Università degli Studi di Torino
DIPARTIMENTO NEUROSCIENZE

Dottorato di ricerca in Neuroscienze

Tesi di Dottorato

[NEUROFUNCTIONAL CORRELATES OF BINGE EATING DISORDER: PERSONAL CONTRIBUTION AND CLINICAL IMPLICATIONS FOR TREATMENTS]

Candidato/a

Dott.ssa Spalatro Angela Valentina

Matricola 283912

Tutor

Prof. Federico Amianto

Co-Tutor

Dott. Federico D'Agata

A. A. 2019/2020

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PART I

BINGE EATING DISORDER (BED)

1.1 INTRODUCTION

Binge Eating Disorder (BED) has been introduced as an autonomous diagnostic category only in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM5), released in May 2013. The key symptom of BED are binge eating episodes without compensatory behavior (a factor that differentiates it from Bulimia Nervosa) and feelings of marked psychological distress associated with them (American Psychiatric Association, 2013).

Despite its recent introduction within the spectrum of Eating Disorders, BED is a relatively common disorder and its incidence will increase further (Amianto et al., 2015) even if for a long time BED has been overlapped with obesity. About a third of the US population is obese (Flegal et al., 2012); the data suggest that obesity has a complex and heterogeneous etiology (Davis et al., 2009). Identifying and conceptualizing specific subtypes of obesity (including people suffering from BED) can lead to more targeted prevention and treatment strategies, indeed. The Binge Eating Disorder is strongly associated with obesity but differs from it (and other forms of eating disorders) in many domains: behavioral, body, psychological and psychiatric. People with BED consume more calories and feel relatively less satisfied after eating than obese individuals without BED. Group differences also extend to non-food stimuli; the Binge Eating Disorder is associated with alterations in executive tasks of cognitive flexibility (Duchesne et al., 2010), suggesting more general self-regulation difficulties. Consistent with this notion, BED is associated with greater psychiatric comorbidity (Yanovski et al., 1993), and the phenomenon of binge explains many differences observed in the psychological and psychiatric domains.

Many research characterized precisely BED differentiating it from obesity and other eating disorders. Recently, for example, some studies have shown that patients suffering from BED report high rates of child maltreatment with a wide range of traumatic experiences during childhood, regardless of the gender, the degree of obesity and the binge-eating behaviors (Rohr et al., 2015). Specifically, it seems that BED disorder could be related to emotional neglect and emotional abuse, and not to physical or sexual abuse that are more common in obesity condition without BED (Amianto et al., 2019).

Although the applications of Neuroimaging in the understanding of the neurobiological bases of psychiatric conditions have shown important evidences, as concerns the BED the situation is little investigated. The contribution of Neuroimaging techniques becomes fundamental in the multidisciplinary approach to this disorder and in the research for therapeutic approaches that reduce the dropout and relapse rates typical of this Eating Disorder. Neuroimaging currently plays the role of being a validated tool in the study of neuronal patterns potentially involved in treatment resistance (Lavagnino et al., 2014). Areas such as the ventral striatum and the prefrontal cortex have shown different functional activation in subjects with BED compared to healthy controls in response to food stimulation (Balodis et al., 2013). Numerous evidences also support the importance of results related to rest brain activity (Resting State), defining it as an indirect mirror of reflective thinking, self-awareness of the interoceptive sphere (Buckner et al., 2008). Some researchers interpret the activity of the Resting State as a direct way to access the functions related to the self; this functional activity could provide valuable information to the clinician to reflect on therapeutic models at times to be reviewed and improved (Amianto et al., 2016; Collantoni et al., 2016)

The aim of this study is to explore functional neuronal circuits in patients with BED using Functional Magnetic Resonance Imaging (fMRI), with particular attention to areas involved in impulsivity and cognitive control correlating any differences with clinical and psychopathological aspects and comparing them with control subjects. We expected that the brain networks show a different activation between the two groups, correlating differently with the clinical, psychopathological

characteristics of the patients, providing greater clarity with respect to primarily neurobiological aspects on which to act with more incisive therapeutic interventions able to counteract the phenomenon of therapeutic dropout.

A second aim of this study is to explore possible gender related differences or similarity from male and female healthy subjects respect to BED patients in order to clarify possible similarities to classical EDs or some possible gender-related mechanism underling this type of Eating Disorder.

1.2 BINGE EATING DISORDER: NEW DIAGNOSIS IN FRONT OF DSM 5

In 1993, shortly before the publication of the fourth edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), a group of researchers known for their work in the field of eating disorders, in obesity and psychiatric nosology published an article arguing strenuously for the inclusion of binge eating disorder (BED) as a psychiatric diagnosis (Spitzer et al., 1993). Recognized for the first time in the 1950s as a distinct eating model among obese subjects, the BED re-emerged in the 1980s as a phenomenon of interest not only in research on obesity but also in eating disorders programs, acknowledging the problematic uncontrolled consumption of large quantities of food beyond the relationship with body weight. These individuals were not included in the diagnosis of bulimia nervosa, because compensatory behaviors or other behaviors to compensate for episodes of binge eating were absent. These researches fixed the validity of the new diagnostic category, its distinction from existing eating disorders (in particular bulimia nervosa without compensatory behaviors), and its usefulness for clinical practice. When the DSM-IV has been published in 1994, this version included the Binge Eating Disorder not as a diagnosis but as an example of an eating disorder not otherwise specified. Despite this lack, the publication of provisional diagnostic criteria was sufficient to stimulate subsequent research, and to develop specific treatments. Two decades later, this knowledge brought to the inclusion of the BED in the DSM-5. This represented a result of the progress made in defining and characterizing the disorder, as well as an improved understanding of its treatment. In the new version of the DSM the criteria are very similar to those included in the previous version. The key diagnostic criteria of BED are:

1. Recurrent and persistent episodes of binge eating
2. Binge eating episodes are associated with three (or more) of the following:

    - Eating much more rapidly than normal
    - Eating until feeling uncomfortably full

- Eating large amounts of food when not feeling physically hungry
- Eating alone because of being embarrassed by how much one is eating
- Feeling disgusted with oneself, depressed, or very guilty after overeating
- Marked distress regarding binge eating

3. Absence of regular compensatory behaviors (such as purging).

The only change from DSM IV concerns the frequency of binge episodes: it goes from a binge rate of two days a week for a period of six months to a frequency of at least one binge episode per week for a period of three months (Keel et al. , 2011). Initially it was thought that the changes made in the criteria would have led to a significant change in prevalence rates, however Hudson and colleagues estimated an insignificant increase, less than 0.2%, regarding the prevalence of this disorder (Hudson et al., 2012). However, it is possible to make a forecast about the increase in the incidence rate over the next few years, due to the general upward trend that is being observed both with regard to obesity then for EDs in general rather than for the expansion of the diagnostic criteria introduced with DSM-5 (Amianto et al., 2015). BED is the most common eating disorder in the United States. In adults it affects 3.5% of women and 2% of men and up to 1.6% of adolescents [Swanson et al., 2011]. In women it is most common in early adulthood but more common in men at midlife. BED seems to affect blacks and whites equally. Comorbid problems are both physical and psychiatric. Although most people with obesity don't have BED, up to 2/3 of people with BED are obese and can have the medical difficulties associated with this condition. Compared with normal weight or obese control groups, people with BED have higher levels of anxiety and both current and lifetime major depression. The characterization of psychological and psychiatric domain of BED remain unclear and the aim of recent studies is to better understand what neural functions are prevalent in this condition in order to better develop specific therapeutic strategies.

1.2.1 IMPULSIVITY SYSTEMS IN BINGE EATING DISORDER

Impulsiveness has a series of definitions that generally include ill-conceived actions, expressed prematurely, unduly risky or inadequate to the situation which often lead to undesirable consequences (Evenden, 1999). The components of impulsiveness include attention, suppression of responses, poor assessment of consequences and inability to forgo small immediate benefits in favor of greater delayed rewards.

Decision making reflects a process in which attention is focused: a choice is made after reflecting on the expected results of possible actions. This process requires attention, while impulsiveness may not require attention (Crews & Boettiger, 2009). The executive functions in cognitive psychology control abstract thinking, the acquisition of rules, the planning and flexibility of responses including the change of rules, as well as the initiation of appropriate actions and the inhibition of inappropriate actions. The choice to diet is an archetypal example of cognitive control: an individual must keep long-term goals in mind and regularly inhibit immediate food-related temptations. In this way, understanding the neural substrates of inhibitory control is particularly relevant in BED individuals who often attempt to restrain their eating in order to lose weight (Hutson et al., 2018).

The executive functions of the frontal lobe receive input from all sensory modalities, integrate memories and use working memory to process temporary information, assemble information on the reward and perform the evaluation of the temporal synchronization of events to perform planned behaviors. They are often invoked to ignore the answers that have been automatically generated. Impulsiveness leads to rapid responses without reflection, due to weak inhibitory control, lack of attention or wrong assessments. Executive functions play a significant role in impulsiveness. Failure to control inhibition reflects a behavioral manifestation of impulsiveness (Newman & Meyer, 2014).

Inhibitory control is one of the main domains of executive functions and can be divided into response inhibition and interference control (Diamond & Diamon, 2013). Interference control is a control mechanism that helps ignore irrelevant information (S. P. Wilson & Kipp, 1998) and improves the

ability to suppress stimuli that normally trigger a competitive reaction. Moreover, it activates the ability to suppress distractors that would normally delay the response (Nigg, 2000). A region involved in impulse control and decision making is the ventromedial prefrontal cortex (vmPFC). Modifications in the activity of this area are consistent with the bio-behavioral results observed in addictions (K. Garber & H. Lustig, 2011; Avena et al., 2011). Interference checking can be measured using the Stroop test of colors and words (Stroop, 1935). In populations characterized by impaired impulse control, such as pathological gambling and bulimia nervosa, the performance of the Stroop test is associated with relatively reduced activity in prefrontal areas, including vmPFC (Kemps & Wilsdon, 2010; Potenza et al., 2003).

Regarding the BED it has been amply demonstrated that during the presentation of food stimuli, important differences are observed at the level of the activity of the prefrontal cortices, in particular in the ventromedial prefrontal cortex, compared to healthy and obese subjects (Geliebter et al., 2006; Schienle et al., 2009). Balodis and colleagues (Balodis et al., 2013) investigated the differences in brain areas that are the basis of cognitive control processes, in BED subjects, obese subjects without BED and control subjects. Functional magnetic resonance imaging (fMRI) measured the neural activity of subjects engaged in the Stroop test, testing the ability to inhibit automatic response trends. All three groups showed similar performance in the Stroop task, demonstrating longer reaction times for incongruent stimuli than congruent ones and committing few errors. Consistent with their hypotheses, the BED group demonstrated decreased activity in the frontal regions underlying the inhibitory control, including vmPFC and IFG. Furthermore, a decrease in activity was also highlighted in the insula, middle-upper temporal areas and the middle occipital gyrus. These significant differences in neurobiological correlates in BED subjects compared to obese subjects without BED confirm the existing literature on the psychological and behavioral diversity of this diagnostic construct and confirm its validity, as proposed in the DMS-5. All together these findings highlight the importance of distinguishing obese BED groups from non-BED obese groups. These

findings also support the idea of a central role for IFG and frontotemporal areas in inhibition and binge behaviors. Nevertheless, to date, no human neuroimaging study has specifically examined inhibitory control processing in BED groups using food cues.

