., (2013). Clinical perfectionism in those with anorexia nervosa (AN) is proposed to motivate extremes of performance at the expense of health even prior to illness onset. Indeed, the rigid structure (e.g., repetitive behavioral routines, constrained behavioral options) self-imposed by those with AN is juxtaposed upon a relentless drive that, even prior to initial manifestations of extreme dietary restriction, serves to neglect biological needs if pitted against a perceived failure to meet stated objectives (Zucker et al. 2007). Perfectionism as an exemplar of a trait feature that would benefit from targeted intervention, and as a springboard to illustrate a general framework for addressing trait features in AN "a psychological (therefore) organismic structure underlying a relatively enduring behavioral disposition, i.e., a tendency to respond in certain ways under certain circumstances." An extensive developmental literature supports the relationship between temperament and the emergence of behavior problems (Graham, Rutter & George, 1973; Eisenberg, Fabes, Guthrie & Reiser, 2000; Eisenberg et al., 2005; Tellegen et al. 1988).

The findings of the current study need to be considered in light of several limitations. The first is the low sample size, in particular of some subtype (AN-BP and BN in particular). Moreover this study did not evaluate maintaining factors prospectively; thus, we do not know from these results whether personality

subtypes and maintaining factors are stable over time. We also cannot comment on whether these factors preceded or followed onset of eating disorder symptoms.

The study suggests that some processes identified in the cognitive-behavioural model of eating disorders may be operating in particular way in AN-R group that seems to represent a phenotypically homogeneous subsample. In conclusion, this study could indicated the clinical utility of personality subtypes in patients with AN and EDs. Future research is needed to identify the mechanisms responsible for differential treatment response among personality subtypes as AN-BP and AN-R.

Table 4.1 Multinomial logistic model. Reference category: AN-R

	Variables in the equation	Multivariate OR*	Confidence Interval 95%	P Value
AN-BP	Age	1.407	(1.007-1.967)	0.045
	Low self esteem (EDI-3)	0.960	(0.861-1.071)	0.463
	Perfectionism (EDI-3)	0.953	(0.861-1.053)	0.344
	Self oriented perfectionism (CAPS)	1.000	(0.962-1.040)	0.995
	Interpersonal problems (EDI-3)	0.991	(0.942-1.043)	0.729
	Affective problems (EDI-3)	1.023	(0.979-1.070)	0.307
	Anxious depressed (YSR)	0.917	(0.859-0.980)	0.010
	Body dissatisfaction (EDI-3)	1.042	(0.983-1.105)	0.164
	Body image concerns (BUT)	1.090	(0.751-1.582)	0.651
	Shape concern (EDE 12.0D)	1.149	(0.730-1.808)	0.549
	Restraint (EDE 12.0D)	1.192	(0.855-1.662)	0.299
	Bulimia (EDI-3)	1.128	(1.057-1.203)	0.000
BN-BP	Age	1.373	(1.030-1.830)	0.031
	Low self esteem (EDI-3)	0.969	(0.878-1.069)	0.530
	Perfectionism (EDI-3)	0.931	(0.850-1.020)	0.126
	Self oriented perfectionism (CAPS)	0.994	(0.957-1.032)	0.755
	Interpersonal problems (EDI-3)	0.979	(0.930-1.029)	0.399
	Affective problems (EDI-3)	0.996	(0.955-1.039)	0.848
	Anxious depressed (YSR)	0.998	(0.936-1.064)	0.949
	Body dissatisfaction (EDI-3)	1.033	(0.981-1.087)	0.219
	Body image concerns (BUT)	1.258	(0.910-1.739)	0.165
	Shape concern (EDE 12.0D)	1.508	(1.001-2.274)	0.050
	Restraint (EDE 12.0D)	0.895	(0.687-1.166)	0.409
	Bulimia (EDI-3)	1.179	(1.110-1.253)	0.000
BN	Age	1.161	(0.691-1.950)	0.573
	Low self esteem (EDI-3)	1.053	(0.891-1.244)	0.544
	Perfectionism (EDI-3)	1.053	(0.913-1.215)	0.480
	Self oriented perfectionism (CAPS)	0.984	(0.922-1.050)	0.617
	Interpersonal problems (EDI-3)	1.025	(0.933-1.125)	0.609
	Affective problems (EDI-3)	0.912	(0.844-.985)	0.019
	Anxious depressed (YSR)	0.992	(0.887-1.110)	0.888
	Body dissatisfaction (EDI-3)	1.024	(0.933-1.125)	0.615
	Body image concerns (BUT)	0.958	(0.551-1.664)	0.879
	Shape concern (EDE 12.0D)	1.848	(0.864-3.954)	0.113
	Restraint (EDE 12.0D)	0.866	(0.534-1.404)	0.560
	Bulimia (EDI-3)	1.276	(1.152-1.412)	0.000
BED	Age	1.082	(0.874-1.340)	0.469
	Low self esteem (EDI-3)	0.958	(0.850-1.079)	0.475
	Perfectionism (EDI-3)	0.931	(0.832-1.041)	0.211
	Self oriented perfectionism (CAPS)	0.950	(0.915-0.986)	0.006
	Interpersonal problems (EDI-3)	0.941	(0.876-1.010)	0.092
	Affective problems (EDI-3)	0.987	(0.935-1.041)	0.626
	Anxious depressed (YSR)	0.981	(0.903-1.066)	0.657
	Low self esteem (EDI-3)	0.958	(0.850-1.079)	0.475
	Body dissatisfaction (EDI-3)	1.030	(0.973-1.090)	0.315
	Body image concerns (BUT)	1.264	(0.902-1.770)	0.174
	Shape concern (EDE 12.0D)	1.437	(1.016-2.032)	0.040
	Restraint (EDE 12.0D)	0.498	(0.374-0.665)	0.000
	Bulimia (EDI-3)	1.209	(1.116-1.310)	0.000
EDNOS	Age	0.863	(0.762-0.978)	0.021
	Low self esteem (EDI-3)	0.943	(0.876-1.014)	0.112
	Perfectionism (EDI-3)	0.958	(0.895-1.026)	0.221
	Self oriented perfectionism (CAPS)	0.989	(0.967-1.012)	0.356
	Interpersonal problems (EDI-3)	1.034	(0.996-1.073)	0.078
	Affective problems (EDI-3)	0.966	(0.936-0.997)	0.031
	Anxious depressed (YSR)	0.978	(0.931-1.028)	0.385
	Body dissatisfaction (EDI-3)	1.049	(1.010-1.089)	0.013
	Body image concerns (BUT)	0.870	(0.698-1.084)	0.214
	Shape concern (EDE 12.0D)	0.807	(0.648-1.005)	0.055
	Restraint (EDE 12.0D)	0.801	(0.680-0.943)	0.008
	Bulimia (EDI-3)	1.085	(1.030-1.142)	0.002

* OR value must be interpreted for each unit change; OR, Odds RatioAN-R, anorexia nervosa restricting type; AN-BP, anorexia nervosa binge-purging type; BN-BP, bulimia nervosa binge-purging type; BN, bulimia nervosa; BED, binge eating disorder; EDNOS, eating disorder not otherwise specified

Chapter 5

Global and specific regional brain volumes in adolescents with anorexia nervosa restricting type: preliminary findings from a brain morphometry study

5.1 Abstract

Objective: To compare the results of brain volume analysis using Voxel Based Morphometry on 24 adolescents with AN restrictive subtype (AN-R) in the early stage of the illness and on 24 healthy controls; to analyze the structural changes of AN-R adolescents with the application of region of interest (ROI) analysis detecting Grey Matter region specific vulnerability possibly related to key features of anorexic adolescent patients.