1.2.2 REWARD SYSTEM IN BINGE EATING DISORDER

Several studies have examined the neural substrates of reward processing. These studies have led to the identification of specific stages of reward processing:

- the anticipatory phases of reward regulated by striatal activity;
- the phases following obtaining the reward involving more medial areas of the prefrontal cortex (Knutson et al., 2001).

In other words, the anticipation of the reward is linked to the activity of the ventral striatum (VS), while a greater activity of the medial prefrontal cortex is associated with the notification of the reward or the outcome phase of the elaboration of the reward. The neural systems underlying the reward mechanism are also implicated in obesity, as they are involved in the regulation of appetite, weight and response to treatment (Kelley et al., 2005). Studies on healthy individuals with food stimuli have well demonstrated the distinction between the anticipatory phase and the outcome phase of the reward process with regard to food. For the first phase, greater activity was detected at VS level, in the midbrain, in the amygdala and in the thalamus, compared to the second phase of notification and reward processing (Pelchat et al., 2004).

Studies on obese subjects have showed hypo and hyper activation of the neurons involved in the reward circuit in response to food-type stimuli (Rothemund et al., 2007; Stoeckel et al., 2008). These seemingly conflicting findings could relate to the heterogeneity existing within the population of obese subjects. In fact, obesity is associated with different forms of eating disorders. For example, groups of obese subjects with BED differ from those with obesity without BED in numerous behavioral and psychological dimensions (Allison et al., 2005). Apparently conflicting findings could

also reflect failures to adequately disambiguate the steps involved in reward processing (anticipation and results).

Balodis and colleagues (Balodis et al., 2013) have used functional magnetic resonance imaging (fMRI) to examine the brain processing of monetary reward, in the phase of anticipation and reception of winnings and losses, in obese individuals with and without BED and in a control group of normal-weight individuals. The results of this work allowed to associate the anticipatory processing with a diminished bilateral striatum (VS) activity in the BED subjects compared to the group of obese subjects without BED. On the contrary, the comparison between obese subjects and normal weight healthy controls, again with regard to the anticipatory phase, revealed an increase in bilateral VS recruitment in obese participants. Furthermore, a different brain activity in BED subjects compared to obese subjects was highlighted in the midbrain, in the amygdala and in the thalamus areas; these areas have been previously identified in food stimulation paradigms as more reactive during anticipation, compared to consumer-related reward processes (O'Doherty et al., 2002; Pelchat et al., 2004). These results, therefore, provide some clarifications on the ambiguous results of the elaboration of the reward with respect to hypoactivation and hyperactivation in obesity, underline the importance of differentiating between the subtypes of obesity and the different phases connected to the reward process.

Balodis and colleagues comment that, similarly to the results related to pathological gambling, the relative fronto-striatal hypoactivity in BED participants is less phase-specific than assumed. The relative reduction of fronto-striatal activity occurred both in the anticipatory and outcome phases, in the conditions of victory and loss, indicating in the subjects with Binge Eating Disorder the presence of a generalized model of reduction of the activity of this region in the process of rewards and losses. The reduction of anticipatory processing could represent an important precursor in the development of the BED. The "reward deficiency syndrome" postulates that individuals with decreased brain activity of reward-related circuits could consume food or take addictive behaviors in compensatory

efforts to stimulate activity in these areas. However, in the comparison between BED subjects and healthy controls few differences of activity were observed in the fronto-striatal regions during the anticipatory phase. These data suggest that the BED group could be characterized by alterations during the outcome phases, while the group of obese subjects distinguishes itself through hyperactivity during the anticipatory phases.

This study concludes that the results support the idea of a generalized modification in reward processing in subjects suffering from uncontrolled feeding. Furthermore, the diminished activity of the insula, responsible for an altered awareness (particularly during the processing and outcome phase), suggests a reduced capacity to integrate information on the reward connected with the current state of the individual. The inferior frontal gyrus (IFG) is implicated in the interaction between cognitive and motivational processing during inhibitory control; therefore the diminished joint IFG activity with decreased insular activity could have implications for measuring hunger and satiety signals (Balodis et al., 2013).

1.2.3 NEGATIVE EFFECTS IN BINGE EATING DISORDER

Recent findings suggest that genetic factors could influence expression of negative emotionality traits and emotional-eating tendencies that emerge early in life. It seems that they are stable throughout development, and predispose youth to eating disorders characterizing persistent negative mood and negative urgency, which refers the tendency to act impulsively in response to negative affective states (Racine et al. 2013). Evidence suggests that genetic predispositions toward altered signaling of serotonin, catecholamines, glucocorticoids, and/or BDNF, which impact corticolimbic circuitry and neuroendocrine systems may play an important role in the causal relationship between negative affects trait disturbances and the early development of eating disorders (Hutson et al., 2018).

Sexual and physical abuse, maternal separation, and social isolation from peers predict significant structural and functional remodeling of corticolimbic neurons (Eiland and Romeo 2013), altered functional connectivity between corticolimbic regions (Burghy et al. 2012), SAM- and HPA-axis

hyperreactivity to stressors, and diminished inhibitory effects of cortisol on the HPA-axis (Sominsky and Spencer 2014). These disturbances are linked to abnormal responses often observed among individuals with binge-type EDs and psychological risk factors for eating disorders. Such stressor-induced biological alterations may serve as mechanisms through which sustained childhood stressors increase risk for binge-type EDs (Díaz-Marsá et al. 2007). The effects of early sustained threats and losses on corticolimbic and neuroendocrine dysregulation often are not apparent until adolescence and are more robust in females (Burghy et al. 2012), which may partly account for the increased risk for binge-type EDs in adolescent females.

Schienle et al. (2009) in their food cue study also included some images of rotting and unappetizing food in order to better understand the neural substrates of disgust across multiple disordered populations. BED individuals showed reduced OFC and insular signaling to disgusting pictures relative to lean controls (Schienle et al., 2009). Stress and negative affect often precede a binge episode yet few studies have examined this neurobiological link in BED. Recently, Lyu and Jackson (2016) examined the role of acute stressors on both neural and behavioral measures in a BED-symptomatic female population. Participants experienced the cold pressor test or a non-stress condition and subsequently viewed palatable food cues while undergoing fMRI. While wing food cues, BED-symptomatic females in the stress condition had reduced IFG, insula and hippocampal activations relative to a non-BED control group. Additionally, diminished hippocampal activity was associated with greater post-fMRI chocolate consumption in the lab. Other fMRI studies have demonstrated a role for the hippocampus in influencing neuroendocrine stress responses as well as in linking interoceptive and exteroceptive signals of satiety (Born et al., 2010).

Similar to children at high risk for anxiety and depression (Casey et al. 2008), children with emotional eating may have a pre-existing imbalance between subcortical limbic and prefrontal cortical structures or dysfunctional neuroendocrine stress systems that is amplified during adolescence. Vulnerable youth, such as those entering puberty with emotional eating and a history of sustained childhood stressors may be at particularly high risk for disproportionate increases in negative mood

intensity, affect lability, emotion dysregulation and the early emergence and maintenance of binge-type EDs (Hutson et al., 2018).

1.2.4 THERAPEUTIC APPROACH: SOME LITERATURE EVIDENCES

The treatment of Binge Eating Disorder must take into account a series of comorbidities that often arise following the development of this pathology (Amianto et al., 2015). The choice of treatment must therefore be multidisciplinary to cope with the set of symptoms and comorbidities. This approach will have to deal with the distinctive features of the BED reflecting in a weak therapeutic alliance associated with treatment dissatisfaction, and consequent early treatment interruption (Flückiger et al ., 2011). In order to adequately address these characteristics as a consequence of the psychopathological traits, the therapeutic approach should be flexible and consider the different psychological and physical problems of the subjects. Before engaging care it would be advisable to work on the motivation of the subjects and increase the possibility to the change of their condition (Fassino et al., 2007).

The primary goal of BED therapeutic approach is not weight loss, but rather the reduction of binge eating behaviours. Only later, body weight loss and stabilization become part of the healing process. "Abstinence" from bingeing should be pursued right at the beginning of treatment, also because the achievement of this goal in some cases leads to a significant weight loss (Grilo et al., 2012). The therapeutic program should promote a stable reduction in caloric intake and a permanent maintenance of eating habits and healthier lifestyles, including the education of patients to control their symptoms. Therapy should also aim at maintaining motivation and modifying those dysfunctional thoughts, attitudes and behaviors. To improve the effectiveness of weight loss, which was said not to be the primary purpose of BED treatment, some evidence supports the association of pharmacological and psychotherapeutic treatments with behavioral interventions, based on weight and diet control, taken in loan from general management of obesity (Brambilla et al., 2009; Vocks et al., 2010).

BEHAVIOURAL APPROACH

Behavioral treatments are mainly focused on diet and lifestyle. Often used in the treatment of obesity, they have been proposed in the treatment of BED patients and have shown appreciable results in patients with low associated psychopathology (Munsch et al., 2012). Dietary approach is essential to promote weight loss, and for this reason it is an important component in patients who are characterized by high body dissatisfaction (Bautista-Díaz et al., 2012). Furthermore, it should be remembered that, although body weight is not directly related to the severity of the disease, it is closely correlated with various medical comorbidities. However, it is known that in BED subjects excessive dietary containment is associated with an increase in binge episodes (Carrard et al., 2012), so it is important that the caloric restrictions prescribed by a diet-centered treatment are moderate; a normal or low-calorie diet seems to be the best strategy to avoid an increase in binge eating (Masheb et al., 2011). The attempt to lose a lot of weight in a short time should be discouraged, due to the increased risk of regaining weight in the following period. Physical activity, combined with a balanced diet, is another basic factor for weight loss that drives this type of therapy. Physical activity has a double action: one aims to reduce the accumulation of fat and to inhibit partially the excessive food intake (Vancampfort et al., 2013). In addition, it also helps to maintain the goals achieved with the diet and improves mood and overall health by lowering the clinical comorbidities of BED. However, due to patients' frequently compromised health conditions, physical activity should be under strict medical supervision and follow a gradual schedule. In conclusion, it should be emphasized that, even if behavioral interventions have shown positive results in various studies (in particular on weight loss), their effectiveness in BED healing is lower than in more specific types of intervention such as psychotherapy. Compared to the latter, behavioral interventions also have higher dropout rates (Grilo et al., 2011).

PSYCHOEDUCATIONAL APPROACH

Psychoeducational treatments promote a deeper understanding of the pathological condition of the subjects, in order to increase the possibility of managing it. As regards the BED, these are aimed at informing patients about the different aspects and the different correlations of their disease (Balestrieri et al., 2013). These interventions provide information on key topics such as the factors that predispose, trigger and maintain food impulsiveness, the negative effects of overweight and unbalanced (or restrictive) diets and the most effective methods of weight regulation (Leombruni et al., 2010). The treatments are focused on the explanation of symptoms, without adopting strategies to influence cognitive or unconscious maintenance factors at a deep level, unlike what happens in psychotherapies. The advantages of these treatments are that they can be managed by unskilled personnel, they can be structured in weekly group meetings of limited duration. Patients are taught to self-control their food intake and are informed about the factors that trigger binge eating and correct, sustainable lifestyles over time. The interventions are focused on lifestyle changes to promote a general improvement in health and quality of life, ratherthan on weight loss itself. These interventions have shown a preliminary efficacy on binge reduction and food impulsiveness, even if the effects on body dissatisfaction, anxiety, depressive symptoms and weight loss are still controversial. Considering these preliminary results, psychoeducational interventions could be useful basic therapies, a useful starting point for more complex treatments.

PSYCHOTERAPEUTIC APPROACH

According to literature data, psychotherapies are the most validated and effective treatments for BED, this data is confirmed by several systematic reviews and meta-analyzes (Vocks et al., 2010). Cognitive behavioral therapies (CBT) are the most developed psychological intervention for the treatment of BED. CBT has shown high efficacy with BED remission rates around 50-60% (Grilo et

al., 2011). CBT is a practical and adaptable intervention, with settings and duration that can be varied according to clinical needs. Another advantage of these techniques is the possibility of being performed independently or in combination with other pharmacological approaches. The long-term effects of CBT approaches include a gradual normalization of dietary patterns and a reduced risk of relapse, these effects are associated with improved disinhibition, hunger, negative feelings and perceived global health (Vanderlinden et al., 2012) . Individual or group settings showed similar efficacy. A rapid response to treatment, a lower frequency of binge eating, lower levels of general psychopathology, greater social inclusion and greater openness have been reported by the literature as predictors of a successful treatment.

Behavioral dialectic therapy (DBT) is another psychotherapeutic approach that has proven its effectiveness with BED patients. It is an approach focused on the regulation of emotions and stress tolerance (Telch et al., 2001; Iacovino et al., 2012). This therapy has proven effective in reducing the number of binges and reducing the stress associated with food and body shape. Some preliminary results show that DBT is effective even when administered as a self-help intervention (Masson et al., 2013).

Another psychological treatment that has showed some evidences in the treatment of BED is interpersonal psychotherapy (IPT). This technique focuses on personal relationships and role transitions that could be a predisposing and maintenance factor in eating disorders. The aim is to obtain better social interactions and cope with interpersonal conflicts (Tasca et al., 2012). Although it does not focus directly on eating symptoms, it may be useful because it addresses a specific area often compromised in patients with BED. This disease often emerges in adolescence, in a context of interpersonal difficulties and maturation, and its maintenance over the years can be related to dysfunctional relational styles that in turn trigger feelings of anger, anxiety and anger related to impulsiveness . It has been observed that CBT and IPT have a comparable efficacy in binge reduction,

both at the end of therapy and at follow-up, with a significant reduction in psychiatric comorbidities and in some cases a significant reduction in body weight (Hilbert et al., 2012).

PHARMACOLOGICAL APPROACH

Drug therapy in BED patients focuses specifically on reducing food impulsiveness, binge eating and negative feelings, aspects that constitute many complications in eating disorders. Unfortunately, there are few data on the long-term efficacy of pharmacotherapy as a treatment for BED. Antidepressants are the drugs most studied and applied to the treatment of BED, showing efficacy on food impulsiveness and general psychopathology, but also on anxiety and depressive symptoms. The positive effects on food impulsiveness also lead secondarily to the lowering of the number of binge eating (Reas & Grilo, 2008). The compounds usually used are antidepressant molecules: high-dose SSRIs have shown efficacy on binge-reduction and associated psychopathology, with some limited evidence of efficacy on weight loss, which are of questionable clinical relevance (McElroy et al., 2015). Although the differences in the long-term action of SSRIs still need to be clearly established, fluoxetine is the most studied and prescribed. It has shown significant efficacy over the placebo drug in reducing binge eating, weight loss and mood improvement. However, its clinical relevance is still uncertain and in any case its effects are consistently lower than in CBT, even in combination treatments (Leombruni et al., 2008). Although SSRI treatments have produced a significant reduction in binge eating, impulsive feeding, and in some cases, even weight loss, the clinical relevance of these changes is still doubtful and limited by small sample sizes, high dropout rates and rather short follow-up times.

1.3 NEUROFUNCTIONAL APPROACH TO EATING DISORDERS

1.3.1 NEUROBIOLOGICAL FEATURES OF EATING DISORDERS

Eating disorders (ED) are considered multifactorial biopsychosocial mental illnesses (Klump et al.,, 2009), and current treatments are only partially successful in ameliorating the symptoms of these disorders (Treasure et al., 2010). Functional neuroimaging techniques like positron emission tomography (PET), single photon emission computer tomography (SPECT) and functional magnetic resonance imaging (fMRI) have also provided a variety of data regarding brain function in ED (Van den Eynde & Treasure, 2009). Structural MRI studies in underweight AN subjects showed large cerebrospinal fluid volumes and deficits in total gray matter and total white matter volumes although there is some degree of variability in the findings (Van den Eynde & Treasure, 2009). Specific regions interested by atrophy have been reported: the paracentral lobule, the cingulum, the thalamus, the midbrain, the extra-striate body area and the cerebellum (Pietrini et al., 2011; Boghi et al., 2011). Othere studies showed a reduced GM volume in the caudate nucleus in BN women with respect to CN and AN, with abnormal activation of this area during task related to food processing (Amianto et al., 2013; Bohon & Stice, 2012). Caudate nucleus is a core unit within the basal ganglia, involved in reward and motivation processes (Robbins and Everitt,1996;Berridge et al., 2010). Recent studies have shown that patients with BN are characterized by the alteration of self-regulation processes, linked to a deficit in the recruitment of fronto-striatal circuits that contributes to the genesis of binge-eating behaviors (Marsh et al., 2009). These findings on BN patients could support the recently outlined concept of the "impulse control model" of eating disorders, in which the alterations of mesolimbic reward response mechanisms could explain the lack of control and the impulsivity that are often present in bulimic patients.

Several groups have used resting-state fMRI that is thought to reflect internally oriented thinking and consciousness (Biswal et l., 2010; Harmelech et al., 2013). This method measures brain activity in

absence of any stimulus and allows to investigate temporal correlations between different brain areas (Carnell et al., 2012).

Despite many different interpretation, the results are generally overlapping in that they show functional alterations in various networks and/or areas. Specifically, alterations in the fronto-parietal network (a brain network involved in cognitive control functions) were found in both patients with Anorexia Nervosa (AN) and participants recovering from AN (Boehem et al., 2015) These resting-state findings may underlie the impaired cognitive control of appetitive processes as well as ruminations concerning the self and body image (Abbate Daga et al., 2011; Canna et al., 2017).
With new functional techniques of analysis, a recent study shows that changes in resting state neuronal variability in Ventral Attention Network (VAN) correlated with various psychopathological measures in ED. This further underlines the central relevance of VAN in ED and its altered capacity of shifting between internal body-related and external environmental non-bodily-related stimuli as it can be observed in psychopathological symptoms (Spalatro et al., 2019).

Although findings vary across studies, based on the available evidence, the following conclusions could be fixed concerning Anorexia Nervosa (Simon et al., 2019):

a) the neural processing of visual food cues is characterized by increased top-down control, which enables restrictive eating,
b) increased emotional and reward processing during gustatory stimulation triggers disorder-specific thought patterns,
c) hunger ceases to motivate food foraging but instead reinforces disorder-related behaviors,
d) body image processing is related to increased emotional and hedonic reactions,
e) emotional stimuli provoke increased saliency associated with decreased top-down control
f) neural hypersensitivity during interceptive processing reinforces avoidance behavior.

Findings on neural processing in both AN and BN patients point to the presence of altered sensitivity to salient food stimuli in striatal regions and to the possibility of hypothalamic inputs being overridden by top-down emotional-cognitive control regions. Additionally, innovative new lines of research suggest that increased activations in fronto-striatal circuits are strongly associated with the maintenance of restrictive eating habits in AN patients. Although significantly fewer studies have been carried out in patients with BN and BED, aberrant neural responses to both food cues and anticipated food receipt appear to occur in these populations. These altered responses, coupled with diminished recruitment of prefrontal cognitive control circuitry, are believed to contribute to the binge eating of palatable foods. Results from functional network connectivity studies are diverse, but findings tend to converge on indicating disrupted resting-state connectivity in executive networks, the default-mode network and the salience network across EDs.

A neurobiological model of ED suggests that there could be an imbalance in information processing between ventral limbic and dorsal executive circuits (Wagner et al., 2008). These circuits are primarily implicated in inhibitory cognitive processes and reward-related behavior, which are altered in ED (Favaro et al., 2013; Kaye et al., 2013).

1.3.2 NEUROBIOLOGICAL EVIDENCES IN BINGE EATING DISORDER: DIFFERENCES AND SIMILARITIES FROM OTHER EATING DISORDERS

The neurobiology of BED is relatively poorly understood but is gradually evolving and has been recently reviewed (Balodis et al., 2015). There is a growing consensus derived from clinical functional imaging and cognitive studies that several interconnected behavioral intermediate phenotypes including attentional bias towards food cues, cognitive flexibility, perseverative or compulsive behavior, impulsivity (Voon, 2015), motivation and reward processing are impaired in BED (Balodis & Potenza, 2015; Manwaring, Green, Myerson, Strube, & Wilfley, 2011). These clinical observations are supported by pharmacological and behavioral studies of the fundamental processes underpinning natural and drug rewards, impulsivity, compulsivity and habitual behavior including the potential role of the mesolimbic dopamine system where the phasic release of dopamine in the ventral striatum motivates animals to seek food. Intriguingly this key pathway is influenced by peripherally originating orexigenic peptides (e.g., ghrelin) acting on specific receptors located in brain stem dopamine and cholinergic cell bodies that modulate ascending dopamine projections to the nucleus accumbens (Valdivia, Cornejo, Reynaldo, De Francesco, & Perello, 2015). This pathway provides not only a potential integrative mechanism between appetite, food intake and motivated behavior but also a novel target for the attenuation of behaviors linked to food or drug rewards. Additionally, animal studies have identified the involvement of several neurotransmitter signaling pathways in models of binge-eating. However, there is a paucity of positron emission tomography (PET) or single photon emission computerized tomography (SPECT) imaging studies that can affirm the involvement of these neurotransmitter pathways in BED subjects (reviewed Kessler et al., 2016). Functional genetic polymorphisms have been associated with BED (Hess et al., 2013) and as with other psychiatric disorders, it is likely that no single gene is responsible and that multiple genes interacting with environmental factors (Klatzkin, Gaffney, Cyrus, Bigus, & Brownley, 2016) are likely to contribute to the potential of developing BED. Replication and expansion of these genetic,

behavioral, neuroimaging and pharmacological studies will be invaluable in our further understanding of the neurobiology of BED.