Method: A total of 48 participants 13-18 years old were enrolled in the study. Before entering the study, AN-R subjects were interviewed with the Eating Disorder Inventory-3 (EDI-3). Magnetic resonance imaging data were acquired using a GE 1.5 T Signa Neuro-optimized System fitted with 40mT/m high-speed gradients. The global volumes and their sum were segmented with Statistical Parametric Mapping 8 (SPM8). The volumes of the regions of interest were extracted according to a parcellation provided by LONI (www.loni.usc.edu). The analysis of variance (ANOVA) was performed to identify any significant between-group difference in global tissue volumes and in specific regions of interest. Correlational analyses were used to assess the relationship between relevant anatomical whole and regional brain volumes and psychological traits measured by EDI-3.

Preliminary results: The voxel based analyses revealed in AN-R subjects, compared to the healty control group, brain volume deficits in total grey matter volumes (p=0.02) and in total intracranial volume (p=0.02) and increased cerebrospinal fluid (p=0.05). The white matter volumes did not revealed significant differences between cases and controls (p=0.14). The comparisons between participants with anorexia nervosa and control group in region of interest cerebral gray matter volumes revealed significantly lower volumes for both frontal lobes (p=0.006), for the left insula (p=0.016) and for the left temporal lobe (p=0.054). Adjusting for age and for Grey Matter total Volume (GMLONI), both left and right caudate (p=0.003) and brainstem (0.014) resulted significantly different in cases and controls. These three regions resulted not decreased in

AN-R than in controls. Significative correlation among left parietal lobe, cerebellum and right insula and some key features of AN-R subjects were found.

Conclusion: Our study contributes to the discussion on brain alterations in adolescents with AN-R.

Keywords: Anorexia Nervosa Restricting Type; Adolescence; Brain Structures; Voxel-based Morphometry Study; Region of Interest Analysis

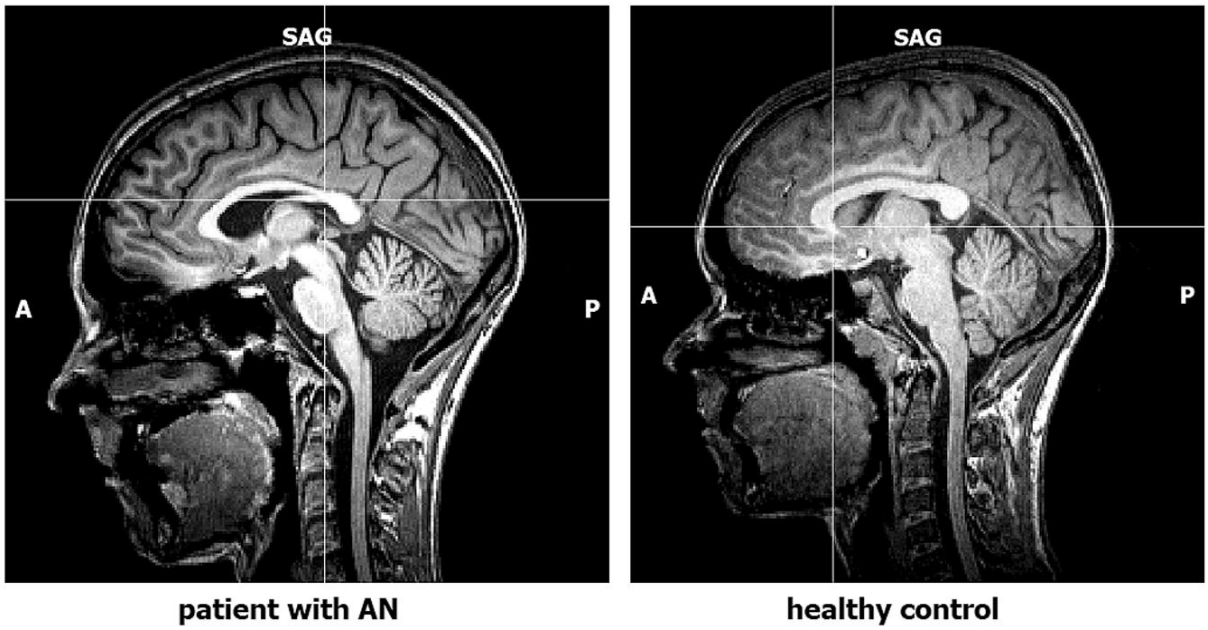
5.2 Background

Neuroimaging techniques have been useful tools for accurate investigation of brain structure and function in eating disorders, mainly in anorexia nervosa (Lask et al., 2005).

The first studies, by means of structural neuroimaging (ie, computed tomography and magnetic resonance imaging), focused on the brain anatomy in patients with anorexia nervosa and consistently showed sulcal widening and ventricular enlargement that usually decreased with refeeding (Palazidou, Robinson & Lishman, 1990; Katzmann Zipursky, Lambe & Mikulis, 1997).

Other specific findings have been a marked reduction in total gray and white matter volumes (GM and WM) compared with healthy controls or the persistence of the gray matter volume changes when weight is restored (Artmann, Grau, Adelmann & Schleiffer , 1985; Krieg, Pirke, Lauer & Backmund, 1988). In general, the majority of the studies on anorexia nervosa have reported brain volume deficits and increased cerebrospinal fluid, suggesting starvation of the brain (Artmann et al., 1985; Dolan, Mitchell & Wakeling, 1988; Golden et al., 1996; Swayze et al., 1996; Kohlmeyer, Lehmkuhl, & Poustka, 1983; Neumarker, Bzufka, Dudeck, Hein & Neumarker, 2000; Katzman et al., 1996). During weight recovery the cerebral volume again increases, even if not completely (J. Castro-Fornieles et al., 2009; Katzman, Zipursky, Lambe,&Mikulis, 1997;Mainz, Schulte-Rüther, Fink, Herpertz-Dahlmann, & Konrad, 2012; Swayze et al., 2003). These marked acute brain changes in AN are often evident by simple visual inspection of an AN patient's MRI or CT scan (see Figure 1) and are among the strongest structural brain changes that can be observed in any mental disorder. In sharp contrast to these marked acute brain changes, adolescent patients usually present themselves even in the extreme phase of starvation with remarkably normal academic performance levels and only small impairments (Buehren et al., 2011).

Figure 5.1. Volume changes in acute anorexia nervosa



In the 2013 meta-analysis and qualitative review by Seiz and collegues (Seitz, Bühren, von Polier, Heussen, Herpertz-Dahlmann & Konrad, 2014) for recovered patients with AN potential residuals of volumetric brain deviations have been examined systematically across different studies. Short-term weight recovery in longitudinal studies resulted in about half of GM and CSF changes being normalized relatively quickly upon initial weight recovery (on average after 4 months). WM seemed to increase more rapidly during the first months after weight gain to almost total recovery, showing a markedly different temporal pattern than GM and CSF. The meta-analysis of the long-term recovered patients did not find a significant residual volume change. However, there could be small persisting deficits even after 2–8 years of weight recovery, as all parameters found in acutely ill patients remained altered in the same direction in long-term weight-recovered patients (GM –1.0%, WM –0.7%, CSF +1.3%). The differential time courses for GM and WM recovery point to the involvement of potentially different mechanisms. Moreover, while GM changes seem to be more pronounced in adolescent patients, WM changes seem not to show an age-related effect. One hypothesis for the age-related effect could be that a greater GM plasticity in the still developing adolescent brain leads to a greater susceptibility to starvation effects.

Some of these findings suggest that the changes are most likely to be due to neuronal damage secondary to malnutrition, with possible regeneration of myelin accounting for the general reversibility. However, these

findings have not improved our understanding of the pathogenesis of anorexia nervosa (Jàuregui-Lobera, 2011).

More recently, studies have highlighted the use of functional neuroimaging, which refers to techniques that obtain images of the brain according to its physiology and biochemistry. Other studies have used magnetic resonance spectroscopy (Rost, Roser, Bubl, Radue & Buergin, 1999) or voxel-based morphometry (VBM) (Muhlau, 2007).

Findings in neurobiology have found that the most frequent traits in AN seem to be associated with an altered serotoninergic neurotransmission (Kaye, Fudge & Paulus, 2009). Neuroimaging studies have found a number of cerebral structures implicated in the clinical aspects of AN, like the frontal lobes, connected with deficits in executive functions and central coherence, the parietal cortex, correlated with body image distortions, the amigdala, related to anxiety, the striatum, connected with obsessive-compulsive behavior. It has been suggested also that the original cause for such dysfunctions could be a disconnections between these areas due to a malfunctioning of the insula, which plays a central role in orchestrating the signals regarding external environment and internal homeostasis (Nunn, Frampton, Fuglset, Törzsök-Sonnevend & Lask, 2011).

A structural imaging study in AN by Joos and colleagues (2010) used VBM, which allows a whole brain analysis, and found a decreased volume for Grey Matter (GM) and an increased space for Celebrospinal Fluid (CSF); regional GM changes were found in dostral and rostral accumbens (anterior cingulate cortex, ACC), the first one related to conditioned emotional learning and the second involved in conflict detection and complex information processing, and in the frontal operculum, linked to mirror neuron system. The same study also reported a positive correlation of drive for thinness with GM volume of the parietal cortex.

Another study by Castro- Fornieles and colleagues (2009) conducted using VBM on 12 adolescents with AN reported structural alterations in temporoparietal regions, with changes in GM and CSF, but not in the white matter (WM), contrary to a study conducted by Katzman and colleagues in 1996.

A study of Friederich et al. (2012) investigated the morphometry of brain regions within cortico-striatal networks in acute anorexia nervosa (AN), in long-term weight-restored anorexia nervosa (AN-WR) patients and in Healty Controls (HC). The analysis conducted by brain voxel-based morphometry (VBM) and brain-atlas based automatic volumetry computation (IBASPM), showed group differences in local grey matter

volume (GMV). AN patients, as compared to Healthy Controls (HC), showed decreased GMVs (VBM and volumetry) in the anterior cingulate cortex (ACC), in the supplementary motor area (SMA), and in subcortical regions (right amygdala, putamen) (Friederich et al., 2012).

This results related to neuropsychological data reported that perfectionism as a personality trait was increased in AN patients (AN and AN-weight restored) independently of the disease stage; while cognitive–behavioral flexibility was state dependent. In effect, structural changes in the dorsal ACC and functional alterations in the rostral and ventral ACC, involved respectively in cognitive processing and in motivational and emotinal processing (Bush, Luu, P., & Posner, 2000), may underlie the psychopatology of AN such as impaired cognitive-behavioral flexibility, a great concern about errors and striving for perfectionism (Pieters et al., 2007; Zastrow et al., 2009). These structural alterations in the SMA and in the dorsal ACC may represent either a trait marker or a "sign" effect caused by severe malnutrition. Probably starvation-induced neurochemical changes may complicate maturation of the ACC during puberty (Casey et al., 1997; Sowell, Thompson, Holmes, Jernigan & Toga, 1999). Within this cortico-limbic-striatal network, the study also found decreased GMV of the Amigdala in AN but not in AN-weight restored (AN-WR) patients. In particular, the volume of the right Amigdala, that plays a key role in all facets of emotional processing (Costafreda, Brammer, David & Fu, 2008), was positively correlated with the performance in the cognitive-behavioral flexibility task and negatively with the level of perfectionism in AN-C patients. So the results of the Friederich 's study (2012) seem to show how structural alterations in subcortical brain regions were state dipendent, while decreased GMV of the ACC and SMA may represent a trait marker in AN, in agreement with personological characteristics.

A Meta-analysis of Titova, Hjorth, Schioth & Brooks, (2013) showed a broad number of areas involved in eating disorders, in particular in anorexic patients. Regionally, in Anorexic patients, there were reductions in the hypothalamus, left inferior parietal lobe, right lentiform nucleus and right caudate. These regions are linked to appetite and somatosensory perception, often dysfunctional functions in AN. Considering volume differences in the context of functional MRI studies of those with AN may help to clarify brain circuits most susceptible to acute malnutrition and the development of AN. In a recent review of neurobiological findings in AN (Brooks, Rask-Andersen, Benedict & Schiöth , 2012), a summary of recent functional MRI data was given. Those with AN have reduced activation in bottom-up regions (e.g. mid-brain), such as the striatum,

hippocampus, amygdala, hypothalamus and cerebellum, often in conjunction with increased top-down activation in prefrontal cortex regions such as the Dorso Lateral Prefrontal Cortex (DLPFC), medial prefrontal cortex (MPFC), ACC and orbitofrontal cortex (OFC) (Titova et al., 2013). Additionally, the review also reported aberrant activation in the insula, a temporal lobe structure associated with interoceptive awareness and cognitive/emotional perceptions of the body. The review of Titova and collegues (2013) founded only one study demonstrating increased activation in the DLPFC in AN (Brooks et al., 2011), suggesting that more VBM studies of AN need to closely examine PFC regions. Bottom-up activations are largely consistent with reward, motivation and general arousal, and top-down activations are linked to cognitive inhibition of appetite, self-referential goals and evaluation of salience: it would be very important better investigate the neural circuitry in the frontal-striatal pathway (associated to impulse control), which also involve connections with the insular cortex and represent the circuit most susceptible to cognitively-maintained restraint of appetite in AN.