SPECT studies

The first neuroimaging study in individuals with BED occurred almost 2 decades ago and examined neural responses to neutral versus food cues (Karhunen et al., 2000). Following an overnight fast, participants were exposed to a neutral landscape picture or to a self-selected full meal. In BED participants, blood flow was markedly increased to frontal and prefrontal regions relative to the other two groups. Although BED and non- BED groups did not differ on eating desire or food pleasantness, only the BED group showed a positive correlation between hunger and regional cerebral blood flow (rCBF) in the left prefrontal cortex (PFC). Peripheral physiological responses were measured through serum insulin, plasma glucose, serum leptin, noradrenaline, adrenaline and cortisol at multiple time points; however, no group differences were observed (Karhunen et al., 2000). Another SPECT study by this research group examined serotonin (5- HT) binding in obese females in a scan before as well as after successful treatment (Tammela et al., 2003). Results showed that relative to control subjects, symptomatically recovered BED individuals showed significant increases in 5-HT binding in the midbrain, relative to control subjects whose binding remained unchanged between the two scans. The therapy consisted of group psychotherapy as well as fluoxetine —thereby making it difficult to disentangle each therapeutic intervention. Nonetheless this first neuroimaging treatment outcome study in BED demonstrated enhanced serotonergic binding following treatment.

Functional magnetic resonance imaging (fMRI) studies

Since the first SPECT studies, several functional magnetic resonance imaging (fMRI) studies have assessed relevant cognitive constructs in BED, including food-reward processing, non-food reward processing (e.g. money) as well as inhibitory control. These studies further support the notion of amplified food-cue sensitivity in BED, particularly through increased BOLD responses in reward and attention networks. Recently, fMRI investigations are moving beyond activation studies and are

examining connectivity between regions as well as using computational modeling of choice behaviors. Most recently, studies are linking imaging with treatment outcome and using brain stimulation techniques in the hopes of better identifying therapeutic targets. However, no many studies are available in this context for BED.

Genetics and pharmacological studies

Novel pharmacological mechanisms that influence behavioral endophenotypes that may become maladaptive as binge-eating develops have been explored for potential efficacy in the treatment of BED. Given the neurobiological complexity in the regulation of binge-eating, it is likely that drug combinations, which may differentially regulate aspects of binge-eating (e.g., μ opiate receptor antagonists and monoamine stimulants), may produce synergistic effects.

Monoamine stimulants and Monoamine reuptake inhibitors

The psychostimulants include multiple structurally related compounds including cocaine, D-amphetamine and methylphenidate that have similar but not identical mechanisms of action. D-Amphetamine has a well-documented history of use in the treatment of obesity. However, while it was shown to be effective as an appetite suppressant, its effects are not maintained and significant side effects including insomnia, dry mouth, cardiovascular effects and potential for abuse led to its discontinuation of use as an anti-obesity agent.

Lisdexamfetamine (LDX) is a prodrug of D-amphetamine decreased compulsive eating and attenuated impulsive choice in the animal studies were consistent with the clinical observations of LDX in BED subjects which revealed a significant reduction of binge-eating frequency and reduced compulsive and impulsive behaviors using the Yale-Brown obsessive compulsive scale modified for binge-eating (YBOCS-BE) (McElroy, Hudson, et al., 2016; McElroy, Mitchell, et al., 2016) which captures aspects of binge-eating psychopathology. LDX is now approved in the USA for the treatment

of moderate to severe BED, and it will be interesting to see if its effects in BED, unlike those on appetite suppression, are maintained with long term therapy.

Selective serotonin reuptake inhibitors (SSRIs, including fluoxetine, fluvoxamine, citalopram, escitalopram) potently and selectively block the serotonin transporter without appreciably affecting dopamine or noradrenaline transporters. Generally and irrespective of which SSRI was used, a significant though moderate improvement in a binge-eating scale score, frequency of binge-eating and weight loss was observed, and in one study improvement in the YBOC-BE scale was reported (McElroy et al., 2003). However, despite these clinical findings, SSRIs are not approved by the U. S. Food and Drug Administration (FDA) for the treatment of BED.

5-HT2C receptor agonists

5-HT2 receptors exist as three subtypes (5-HT2A, 5-HT2B and 5-HT2C) and are widely located throughout the brain where they regulate a broad array of physiological functions including appetite, mood, motivation and impulsivity. To date, there are no reported clinical studies of lorcaserin in BED subjects, and its effects on homeostatic feeding would suggest that this mechanism is unlikely to have specific effects on binge-eating.

Mu opioid receptor antagonists

There are three principle opioid receptor subtypes (mu (μ), delta (δ), and kappa (κ)) in the mammalian CNS. Each receptor subtype has a wide and overlapping distribution within the CNS and consequently is involved in modulating a broad array of physiological functions including homeostatic and compulsive feeding behavior, motivated behavior, addiction, pain processing and mood.

There are several lines of evidence that suggest a role for μ opioid receptors in the regulation of binge-eating behavior. PET imaging studies in BED subjects showed a reduction of μ opioid receptor binding in several brain regions (Majuri et al., 2016), although this contrasts with the small but

significant increase of striatal μ opioid receptor density found in binge-eating non-obese rats (Heal et al., 2017) and a more widespread increase of μ opioid receptor density in rats trained to intermittently drink sucrose (Colantuoni et al., 2001). However, despite the wealth of pre-clinical evidence and imaging studies in binge-eating subjects (Cambridge et al., 2013), placebo-controlled clinical studies in binge-eating disorder with opioid receptor antagonists have been disappointing.

Orexin 1 receptor antagonists

Orexin is a neuropeptide transmitter and exists as two separate peptides orexin A and orexin B formed from a common precursor prepro-orexin. Selective OX1 receptor antagonists (SB-334867 and GSK1059865) preferentially reduced palatable versus normal food intake in two different rat compulsive binge-eating models (food restriction and stress-induced consumption of highly palatable food, and the use of limited, irregular access to highly palatable food but without food restriction or stress) (Vickers et al., 2015).

Preclinical studies provide evidence in a variety of animal models of compulsive eating that suggest selective OX1 receptor antagonists may have a novel therapeutic role in compulsive BED. The data showing that OX1 receptor antagonism may also reduce impulsivity are also intriguing given the importance of impulsive responding in binge-eating. However, to date there are no documented clinical studies of selective OX1 receptor antagonists in BED.

Cannabinoid receptor antagonists

The endocannabinoid system is comprised of two cannabinoid receptor subtypes, CB1 and CB2, the lipid-based ligands anandamide and 2-arachidonoylglycero. The localization of CB1 receptors within the basal ganglia and corticolimbic system are consistent with a proposed role for these receptors in the regulation of motivated behavior and synaptic plasticity.l (2-AG) and enzymes required for their synthesis and degradation. CB1 receptors contribute to the regulation of both homeostatic eating and compulsive eating behavior. CB1 receptor antagonists (SR141716A, AM 251 and rimonabant

(SR147778)) significantly decreased normal food intake and body weight when administered chronically to either normal or obese rodents (Buckley, & Boomhower, 2012) and decreased consumption of both palatable food and normal chow in nonhuman primates (Foltin & Haney, 2007). body weight compared with the placebo group and showed a greater reduction on the binge-eating scale total score. However, there were no measures of impulsivity or compulsivity.

Consistent with many of the preclinical studies, these clinical findings suggest that CB1 antagonism may not be selective for binge-eating versus normal food intake. Unfortunately, rimonabant was the only CB1 receptor antagonist to be approved for use in humans, but was removed from the market due to severe psychiatric side effects in obese subjects (Scheen et al., 2006). Consequently, the therapeutic utility of selective CB1 receptor antagonists for the treatment of BED would seem doubtful.

Glutamate N-methyl-D-aspartate (NMDA) receptor antagonists

Glutamate is the primary excitatory neurotransmitter in the CNS, and its effects are mediated by both ionotropic and metabotropic receptor families (for review see Kew & Kemp, 2005). A substantial body of anatomical, behavioral and pharmacological evidence suggests that NMDA receptors modulate mesocorticolimbic and nigrostriatal dopamine pathways that may influence aspects of motivation, impulsivity and compulsivity relating to eating behaviors. Memantine was shown to be effective in different animal models of binge-eating including a non-human primate model and a rodent model that determined the effects on compulsive eating under aversive conditions (Bisaga, Danysz, Richard, & Foltin, 2008; Smith et al., 2015). Memantine also improved the frequency of binge days and binge episodes in a small open-label study of subjects with BED, although measures of compulsiveness were not assessed (Brennan et al., 2008). Collectively, these findings indicate that antagonism of the NMDA receptor via drugs such as memantine could be a novel approach to the treatment of BED.

However, extending this to other antagonists of the NMDA receptor complex (e.g., ketamine) is not straightforward due to mechanism based tolerability and safety concerns.

1.3.3 NEUROIMAGING DATA IN BINGE EATING DISORDERS: IMPLICATION FOR TREATMENTS

Concerning more classical EDs, such as Anorexia Nervosa, the evidence presented suggests that divergent responses in bottom-up regions such as the striatum during food reward processing mediated by increased activation in top-down information processing regions may contribute to the formation of restrictive eating habits.

Despite the number of studies are much more limited concerning BED and BN, abnormalities in top-down control regions have also been identified with different results regarding hypo- or hyper-activation in comparison to controls during cognitive tasks (Donnelly et al.,2018).