5.3 Early-onset anorexia nervosa and adolescent patients: investigation of brain structure

In a sample of adolescents with restrictive-type anorexia nervosa, in the early stages of the illness, morphometric gray matter changes were characterized by means of preprocessed MRI according to optimized VBM. The analyses revealed a significant decrease in global gray matter, and a significant region-specific decrease in gray matter volume was found bilaterally in the middle cingulate cortex, the precuneus, and the inferior and superior parietal lobules (Gaudio et al., 2011).

In this regard, another study reported that right dorsal anterior cingulate cortex volume was significantly reduced in patients with anorexia nervosa versus controls, and was correlated with lower performance intelligence quotients (McCormik et al., 2006).

There is some debate about the abnormalities of cerebral structures in anorexia nervosa as to whether these abnormalities are secondary to starvation or indicative of a primary abnormality predating the illness, representing an underlying biological substrate. In a recent study, changes in regional cerebral blood flow (rCBF) were found at both baseline and follow-up (at more than 4 years). The main affected cerebral area was the medial temporal region, the data suggesting that rCBF does not return to normal following weight restoration (Frampton, Watkins, Gordon & Lask, 2011).

In a pioneer study by Gordon et al (Gordon, Lask, Bryant-Waugh, Christie & Timimi, 1997), temporal lobe hypoperfusion persisted in three of four patients who had regained their normal weight. Furthermore, although two of the four patients had recovered a normal weight/height ratio after refeeding, the cognitive distortions of anorexia nervosa persisted, as well as the abnormal rCBF. This suggests that the hypoperfusion is not related directly to weight loss.

Another study using VBM showed that several temporal and parietal gray matter regions were reduced. During follow-up, there was a greater global increase in gray matter in anorectic patients, and this increase correlated with a decrease in cortisol. At follow-up (7 months), there were no differences in global gray matter and white matter volumes between anorectic patients and controls. The authors concluded that, in adolescent anorectic patients, gray matter is more affected than white matter and mainly involves the posterior regions of the brain. Overall, gray matter alterations are reversible after nutritional recovery (Castro-Fornieles et al., 2010).

The majority of the studies have been developed taking into account samples of adolescents and adults with restrictive-type anorexia nervosa. Considering the fact that it may be possible to find differences between patients at normal weight, patients after weight restoration, and controls, a recent study showed that patients with anorexia nervosa had a significant increase in gray and white matter volume after weight restoration. In addition, this study showed that patients had lower levels of gray matter at low weight compared with controls, which increased with weight restoration (Roberto et al., 2011).

The interaction among low weight, duration of illness, and brain changes remains controversial to some extent. Thus, while some authors have reported an inverse correlation between duration of illness and lower volume of gray matter at low body weight, but no correlation between low body weight and measures of brain volume, other authors have found a correlation between body mass index and brain volume, but not with duration of illness (Katzmann et al., 1996; Roberto et al., 2011). Studying patients with anorexia nervosa who had a different duration of illness, Boghi et al (2011) found a significant reduction in total white matter volume and focal gray matter atrophy in the cerebellum, hypothalamus, caudate nucleus, and frontal, parietal, and temporal areas. The cerebellum was more affected in patients with longer disease duration, whereas the hypothalamic alterations were more pronounced in patients with a shorter period of food

restriction. A correlation between body mass index and gray matter was found in the hypothalamus. These authors suggested that atrophy of cerebellar gray matter could play a role in the chronic phase of the disease.

A study using functional MRI reported that recovered patients with anorexia nervosa showed altered task-related activation in the medial prefrontal cortex, a critical node of the inhibitory control network. Specifically, whereas recovered patients with anorexia nervosa and control women showed similar medial prefrontal cortex activity during trials when inhibitory demand was low (ie, easy trials), recovered patients with anorexia nervosa showed significantly less medial prefrontal cortex activation than control women as inhibition trials became more difficult (ie, hard trials), suggesting a demand-specific modulation of inhibitory control circuitry in recovered patients with anorexia nervosa (Obendorfer, Kaye, Simmons, Stigo & Matthews, 2011).

5.4 Associations between brain volume changes and clinical parameters

Inconsistent findings exist with respect to the association between brain volume changes and the severity of starvation as measured by the body mass index (BMI). BMI correlated inversely with GM and WM changes (Muhlau et al., 2007), while delta BMI (i.e., difference between premorbid BMI and BMI at the acute stage) correlated with GM loss (Bomba et al., 2013). A more rapid weight loss (delta-BMI/disease duration) correlated with a higher CSF increase (Boghi et al., 2011). The ACC volume correlated with the lowest lifetime BMI (Muhlau et al., 2007). GM cerebellar changes were more pronounced in patients with longer duration of illness (Boghi et al., 2011). Because other studies could not find clear associations, these results have to be regarded as preliminary. Further studies were able to show correlations of global or regional GM changes with neuropsychological and psychopathological parameters. Global GM reduction correlated with visuospatial functioning (Rey-Figure copying, Castro-Fornieles et al., 2009). Reduced right dorsal ACC volume was related to perceptual organization and reasoning skills (McCormick et al., 2008), and reduced right inferior parietal cortex GM correlated with drive for thinness (Joos et al., 2010). Dietary restraint and BMI combined predicted 57% of the variance of increased DLPFC volume (Brooks et al., 2011), and sucrose pleasantness ratings were correlated with increased medial orbitofrontal cortex volume (Frank, 2013). Suchan et al. (2010) showed that the extrastriatal body area GM that was reduced in acute AN also had less functional connectivity with related brain areas in an fMRI examination of body-image distortion (Vocks,

Busch, Grönemeyer, et al., 2010). After a body-image directed therapy the latter finding remained no longer significant (Vocks, Busch, Schulte et al., 2010).

5.5 Purposes of the present study

Findings from neuroimaging research in people with EDs highlight contemporary knowledge of eating disorders (EDs) in to the debate on how to best improve their classification. As findings support the clinical utility of the examination on personality subtypes and homogeneous endophenotypes in EDs research, starting from the multicenter study of all eating disorders in children and adolescents, in this session we focused on anorexia nervosa and in particular on the restrictive subtype (Calderoni, Fantozzi, Maestro, Brunori, Narzisi, Balboni & Muratori,2013a; Calderoni, Muratori, Leggero, Narzisi, Apicella, Balottin, Carigi, Maestro, Fabbro, Urgesi , 2013b).

The aims of the present study are

1) To compare the results of brain volume analysis using VBM on 24 adolescents with AN restrictive subtype (AN-R) in the early stage of the illness and on 24 healthy controls.
2) To analyze the structural changes of AN restrictive subtype adolescents with the application of region of interest (ROI) analysis detecting Grey Matter region specific vulnerability related to key features of anorexic adolescent patients

5.6 Methods

Participants

Thirty acute AN restrictive subtype adolescent patients underwent structural MRI from May 2013 to December 2014. The patients were all female 12-18 years old. Six subjects were excluded from the analysis for anomalies detected by MRI. Control female subjects were selected from a database of clinical three-dimensional structural MRI.

Exclusion criteria included: 1) anomalies detected by MRI; 2) neurological syndromes or focal neurological signs; 3) dysmorphic features suggestive of a genetic syndrome; 4) significant sensory impairment (e.g., blindness, deafness); 6) anthropometric parameters (head circumference) lying outside two SD from the

mean of normal subjects; 7) anamnesis of birth asphyxia, premature birth, head injury or epilepsy; 8) presence or history of any other axis I mental disorder and 10) insufficient image quality for VBM.

A total of 48 participants 13-18 years old were enrolled in the study: 24 acute AN restrictive subtype patients and 24 age-matched healthy girls in the normal weight range.

Procedure

Before entering the study, for an accurate phenotyping of patients, AN-R subjects were interviewed with the Eating Disorder Inventory-3 (EDI-3) (Clausen, Rosenvinge, Friborg & Rokkedal, 2011): The Eating disorder inventory-three (EDI-3) was designed for use with females aged 13–53 years and consists of 91 items organized into 12 primary scales: Drive for Thinness, Bulimia, Body Dissatisfaction, Low Self-Esteem, Personal Alienation, Interpersonal Insecurity, Interpersonal Alienation, Interoceptive Deficits, Emotional Dysregulation, Perfectionism, Asceticism, and Maturity Fears. Yields six composites: one is eating-disorder specific (Eating Disorder Risk) and five are general integrative psychological constructs (Ineffectiveness, Interpersonal Problems, Affective Problems, Overcontrol, and General Psychological Maladjustment). It is a self report questionnaire administered in twenty minutes (Clausen et al., 2011).

The Voxel-based morphometry

The voxel-based morphometry (VBM) technique consists in a voxel-wise comparison of the local volume or concentration of grey/white matter between two groups of subjects (Ashburner & Friston, 2000). The procedure involves spatially normalizing high-resolution images from all subjects in the study into the same stereotactic space. This is followed by the segmentation of the grey/white matter from the spatially normalized images, and the smoothing of the grey/white matter segments. Voxel-wise parametric statistical tests, which compare the smoothed grey/white matter images from the two groups, are performed. Corrections for multiple comparisons are made using the theory of Gaussian random fields. VBM is crucially dependent on registration performance. The recently introduced Diffeomorphic Anatomical Registration using Exponentiated Lie algebra (DARTEL) algorithm implements several methodological advances to address this limitation (Ashburner, 2007). A diffeomorphic warping is implemented to achieve anaccurate inter-subject registration with an improved realignment of small inner structures.

Application of region of interest analysis detecting Grey Matter region specific vulnerability

A previous case control study by Retico et al. (Retico, Giuliano, Biagi, Pasquariello, Tosetti, Maestro, Muratori, Calderoni, 2015) underlined that the Whole Brain Analysis in AN-R adolescent patients revealed decreases changes in significant region-specific in gray matter volume: left superior frontal gyrus (Brodmann area BA10); middle fontal Gyrus and anterior cingulate (BA 6/32); Medial prefrontal cortex (BA4 / 6/9); Posterior cingulate gyrus (BA31); Anterior insula; Cerebellum. These preliminary results may support also the importance of a network vision instead of a focal analysis based on a limited number of regions of interest (Downing & Peelen, 2011).

In the present study the global volumes WM-GM-CSF and their sum (TIV) are segmented with Statistical Parametric Mapping 8 (SPM8). Image processing and data analysis were performed using SPM8 software (Wellcome Department of Cognitive Neurology, London, UK), SPM toolbox. The volumes of the regions of interest were extracted according to a parcellation provided by LONI (www.loni.usc.edu), reported in the paper "Construction of a 3D probabilistic atlas of human cortical structures" by David W. Shattuck and collegues (Shattuck, Mirza, Adisetiyo, Hojatkashani, Salamon, Narr, Poldrack, Bilder, Toga, 2008). The LONI volumes are expressed in ml and they have to be adjusted for WholeGMLONI. The LONI (Laboratory of Neuroimaging) pipeline (http://pipeline.loni.usc.edu/), a graphical workflow environment, was used to obtain total and regional brain volumes for all subjects (Figure 5.2). The GMloni is systematically lower than GM because excludes some areas of deep gray.

The MR protocol for children and adolescents

In the present research MRI data were acquired using a GE 1.5 T Signa Neuro-optimized System (General Electric Medical Systems) fitted with 40mT/m high-speed gradients. The standard MR protocol for children and adolescents included FSE T2-weighted, FLAIR, DWI, SE T1-weighted sequences. The written informed consent from a parent or guardian of children was obtained. The research protocol was approved by the Institutional Review Board of the Clinical Research Institute for Child and Adolescent Neurology and Psychiatry. All subjects gave written consent before the structural scans were acquired. The study was approved by the local ethic committee

Figure 5.2 Brain structures in the probabilistic atlas

Note: a. the fusiform and lingual gyrus can be considered to reside in both the occipital lobe and temporal lobe; b. the hippocampus can be considered to reside in both the temporal lobe and the limbic lobe.

Statistical analysis

Whole-brain volume comparison: Group differences were evaluated for gray matter (GM), white matter (WM), cerebrospinal fluid (CSF) absolute volumes and total intracranial volume (TIV), obtained in the brain segmentation step of the VBM-DARTEL preprocessing. The TIV was calculated as the sum of GM, WM and CSF volumes. The analysis of variance (ANOVA) was performed to identify any significant between-group difference in global tissue volumes and in specific regions of interest (Calderoni, 2012). Correlational analyses (parametric and not parametric) will be used to assess the relationship between relevant anatomical whole and regional brain volumes and psychological traits measured by Eating Disorders Inventory 3 (EDI-3) that was administered at admission to all patients.

5.7 Preliminary results

The cases sample comprised 24 subjects (mean age: 16.5 years; SD 1.4 years) who met the criteria for AN restrictive subtypes defined by the 4th edition of the Diagnostic and Statistical Manual of Mental Disorders. The patients, with a mean age of 15.2 years (182.3 months, SD=23.9), had a mean body mass index (BMI) of 14.5 kg/m^2; SD = 1.7); mean disease duration was 1.7 years (20.62 months, SD = 23.59) and delta BMI was of 4.9 kg/m^2 (SD=2.6) (see Table 5.1). Twentyfour female adolescent without history of neurological or psychiatric diseases, a mean age of 15.4 years and a mean BMI of 21 kg/m^2 served as a control group. Healthy controls and AN-R patients were comparable with respect to their age ($p > 0.05$). Due to the nature of the disorder, participants with AN displayed significantly lower BMI compared to healthy controls ($t = -8.5$, $p < 0.001$) (Table 5.1). Five AN subjects (20.8%) were in pre-pubertal phase and all the others in condition of amenorrhea (79.2% of AN patients).

The voxel based analyses revealed in AN subjects, compared to the healty control group, brain volume deficits in total grey matter volumes (p=0.02) and in total intracranial volume (p=0.02) and increased cerebrospinal fluid (p=0.05). The white matter volumes did not revealed significant differences between cases and controls (p=0.14) (Table 5.2).