Several neuroimaging studies now link reward processing with treatment outcome in BED. These studies are particularly important for understanding recovery processes. One study scanned treatment seeking BED individuals prior to treatment and at follow up condition (Balodis et al., 2014). Findings showed diminished anticipatory processing in IFG and striatal regions predicted persistent binge-eating at the end of treatment. Notably, individuals with persistent binge-eating at the end of treatment did not differ in BMI at treatment onset, thereby highlighting striatal alterations as a potential therapeutic target (Hutson et al. 2018). Indeed, a blunted striatal response to food cues is linked with weight-gain (Pelchat et al., 2004), and reduced IFG responding during food cue exposure is associated with a diminished outcomes related to maintenance of weight loss (McCaffery et al., 2009). During the outcome reward phase, reduced mPFC/ACC activity also differentiated groups with and without persistent binge-eating at the end of treatment. Reduces fronto-striatal responses to nonfood reward appear to play a role in treatment response and provide some indication of pathophysiology of this disorder.

Considering experimental therapeutic protocol, the first proof of concept study examining Transcranial Direct Current Stimulation (tDCS) has been recently published in BED (Burgess et al., 2016). Thirty adults with full- or sub-threshold BED were administered tDCS to dorsolateral PFC (dlPFC) areas. Participants then completed a food-photo craving test and eating test as well as a binge

eating survey at home for the subsequent 5 days. Relative to a sham condition, one 20-minute session of 2 mA tDCS on the dlPFC reduced in-lab food craving and consumption, but also diminished at-home eating desire. The functional mechanism of tDCS on the dlPFC is currently unclear: stimulation may disrupt reward neurocircuitry from signaling; alternatively, it may accelerate satiety signaling, thereby decreasing food consumption. This first tDCS study in BED provides some evidence about the role of neuromodulation technique as a noninvasive, safe and effective adjunct tool to other therapies.

Clinical imaging and cognitive studies highlight important differences in neural function and behavior that may underpin this disorder. Moreover, these clinical observations have led to the development of improved animal models of binge-eating which display clinically relevant behavioral intermediate phenotypes or endophenotypes relating to reward processing, impulsivity and compulsivity. These processes may be maladaptive in the current food environment for individuals who may be genetically at increased risk for developing BED. While the neurochemistry of BED is relatively unexplored in patients, animal studies are beginning to reveal the involvement of different neurotransmitter pathways in these behavioral intermediate phenotypes or endophenotypes which may ultimately lead to the identification of novel therapeutics. Clearly, further studies in these and other aspects of BED are required to gain an improved understanding of this disorder.

Nevertheless, clinical and basic research in BED is in an exciting phase with changes to the DSM 5 recognizing BED as a psychiatric disorder,. Interestingly, the majority of pharmacological targets that may be of therapeutic value in BED appear to either directly or indirectly modulate forebrain dopamine which is perhaps not surprising given the role of these pathways in regulating many of the behavioral functions associated with binge-eating. It seems likely therefore that it will emerge additional novel and well tolerated and effective treatments to improve the clinical options that are available for individuals who experience the negative impacts of BED.

PART II

PERSONAL CONTRIBUTION AND CLINICAL IMPLICATIONS FOR TREATMENTS.

2.1 INTRODUCTION

With the new version of the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 2013), Binge Eating Disorder (BED) assumed its psychopathological identity, becoming one of the three major Eating Disorders (EDs) classified in the scientific community (Vo et al., 2017). Recently psychopathological aspects of BED have been investigated from the theoretical assumption that one of the main differences and specificities of this pathology with respect to a simple obesity was represented by an impairment of the system of impulsiveness and reward / gratification mechanisms (Amianto et al., 2016; Leombruni et al., 2014).

BED has been often associated with obesity but differs from this condition in many domains: comparative studies between obese subjects with BED and those without BED show extremely different personality, behavioral and psychopathological profiles (Amianto et al., 2011). Group differences have been also extended to non-food stimuli: BED is associated with psychiatric comorbidity (Yanovski et al., 1993) and the phenomenon of binge eating explains many differences observed in the psychological and psychiatric domains.

However, the relationship between neurobiological aspects, clinical features and the onset of BED is still largely unclear. From a clinical point of view, this complexity is reflected by a difficulty in the therapeutic approach to the BED disorder: despite the existence of multidisciplinary interventions of different orientations, one of the major problems in the treatment of BED today remains the strong resistance to treatments and the high percentage of drop- out, also typical of other EDs (Abbate Daga et al., 2013; Fassino & Abbate Daga, 2013; Fassino et al ; 2009).

In this context, Neuroimaging currently plays the role of being a validated tool in the study of neuronal patterns potentially involved in treatment resistance (Lavagnino et al., 2014). Areas such as the ventral striatum and the prefrontal cortex have shown different functional activation in subjects with BED compared to healthy controls in response to dietary stimulation (Balodis et al., 2013). Numerous evidences also support the importance of resting state activity functional studies on BED giving important considerations about self-awareness and enteroceptive sphere (Buckner et al., 2008).

However, for BED, these techniques are still limited. Recently nucleus accumbens, ventral striatum and orbitofrontal cortex have been hypothesized as possible circuits involved in the pathogenesis of BED. Data are still limited.

The aim of this research is to explore through fMRI the neurofunctional circuits of patients affected by BED with particular attention to the areas involved in impulsivity and cognitive control, focusing on possible gender related difference highlighting on one hand any differences from healthy subjects and on the other hand possible similarities to classical EDs, such as Anorexia and Bulimia Nervosa in order to help clinicians to identify more specific short or long term therapeutic protocols.

2.2 MATERIAL AND METHODS

2.2.1 EXPERIMENTAL DESIGN

The study is an exploratory case-control protocol. The study includes a sample of female subjects affected by Binge Eating Disorder (BED) afferent to the Regional Expert Center for Eating Disorders (CER), active in the Department of Neuroscience of the AOU City of Health and Science of Turin. This study includes also a sample of healthy female and male subjects recruited by local advertising. The study was conducted on data collected between October 2016 and May 2019 and all the procedures were conducted according to the 1995 Declaration of Helsinki as revised in Edinburgh in 2000. Study was approved by the Ethics Committee of AOU City of Science and Health, Turin (protocol number: 0089968).

2.2.2 PARTICIPANTS

The sample consists of 65 subjects, 15 patients and 50 control subjects (respectively 28 female and 22 male subjects). All patients received a diagnosis of Binge Eating Disorder (BED) by a psychiatrist according to the criteria of the DSM 5 (American Psychiatric Association, 2013).

Inclusion criteria for patients were:

- Female sex
- Age between 18 and 45 years
- BMI> 25
- No cognitive impairment
- No substance abuse
- No other major psychiatric disorders according to the DSM 5
- No internistic or endocrinological diseases
- No left-handedness

The group of healthy controls for the study consists of 50 volunteers. Inclusion criteria for these subjects were:

- No diagnosis of BED or obesity or of other Eating Disorders
- Age between 18 and 45 years
- BMI <25
- No cognitive impairment
- No substance abuse
- No other major psychiatric conditions according to the DSM 5
- No internistic or endocrinological diseases
- No left-handedness

2.2.3 MEASURES

Toronto Alexithymia Scale (TAS--20) (Bagby et al., 1996): 20-item questionnaire used to assess the level of alexithymia. This scale had a strong support for its reliability and factorial validity.

Beck Depression Inventory (BDI-II) (Beck et al., 1991): this test is composed of two different scores, respectively related to the "Somatic--Affective" and to the "Cognitive" area of depressed mood. It shows a high internal consistency and content validity.

Temperament and Character Inventory (TCI): this questionnaire provides an estimate of the personality structure of the subject, according to the neurobiological model proposed by Cloninger (1994). Its psychometric properties support its clinical usefulness in the assessing of personality psychopathology.

Eating Disorder Inventory 2 (EDI-2): is a questionnaire that evaluates the salient psychopathological characteristics in eating disorders (Garner et al., 1982). This test was originally created by Garner in 1982, has since been revised several times. The second version of the EDI consists of 91 items divided

into eleven subscales: Impulse to thinness (IM), Bulimia (BU), Body dissatisfaction (IC), Inadequacy (IN), Perfectionism (PER), Interpersonal distrust (SI), Interoceptive awareness (CE), Fear of maturity (PM), Ascetism (AS), Impulsiveness (II) and Social insecurity (IS).

Binge Eating Scale (BES): is a self-assessment tool that measures the behavioral and emotional symptoms associated with binge eating disorder (Gormally et al., 1982). It consists of 16 multiple-choice items with four options, which reflect the severity of each of the measured features. The total score ranges from 0 to 32, higher scores indicate more severe binge eating symptoms.

Parental Bonding Instrument (PBI):) is a questionnaire composed of 50 statements describing a series of behaviors of parental figures (Parker, Tupling, & Brown, 1979. Each item is repeated twice, first with reference to the mother and then to the father. The subject must indicate the degree of identification with each statement on a 4-step lickert scale. Scoring is carried out with reference to two dimensions: parental care (maternal and paternal care) and hyperprotection (maternal and pateranl overprotection).

2.3 PROCEDURE

During the two first psychiatric consultations medical history was collected by a specialist in psychiatry and a diagnosis of BED was done. During the first visit, patients were given a battery of self-administered tests according to the reference model of the Center (Amianto et al., 2017; Fassino et al., 2002). This battery includes the measures described before. On the second visit the results of the psychometric tests were explained to the patients and the research protocol was proposed.

According to the protocol, patients then underwent fMRI single section at the Unit of Neuroradiology of AOU City of Health and Science of Turin. The fMRI was performed on a 3T tomograph. The exam had a total duration of approximately 25 minutes.

2.3.1 FMRI DATA ACQUISITION

The images were acquired on a 3 Tesla Philips Ingenia MRI, equipped with a dedicated 32-channel head coil. The resting state series were acquired using a gradient echo planar sequence (EPI) with the following parameters: TE 30 ms, TR 2500 ms, 80 x 80 in-plane matrix, 46 slices, 3 mm isotropic voxel, posterior to anterior phase encode direction. For anatomical reference a 3D T1-weighted MPRAGE image was acquired with the following parameter: 180 slices, TE 2.9 ms, 1 mm isotropic voxel. Subjects were scanned with their eyes open fixing a cross fixed point to reduce motion and not to fall asleep.

2.3.2 DATA PROCESSING

First of all, data were converted from dicom to nifty format using the dc2nii software. To identify specific RSN (resting State networks) all data sets (preprocessed and de-noised) were concatenated in temporal order to create a single data set. This concatenated data set was then decomposed into 20 spatially independent components using group ICA with MELODIC. To carry out group-wise ICA,

a single 4D data set was created by temporally concatenating preprocessed functional data, containing 80 time points for each subject. Finally, 20 components were used as explained data variance was sufficient to obtain good estimates of the signals and well known RSNs were identified. RSNs of interest covered the entire brain and were selected by visual inspection against sets of previously defined maps (Smith et al., 2009). The set of spatial maps from the group-average analysis was used to generate subject-specific versions of the spatial maps, and associated time series using dual regression technique. These 20 components will be used as template maps for dual regression.

First, for each subject, the group-average set of spatial maps is regressed (as spatial regressors in a multiple regression) into the subject's 4D space-time dataset. This results in a set of subject-specific time series, one per group-level spatial map. Next, those time series are regressed (as temporal regressors, again in a multiple regression) into the same 4D dataset, resulting in a set of subject-specific spatial maps, one per group-level spatial map, which are then tested at cluster level for statistically significant differences between the groups using FSL's *randomise* (CIT) permutation-testing tool (10,000 permutations).

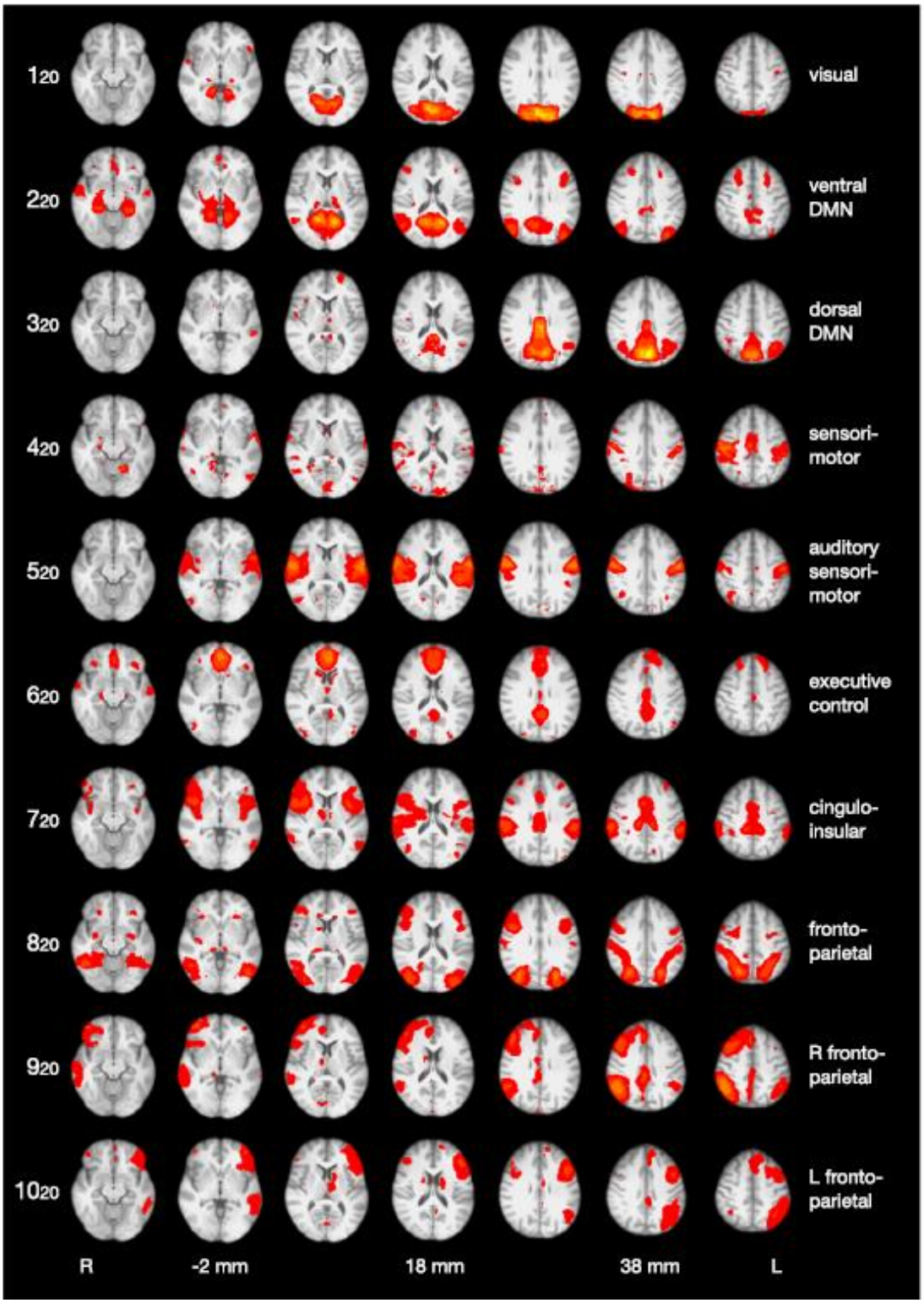

Fig. 1. ICN (Intrinsic Connectivity Network) or RSN (Resting State Network).

2.4 STATISTICAL ANALYSIS

Comparisons of clinical and socio-demographic indices were performed between the patient group and the control group with t-test analysis and ANOVA analysis. A comparison was also made between the personality and psychopathological indices between the two groups, using t-test and ANOVA analyses.

To identify differences between BED patients and healthy controls within the 20 networks, a voxel-wise two-sample unpaired t-test was performed on the participant-specific spatial maps for each network using a general linear model (GLM). The t-contrasts were 8 in total (female healthy controls > male healthy controls; male healthy controls > female healthy controls; patients < male healthy controls; patients < male healthy controls; patients > female healthy controls; patients < male healthy controls; patients > male+female healthy controls; patients < male+female healthy controls).

Anatomical localization of significant clusters was established according to the Harvard-Oxford Cortical Structural Atlas included in the FSL (http://www.fmrib.ox.ac.uk/fsl/data/atlas descriptions.html).

The relationship between RSFC regional (cluster maximal z-score) and global (FC maps) differences and clinical variables (drive for thinness, body dissatisfaction, interoceptive awareness, bulimia, harm avoidance, and BMI) were tested by non parametric Spearman's correlation analyses at the significant level of $p < 0.01$ and using GLM analysis in FSL at significant level of $p < 0.05$ corrected, respectively.

All statistical analyses were performed using SPSS (Statistical Package for Social Science) software. Neurofunctional data were analyzed with FSL (FMRIB Software Library) (Jenkinson, 2008). Level of significance was set to $p<.05$.

2.5 RESULTS

2.5.1 DEMOGRAPHIC AND CLINIC CHARACTERISTICS OF THE SAMPLE

	BED (14)	HS (46)	t	p
Age	36.67 ± 6.05	31.92 ± 5.85	-1.694	.101
BMI	32.73 ± 4.51	22.70 ± 3.08	2.682	.087
Education	15.93 ± 2.46	13.71 ± 2.37	-6.014	.000
BES	31.68 ± 4.64	4.91 ± 3.17	-20.38	.000

Tab 1. BED= Binge Eating Disorder; HS= Healthy subjects; BMI= Body Mass Index; BES= Binge Eating Scale

We observed significant differences between BED patients and healthy subjects in BES scale (t=-20.38; df=2; p<.000). Age, BMI and educational level did not differ between BED patients and healthy subjects.

	BED (15)	mHS (26)	fHS (22)	F	p	Post hoc
Age	36.67 ± 6.05	34.38 ±7.17	30.83± 5.07	2.41	.108	ns
BMI	32.73 ± 4.51	23.00 ± 2.52	22.65±3.36	17.15	.000	a>b,c
Education	15.93 ± 2.46	16.28 ± 2.71	17.41 ± 1.15	2.66	.085	ns
BES	31.68 ± 4.64	4.07 ± 1.27	5.50 ± 3.92	21.35	.000	a>b,c

Tab 2. BED= Binge Eating Disorder; mHS=male Healthy subjects; fHS=female Healthy subjects BMI= Body Mass Index; BES= Binge Eating Scale

We observed significant differences between BED patients, male healthy subjects and female healthy subjects in BES scale (F=-21.38; p<.000) and BMI (F=17.15; p<.000). No differences were found concerning age and educational level within three different groups.

2.5.2 PERSONALITY AND PSYCHOPATHOLOGICAL CHARACTERISTICS OF THE SAMPLE

	BED (14)	HS (46)	T	P
TCI				
Harm avoidance	24.67 ± 6.27	18.67 ± 6.23	-2.07	0.04
EDI-2				
Drive of thinness	13.44±6.24	3.00 ± 4.24	-5.44	.000
Bulimia	8.44 ± 4.58	1.15 ± 1.41	-8.04	.000
Body dissatisfaction	18.56 ± 7.96	5.91 ± 6.59	-4.88	.000
Ineffectiveness	10.12 ± 5.11	2.76 ± 4.66	-4.10	.000
Interoceptive awareness	9.01 ± 4.60	1.58 ± 2.04	-7.16	.000
Impulsivity	5.22 ± 4.54	1.45 ± 2.50	-3.31	.002
TAS 20				
Difficulty identyfing feelings	23.38 ± 5.12	12.43 ± 5.50	-4.90	.000
Total	58.88 ± 8.44	43.42 9.28	-4.06	.000

PBI				
Maternal care	19.11 ± 8.98	29.45 ± 6.41	3.64	.001
Paternal care	15.56 ± 7.68	25.58 ± 9.10	3.01	.004
Paternal overprotection	16.67 ± 9.22	7.94 ± 6.23	-3.34	.002

Tab 3. *BED= Binge Eating Disorder; HS= Healthy subjects; TCI= Temperament and Character Inventory; EDI-2= Eating Disorder Inventory; TAS-20=Toronto Alexithymia Scale; PBI =Parental Bonding Instrument.*

Concerning personality, BED patients showed higher level of harm avoidance (HA) respect to healthy subjects at TCI (t=-2.07; df=2; p<.04). Concerning eating psychopathology, BED patients showed higher level in different subscales of EDI-2: drive to thinness (-5.44; df=2; p<.000), bulimia (-8.04; df=2; p<.000),), ic (-4.88; df=2; p<.000), ineffectiveness (-4.10; df=2; p<.000),), interoceptive awareness (-7.16; df=2; p<.000) and impulsivity (-3.31; df=2; p<.000). BED patients showed also higher level of alexythimia respect to healthy subjects (t=-4.06; df=2; p<.000). At PBI, BED patients showed lower level of maternal (3.64; df=2; p<.001), and paternal (3.01; df=2; p<.004), care and higher level of paternal overprotection (-3.34; df=2; p<.002), compared to healthy subjects.