The comparisons between participants with anorexia nervosa and control group in region of interest cerebral gray matter volumes revealed significantly lower volumes for both frontal lobes (p=0.006), for the left insula (p=0.016) and for the left temporal lobe (0.054). Of borderline significance resulted the differences between

cases and controls volumes in right occipital lobe (p=0.062), right insula (p=0.068), left and right parietal lobes (p=0.072 and p=0.074 respectively), and cerebellum (0.083) (Table 5.3).

In the comparison of the ROI volumes in the two groups, adjusting / controlling for age and for Grey Matter total Volume (procedures implemented in the Laboratory of Neuro Imaging, LONI) (GMLONI), both left and right caudate (p=0.003) and brainstem (0.014) resulted significantly different in cases and controls. These three regions, doing precisely the correction, resulted not decreased in AN-R patients (Table 5.3).

Both parametric and nonparametric correlations were performed between EDI-3 scores in AN subjects (mean values and standard deviation are reported in Table 5.4) and global grey volume and ROI volumes.

1) Significative correlations

-Left parietal lobe and Maturity Fears (parametric) [Pearson correlation index=0.436; p=0.038]

-Cerebellum and Global Psychological Maladjustment Composite (non parametric) [Correlation coefficent=0.515; p=0.050]

1) At the limit of significance

-Cerebellum and Interpersonal Alienation (parametric) [Pearson correlation index=0.449; p=0.062]

-Left parietal lobe and Interoceptive Deficits (non parametric) [Correlation coefficent= -0.383; p=0.071]

-Cerebellum and Global Psychological Maladjustment Composite (parametric) [Pearson correlation index=0.473; p=0.075]

-Right insula and Interpersonal Problems (non-parametric) [Correlation coefficent= -0.436; p=0.091]

Table 5.1 Comparison between participants with anorexia nervosa and control group in terms of socio-demographic and clinical variables

	AN group (n=24)		Control group (n=24)		sig
	Mean	**SD**	**Mean**	**SD**	
Age, month	182.3	23.9	184.6	26.0	p=0.75
BMI, kg/m²	14.5	1.7	21.0	2.1	p=0.001
Delta BMI	4.9	2.6	-	-	-
Disease duration, month	20.6	23.6	-	-	-

p=Anova: t= Student's t-test

Table 5.2 Comparison between participants with anorexia nervosa (AN) and control group in cerebral volumes (mm^3)

	AN group (n=24)		Control group (n=24)		p
	Mean	SD	Mean	SD	
Gray matter (GMSPM)	651.1	42.1	678.3	38.9	0.02
White matter (WMSPM)	443.3	30.8	456.6	31.6	0.14
Cerebro Spinal Fluid (CSF)	251.5	17.5	242.2	15.2	0.05
Total Intracranial Volume (TIV)	1 346.0	82.2	1 377.1	79.2	0.02

*p=Anova

Table 5.3 Comparison between participants with anorexia nervosa (AN) and control group in Region of Interest cerebral gray matter volumes (ml), also adjusted for Whole GM LONI

Anatomical label	AN group (n=24)		Control group (n=24)		p	p_1
	Mean	SD	Mean	SD		
Left frontal lobe	90.606	7.230	96.191	6.049	0.006	0.126
Right frontal lobe	89.964	7.150	95.307	5.493	0.006	0.117
Left parietal lobe	51.502	4.195	53.625	3.781	0.072	0.717
Right parietal lobe	50.621	4.189	52.649	3.463	0.074	0.606
Left limbic lobe	14.803	1.234	15.272	0.884	0.137	0.405
Right limbic lobe	14.271	1.257	14.721	0.882	0.158	0.277
Left occipital lobe	25.253	2.182	26.218	1.981	0.115	0.625
Right occipital lobe	27.051	2.427	28.319	2.151	0.062	0.941
Left temporal lobe	69.685	4.526	72.326	4.705	0.054	0.738
Right temporal lobe	69.261	4.518	71.406	4.495	0.106	0.151
Left insula	7.635	0.700	8.078	0.520	0.016	0.420
Right insula	7.319	0.680	7.665	0.602	0.068	0.999
Left caudate	3.819	0.326	3.683	0.249	0.110	0.003
Right caudate	3.745	0.310	3.627	0.271	0.170	0.003
Left putamen	3.186	0.309	3.149	0.324	0.684	0.125
Right putamen	3.255	0.343	3.278	0.368	0.823	0.257
Cerebellum	88.320	6.822	92.429	9.084	0.083	0.812
Brainstem	5.327	0.494	5.189	0.428	0.308	0.014

p=Anova; p_1=Anova, adjusting for age and WholeGMLONI

Table 5.4 Mean values and standard deviation (SD) in EDI-3 scores in AN group

EDI-3 scores	AN group (n=24)	
	Mean	SD
Drive for thinness	15.5	9.3
Bulimia	2.4	5.7
Body Dissatisfaction	20.0	11.1
Low Self-Esteem	12.4	5.7
Personal Alienation	10.0	6.3
Interpersonal Insecurity	10.2	5.7
Interpersonal Alienation	11.0	6.4
Interoceptive Deficits	11.0	7.4
Emotional Dysregulation	7.4	6.8
Perfectionism	6.8	5.2
Ascetism	7.9	5.2
Maturity Fears	14.0	9.0
Eating Disorder Risk Composite	36.3	21.6
Ineffectiveness Composite	21.6	11.1
Interpersonal Problems Composite	22.2	11.1
Affective Problems Composite	19.0	13.0
Over control Composite	14.7	9.5
Global Psychological Maladjustment Composite	112.5	54.7

5.8 Discussion

The aim of this study has been to assess differences in global brain volume and regional brain volume in twentyfour adolescent cases with AN restrictive subtype in the early stage of the illness compared with the same number of healthy controls and to detect possible Grey Matter (GM) region specific vulnerability.

The major findings in this study were that AN was associated with decreased brain volume. Further, global gray matter was more affected than global white matter (WM). In fact the voxel based analyses revealed in AN subjects, compared to the healthy control group, brain volume deficits in total grey matter volumes ($p=0.02$), in total intracranial volume ($p=0.02$) and increased cerebrospinal fluid (CSF) ($p=0.05$). Conversely, the white matter volumes did not reveal significant differences between cases and controls. An overall reduction of brain mass is commonly thought of as a result of starvation and malnutrition. The most frequently reported structural brain findings in adult patients with AN compared to healthy controls are brain

alterations at a global level, which involves an overall reduction of white matter (myelinated axons) and gray matter (cell bodies of neurons and glial cells), and increased volume of the ventricles and cerebrospinal fluid (Frank, Bailer, Henry, Wagner, & Kaye, 2004). Contrary to a study conducted by Katzman and colleagues in 1996, the present study and the study by Castro- Fornieles and colleagues (2009) reported structural alterations with changes in GM and CSF were found, but not in the white matter. The greater GM plasticity in the developing adolescent brain could lead to a particular susceptibility to starvation effects (Seiz, 2014).