	BED (15)	mHS (26)	fHS (22)	F	P	Post hoc
TCI						
Harm Avoidance	24.67 ± 6.27	16.93 ± 6.50	19.95 ± 7.14	3.48	0.05	a>b,c b<c
Cooperativeness	29.78 ± 7.16	28.07 ± 6.70	34.48 ± 4.68	5.22	0.01	b<c
EDI-2						
Drive of thinness	13.44 ± 6.24	1.93 ± 3.85	3.79 ± 5.42	15.36	.000	a>b,c
Bulimia	8.44 ± 4.58	1.14 ± 1.46	1.16 ± 1.42	31.55	.000	a>b,c
Body dissatisfaction	18.56 ± 7.96	4.07 ± 3.85	7.6 ± 7.37	13.02	.000	a>b,c
Ineffectiveness	10.12 ± 5.11	2.76 ± 5.86	2.79 ± 3.72	8.17	.001	a>b,c
Impulsivity	5.22 ± 4.54	1.7 ± 3.36	1.26 ± 1.69	5.46	.008	a> b,c
Interoceptive awareness	9.01 ± 4.60	1.15 ± 1.35	2.01 ± 2.41	26.21	.000	a>b,c
TAS 20						
Difficulty identyfing feelings	23.38 ± 5.12	11.75 ± 7.51	12.59 ± 5.27	11.69	.000	a>b,c
Total	58.88 ± 8.44	43.64 ± 9.39	43.26 ± 9.49	8.05	.001	a>b,c
PBI						
Maternal care	19.11 ± 8.98	28.01 ± 7.35	30.53 ± 5.67	7.06	.002	a>b,c
Paternal overprotection	16.67 ± 9.22	7.64 ± 6.16	8.16 ± 6.44	5.48	.008	a>b,c

Tab 4. *BED= Binge Eating Disorder;mHS= male healthy subjects; fHS=female healthy subjectsTCI= Temperament and Character Inventory; EDI-2= Eating Disorder Inventory; TAS-20=Toronto Alexithymia Scale; PBI =Parental Bonding Instrument.*

Considering separately three different subgroups, Harm Avoidance (HA) and Cooperativeness (C)shows a significant difference between patients and healthy subjects differently from previous

analysis on two groups. Specifically HA show higher level in patients respect to healthy subjects ($F=3.48$; $p<0.05$) and C show lower level in patients respect to control ($F=5.22$; $p<0.01$). Post hoc analysis reveals a significant difference between male and female healthy subjects with significant lower level of HA and C in male compared to female healthy subjects. No differences in significant differences indices were found in other variables respect to t-test analysis on two groups (tab 1).

2.5.3 DIFFERENCES OF RESTING STATE FUNCTIONAL ACTIVITY BETWEEN PATIENTS AND FEMALE HEALTHY SUBJECTS

RSN	x y z [mm]	L/R	Region	Contrast
Visual	-16 62 46	R	Post central gyrus	BED>fHS
Right frontoparietal executive	16 14 -8	R	Caudate	fHS> BED
Auditory Sensori-motor	-62 -34 -6	L	Fusiform gyrus	fHS> BED

Tab 5. *RSN=Resting State Network; X Y Z = MNI coordinates; L/R= right/left; BED= Binge Eating Disorder; fHS= female healthy subjects*

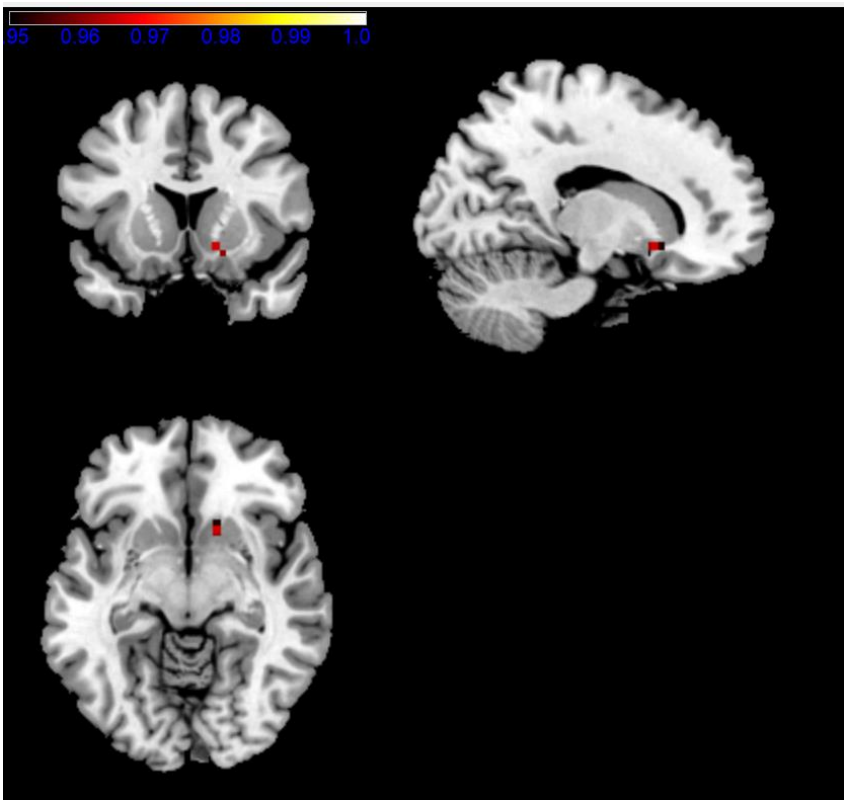

Fig 2. Significant lower activity in Caudate in BED compared to healthy subjects.

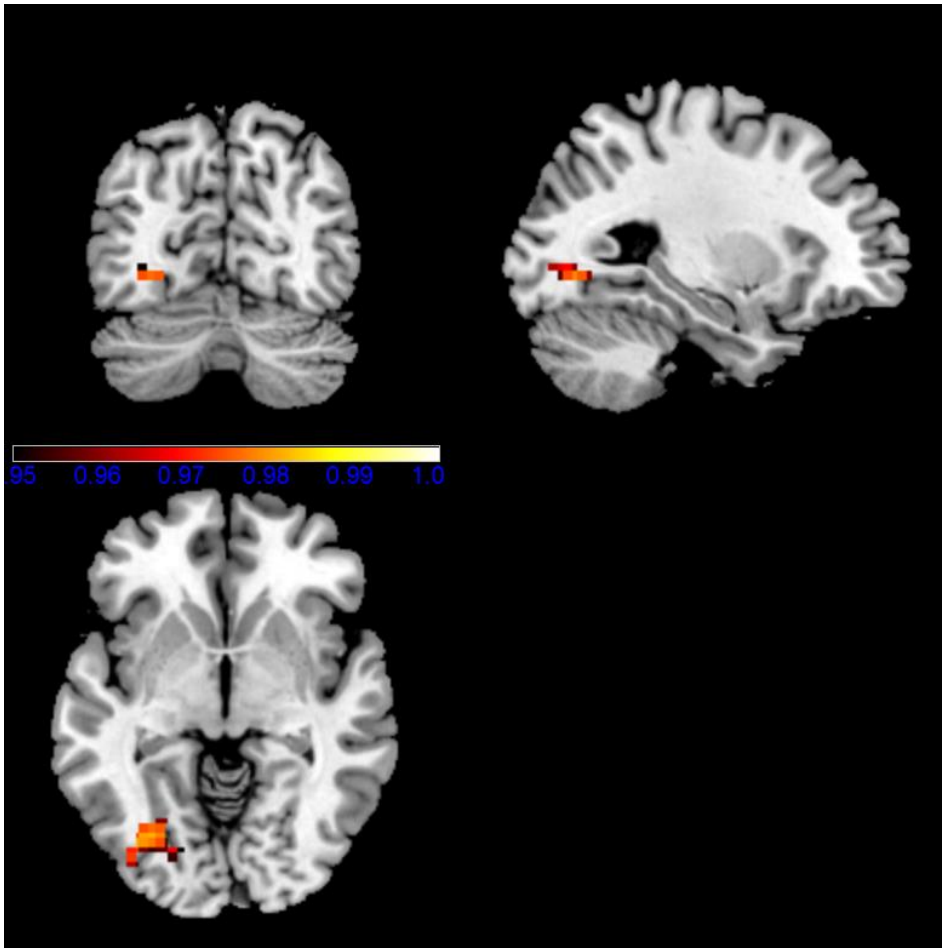

Fig 2. Significant lower activity in fusiform gyrus in BED compared to healthy subjects.

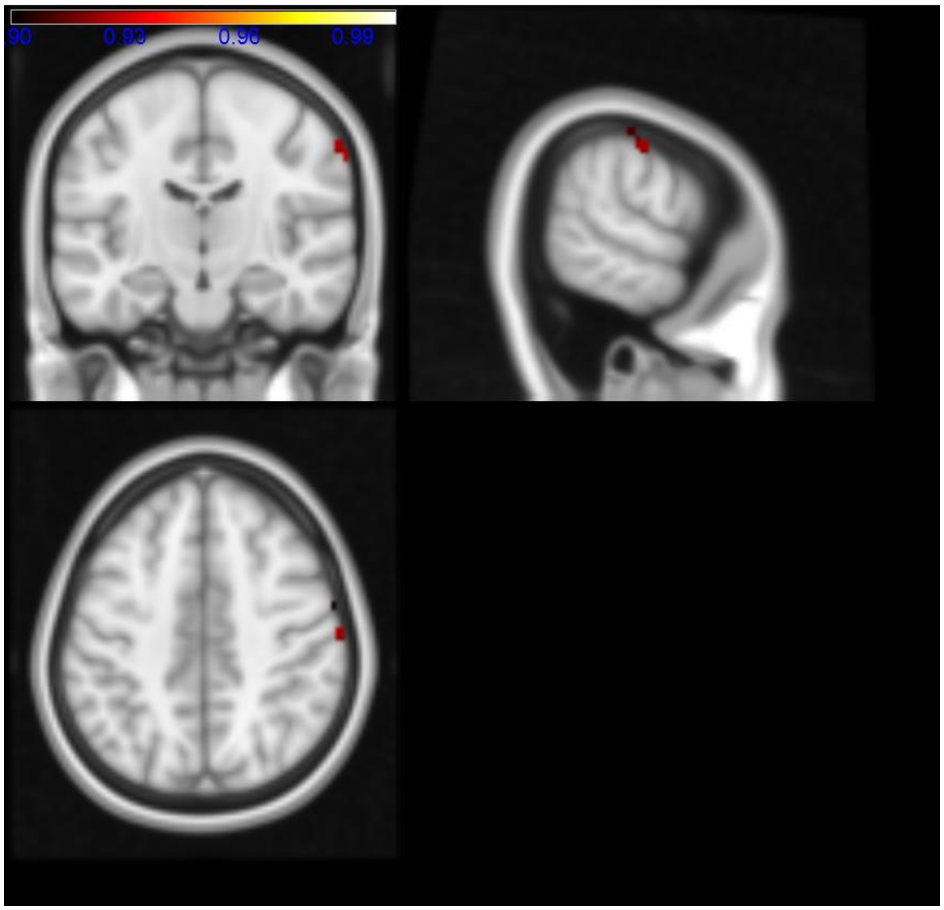

Fig 3. Significant greater activity in post central gyrus in BED compared to healthy subjects.