In the present study several differences were observed also at a regional level. This could indicate that these brain structures are more vulnerable to starvation and malnutrition than others, and/or these structures are a part of the pathophysiology of AN. In previous studies there is no agreement upon which regions of the brain are most affected in patients with AN (Brooks et al., 2011; Joos et al., 2010; McCormick et al., 2008; Suchan et al., 2010).

In our data, the largest regional changes were found in both frontal lobes ($p=0.006$), in the left insula ($p=0.016$) and in the left temporal lobe (0.054).

Insula gray matter reduction could reflect evidence for disturbances in the system that is involved in interoceptive deficit, body dissatisfaction and low self esteem. The insular cortex (IC) would provide the convergence point for emotional and cognitive states related to the coordination between external and internal milieus, facilitating the fronto-temporal interaction in social context processing.

The frontal lobe has been associated with cognitive functions, such as attention, working memory, inhibition, and executive functions (Foster, Eskes, & Stuss, 1994; Siddiqui, Chatterjee, Kumar, Siddiqui, & Goyal, 2008). It has been suggested that the mechanisms involved in developing AN are related to dysfunctions within frontostriatal circuits, associated with either the strength of the connection between frontal and subcortical areas (Southgate, Tchanturia, & Treasure, 2005), habit learning as in obsessive-compulsive disorder (Steinglass & Walsh, 2006), selfregulation (Marsh, Maia, & Peterson, 2009), reward processing difficulties (Kaye, Fudge, & Paulus, 2009), and emotion processing (Hatch et al., 2010).

The temporal lobe is associated with auditory (Binder et al., 2000) and visual (Doyon & Milner, 1991) sensory information processing, language comprehension and speech (Scott, Blank, Rosen, & Wise, 2000), and storing new memories (Squire & Zola-Morgan, 2013). Results from functional imaging studies suggest that anorexia could be related to a dysfunction in the temporal lobes as these studies have reported unilateral

hypoperfusion in the temporal region (Gordon, Lask, Bryant-Waugh, Christie, & Timimi, 1997) and disturbances in the mesial temporal lobe related to altered serotonin function (Frank et al., 2002). It has also been demonstrated that lesions occurring in the frontal and temporal lobes have caused characteristic eating disorder pathology (Uher & Treasure, 2005).

Of borderline significance resulted the differences between cases and controls volumes in right occipital lobe (p=0.062), right insula (p=0.068), left and right parietal lobes (p=0.072 and p=0.074 respectively), and cerebellum (0.083). Research by Janet Treasure on exploration of cerebral activity during presentation of food images has identified activations common to the whole eating disorders group, and specific to subgroups with particular eating disorder diagnoses. An abnormal prefrontal reaction was specifically manifested in response to food stimuli, whereas differences in cerebellar, occipital, and parietal activity were present in reaction to both emotional and food images (Uher et al., 2004).

Gaudio et al. (2010) investigated morphometric gray matter changes in a sample of AN restrictive subtype aged 12–18 years in the early stages of the illness (16 patients with AN vs. 16 healthy controls). The results showed a significant decrease in global gray matter in patients, as well as a significant region-specific decrease in gray matter volume bilaterally in the middle cingulate cortex, the precuneus, and the inferior and superior parietal lobules. Mainz and colleagues (Mainz, Schulte-Ruther, Fink, Herpertz-Dahlmann, & Konrad, 2012) found in 19 patients with AN (age 12–17 years) reduced GM in several regions along the cortical midline, which were mostly reversible after weight restoration. The strongest association between regional GM increase and weight gain was found in the cerebellum.

In a recent review of neurobiological findings in AN (Brooks, Rask-Andersen, Benedict & Schiöth, 2012), a summary of fMRI data was given. Those with AN have reduced activation in bottom-up regions (e.g. mid-brain), such as the striatum, hippocampus, amygdala, hypothalamus and cerebellum, often in conjunction with increased top-down activation in prefrontal cortex regions such as the Dorso Lateral Prefrontal Cortex (DLPFC), medial prefrontal cortex (MPFC), ACC and orbitofrontal cortex (OFC) (Titova et al., 2013). Additionally, the review also reported aberrant activation in the insula, the temporal lobe structure associated with interoceptive awareness and cognitive/emotional perceptions of the body.

On the other hand, in our data, comparing the ROI volumes in the two groups, adjusting for age and for Grey Matter total Volume (GMLONI) both left and right caudate (p=0.003) and brainstem (0.014) resulted

significantly different in cases and controls (Table 5.3). The aforementioned regions were not significantly different between cases and controls without adjustment for age and GMLONI , but resulted significantly "wider" after accounting for age and GMLONI. This means that the overall reduction of GM does not correspond to a reduction in the left and right caudate and in the brainstem, so these regions seemed not vulnerable to starvation and malnutrition.

In reserch by Krieg and collegues (1991) regional cerebral glucose metabolism was measured with 18F-2-fluoro-2-deoxyglucose and positron emission tomography in patients with eating disorders. Relative caudate glucose metabolism (caudate glucose metabolism divided by global cerebral glucose metabolism) was significantly higher in anorexia nervosa than in bulimia nervosa, suggesting that caudate hyperactivity is characteristic of the anorexic state. Whether an increased caudate function is a consequence of anorexic behaviour or whether it is directly involved in the pathogenesis of anorexia nervosa is an issue still to be clarified (Krieg, Holthoff , Schreiber, Pirke & Herholz, 1991). These results were confirmed by Delevenne and collegues (Delvenne, Goldman, De Maertelaer, Wikler, Damhaut, Lotstra, 1997). Brain glucose metabolism of anorectic patients has been demonstrated to be reduced both globally and regionally, with a particular relative hypometabolism in the parietal cortex. To explore the possible influence of weight loss or depressive symptomatology on brain metabolism, Delevenne and collegues studied age- and sex-matched low-weight anorectic and depressed patients, normal-weight depressed patients, and healthy volunteers. In that research absolute global and regional glucose activity levels were reduced in low-weight patients, with the lowest values being found in anorectic patients. In relative values, anorectic patients showed a significant parietal hypometabolism in comparison to control subjects while they had higher metabolism in the caudate nuclei when compared with the other groups. Absolute hypometabolism of glucose seems to be a consequence of low weight as it was found in both low-weight anorectic and low-weight depressive patients. In addition, absolute glucose values were significantly correlated with body mass index in all subjects. Wagner, Kaye and collegues (Wagner, Aizenstein, Venkatraman, Fudge, May, Mazurkewicz, Frank, Bailer, Fischer, Nguyen, Carter, Putnam & Kaye, 2007) found that recovered women showed greater hemodynamic activation in the caudate than comparison women. The exaggerated activation of the caudate, a region involved in linking action to outcome, may constitute an attempt at "strategic" (as opposed to hedonic) means of responding to reward stimuli. The authors hypothesize that individuals with Anorexia Nervosa

have an imbalance in information processing, with an impaired ability to identify the emotional significance of a stimulus but have an increased traffic in neurocircuits concerned with planning and its consequences. The characteristics of the cognitive processing of food, body and emotional information in patients with anorexia nervosa (AN) are debatable. Zhu and collegues (Zhu, Hu, Wang, Chen, Guo, Li, Enck, 2012) reviewed functional magnetic resonance imaging studies to assess whether to date there were consistent neural basis and networks in the studies. Results showed that for both food stimuli and body stimuli, AN patients showed an increased hemodynamic response in the emotion-related regions (frontal, caudate, uncus, insula and temporal) and decreased activation in the parietal region. Although no robust brain activation has been found in response to emotional stimuli, emotion-related neural networks are involved in the processing of food and body stimuli among AN. It suggests that negative emotional arousal is related to cognitive processing bias of food and body stimuli in AN.

Concerning brainstem abnormalities Potes and Lutz (2010) in the paper “Brainstem mechanisms of amylin-induced anorexia” concluded that amylin actions on food intake seem to reside primarily within the brainstem, and the associated mechanisms start to be unraveled. Amylin is secreted by pancreatic beta-cells and is believed to be a physiological signal of satiation. Amylin's effect on eating has been shown to be mediated via a direct action in the area postrema (AP) via amylin receptors that are heterodimers of the calcitonin receptor core protein with a receptor activity modifying protein. Peripheral amylin leads to accumulation of cyclic guanosine monophosphate, phosphorylated extracellular-signal regulated kinase 1/2 and c-Fos protein in AP neurons. The particular amylin-activated AP neurons mediating its anorexigenic action seem to be noradrenergic. The central pathways mediating amylin's effects have been characterized by lesioning and tracing studies, identifying important connections from the AP to the nucleus of the solitary tract and lateral parabrachial nucleus. Amylin was shown to interact, probably at the brainstem, with other signals involved in the short term control of food intake, namely cholecystokinin, glucagon-like peptide 1 and peptide YY. Amylin also interacts with the adiposity signal leptin; this interaction, which is thought to involve the hypothalamus, may have important implications for the development of new and improved hormonal obesity treatments. Moreover in the paper “Brain lesions and eating disorders” Uher and Treasure (2005) evaluated the relation between lesions of various brain structures and the development of eating disorders to inform the neurobiological research on the aetiology of these mental illnesses. The authors

reviewed 54 case reports of EDs with brain damage, and concluded that changes in appetite occur with hypothalamic and brain stem lesions and more complex syndromes are associated with right frontal and temporal lobe damage. These findings challenge the traditional view that eating disorders are linked to hypothalamic disturbance and suggest a major role of frontotemporal circuits with right hemispheric predominance in the pathogenesis. Of the seven anorexia cases associated with primary tumours in the area of brain stem and the fourth ventricle, two presented as typical restrictive anorexia nervosa with fear of fatness; surgical removal of the tumours led to remission and sustained weight gain in both cases.The other five cases were clearly atypical with weight loss in the absence of weight concerns or body image disturbance. In a case, atypical anorexia fully remitted after radiation treatment. In summary, brain stem lesions are associated with loss of appetite. The suggestive association with typical cases of restrictive anorexia nervosa relies on two case reports and needs to be substantiated by further evidence.

In the present context it is important to underline that the nature of the interplay between functional activities and brain volumes remains unclear. The decrease in whole brain volume might affect functional resources globally causing a need for neural compensation. The association between functional activity and index of whole brain volume or regional grey matter volume change would suggest neural compensation but further studies are needed to clarify these issues. Discrete brain volume differences could provide candidate brain regions for further structural and functional study in people with eating disorders. Despite evidence from fMRI studies that brain activation correlates with global brain volume (Brodtmann, Puce, Darby & Donnan, 2009) it is not known whether functional differences are associated structural anatomical differences in women with AN. Therefore, it is important for future functional brain imaging studies of AN to correlate Blood Oxygen Level Dependency (BOLD) signal with gray matter volume.

In our study both parametric and nonparametric correlations were performed between EDI-3 scores in AN subjects (mean values and standard deviation are reported in Table 5.4) and global grey volume and ROI volumes; it is worth noting that the results reported are merely explorative and the issue needs further study. Significative correlations or at the limit of significance were found between - cerebellum and global psychological maladjustment / interpersonal alienation; - left parietal lobe and maturity fears / interoceptive deficits; - right insula and interpersonal problems. Eating disorders are complex psychiatric illnesses that include alterations in the neural systems related to reward, decision-making, and social processing

(McAdams & Smith, 2015); because the present study and previous studies could not find or explain clear associations, these results have to be regarded as preliminary. Further studies were able to show correlations. At the same time, from our point of view, these correlations of global or regional GM changes with neuropsychological or psychopathological parameters are hazardous operations on the epistemological level, and then have to be treated with great caution.

Although the underlying mechanism responsible for anatomical brain alterations in AN is not fully understood, it is feasible that changes in the brain are attributable to malnutrition. However, only a few studies have investigated brain structure in patients before and after weight restoration. Some studies report that the brain normalizes completely at both a global and regional level after weight restoration (Wagner et al., 2006), while other studies have reported nonreversible regional changes in gray matter in the anterior cingulate cortex (Friederich et al., 2012; Muhlau et al., 2007), supplementary motor area (Friederich et al., 2012), and precuneus (Joos et al., 2011). Collectively, these latter studies suggest that gray matter is more affected than white matter in patients with AN, and gray matter reductions may be only partially reversible. The majority of these studies have focused largely on adults, however, while structural magnetic resonance imaging (sMRI) studies including adolescents and young individuals with AN remain scarce. Adolescence is an important developmental stage warranting additional study, as the teenage brain is still undergoing major changes, such as synaptic pruning, dendritic arborization, and increased myelination. Further, the onset of eating disorders frequently occurs during adolescence and adolescent AN samples are typically less confounded by a long duration of illness.

It is worth noting that the participants in the present study were severely ill and, also due to the limitations of the study as cross- sectional, caution should be exercised when interpreting results.

This study provided an investigation of cerebral tissue alterations associated with AN in young females but in this kind of group studies, valuable data pertaining to each individual might disappear; cautionary comments notably by clinicians directly responsible for diagnosis, treatment and advice for adolescence psychiatric disorders are significant and scientific focus on detail gives no justification for dismissing clinical case studies (Trevarthen, 2001).

To demonstrate that their brains are physically affected by malnutrition might prove useful for patients to obtain an understanding of their own illness from a neurobiological point of view in a clinical setting.

Findings are noteworthy in light of prior suggestions that patients with AN have a dysfunctional reward system (Kaye et al., 2009; Keating, Tilbrook, Rossell, & Fitzgerald, 2012) and alterations in decision-making abilities and social behavior (McAdams & Smith, 2015). The results from a recent meta-analysis of structural imaging studies suggest that AN is linked to reduced brain structure in reward and somatosensory regions (Titova, Hjorth, Schioth, & Brooks, 2013).

Our research supported previous notions that weight changes are associated with cerebral tissue alterations, and that gray matter is more affected than white matter. Results contribute to increased knowledge regarding the specific brain regions associated with changes in weight and clinical measurements in patients with AN restricting subtype. Further studies are needed to consider the insights into translational treatments of people with eating disorders that can be gleaned from neuroimaging studies.

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