BED patients showed a greater activity in visual network in right post central gyrus ($p<0.05$) compared to healthy subjects. BED patients showed a lower activity in right frontoparietal executive network and in auditory sensori-motor network in right caudate ($p<0.05$) and left fusiform gyrus ($p<0.05$) when compared to healthy subjects.

2.5.4 DIFFERENCES OF RESTING STATE FUNCTIONAL ACTIVITY BETWEEN PATIENTS AND HEALTHY SUBJECTS

RSN	x y z [mm]	L/R	Region	Contrast
Auditory Sensori-motor	-62 -34 -6	L	Fusiform gyrus	BED < HS
Visual	-16 62 46	R	Post central gyrus	BED > HS

Tab 6. *RSN=Resting State Network; X Y Z = MNI coordinates; L/R= right/left; BED= Binge Eating Disorder; HS= healthy subjects;*

BED patients showed a greater activity in visul network in right post central gyrus ($p<0.05$) compared to female healthy subjects. BED patients showed a lower activity in auditory sensori-motor network in left fusiform gyrus ($p<0.05$) when compared to female healthy subjects.

2.5.5 DIFFERENCE BETWEEN BED PATIENTS AND MALE HEALTHY SUBJECTS

RSN	x y z [mm]	L/R	Region	Contrast
Visual	-16 62 46	R	Post central gyrus	BED > mHS
Visual	-102 18 -4	R	Calcarine	mHS > BED
Precuneus (Default Mode)	-60 -6 24	L	Precuneo	mHS > BED

Tab 7. *RSN=Resting State Network; X Y Z =MNI coordinates; L/R= right/left; BED= Binge Eating Disorder; mHS= male healthy subjects*

BED patients showed a greater activity in visual network in right post central gyrus ($p<0.05$) compared to male healthy subjects. BED patients showed a lower activity in visual network in calcarine ($p<0.05$) and in precuneus network (Defult mode) in precuneus ($p<0.05$) when compared to male healthy subjects.

2.5.6 DIFFERENCES BETWEEN FEMALE AND MALE HEALTHY SUBJECTS

RSN	X Y Z [mm]	L/R	Region	Contrast
Visual	-50 14 18	R	Precuneus	fHS > mHS
Right frontoparietal	30 32 24	R	G frontal middle	fHS > mHS
Visual	-76 4 10	L	Calcarine	mHS > fHS
Cerebellar	-38 -20 -24	L/R	Cerebellum	mHS > fHS
Visual		L/R	Occipital pole	mHS > fHS
Cingulo-insular	-8 36 -24	L	Hippocampus	mHS > fHS
	-6 -14 44	L	Cingulum	mHS > fHS
	-14 -18 10	L	Thalamus	mHS > fHS
Dorsal default mode	-70 14 34	L	Cuneus	mHS > fHS

Tab 8. *RSN=Resting State Network; X Y Z =MNI coordinates; L/R= right/left; fHS=female healthy subjects; mHS= male healthy subjects*

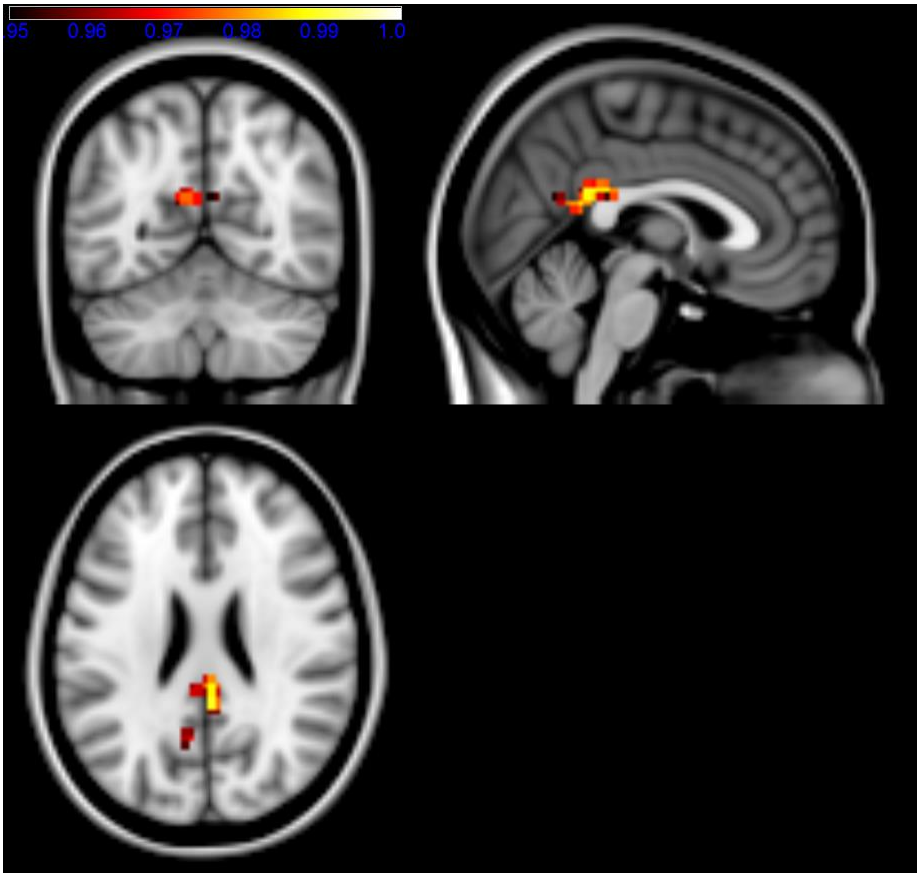

Fig 4. Significant greater activity in precuneus in female healthy subjects compred to male healthy subjects. .

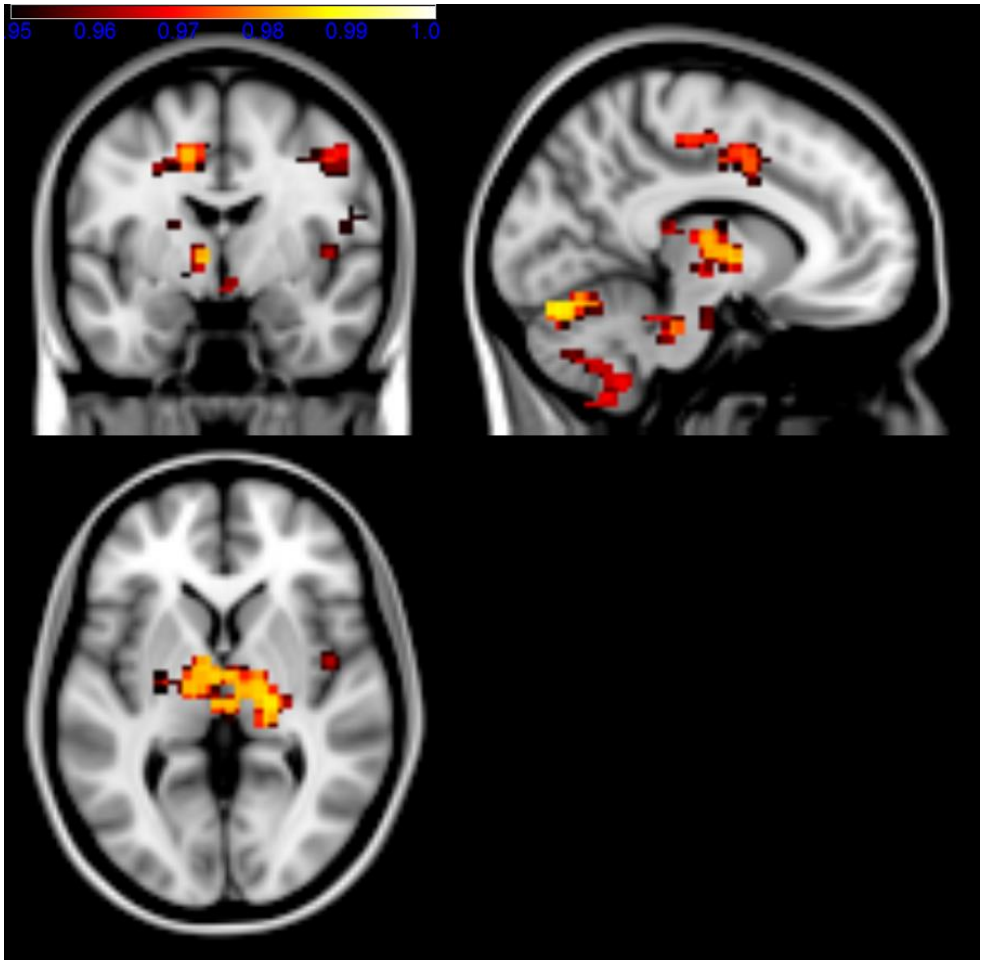

Fig 7. Significant greater activity in cingulo insular network in male healthy subjects respect to female healthy subjects.

Female healthy subjects (fHS) showed a greater activity in visual network in right precuneus ($p<0.05$) and in right frontoparietal network in right frontal middle ($p<0.05$) compared to male healthy subjects (mHS). fHS showed a lower activity in visual network in calcarine ($p<0.05$), in cerebellar network in cerebellum ($p<0.05$), in visual network at the occipital lobe ($p<0.05$), in cingulo insula network in hippocampus, cingulum and thalamus ($p<0.05$) and in dorsal default mode network in the cuneus ($p<0.05$) when compared to mHS.

2.6 DISCUSSION

2.6.1 CONSIDERATIONS ABOUT PERSONALITY AND PSYCHOPATHOLOGICAL CHARACTERISTICS OF THE SAMPLE

In our sample, BED patients are characterized by higher harm avoidance (HA) compared to healthy controls. According to Cloninger model, HA is temperamental trait characterized by insecurity, nervousness and passivity (Fassino et al., 2002; Grucza et al., 2007; Sancho et al., 2008). High levels of harm avoidance have been correlated with difficulties in controlling diet and food impulsiveness even in populations of bulimics patients with which BED subjects share the phenomenon of binge eating (Bulik et al., 1995). Literature showed that a compromission of this trait is a common pattern within different psychiatric disorder (Fassino et al., 2009).

Nevertheless, on the other hand, patients of our sample are not characterized by significantly lower values of self-directedness (SD) respect to healthy subjects. SD represents a character trait that refers to self-determination and "willpower". It would seems that patients affected by BED are less "immature" and unsure of their own identity unlike the more classical EDs (Fassino et al, 2002). These data contradict our previous studies in which we highlighted that BED patients show lower scores in Self-Directedness (SD) with respect to healthy subjects and obese subjects without BED (Amianto et al., 2015; Amianto et al., 2018). If it is true that on the one hand the combination of high HA and low SD has been associated with many psychiatric pathologies representing a transversal personological pattern (Fassino et al., 2009), this is not replicated in our BED sample. This difference from previous finding could also depend on two specific characteristics of our sample of BED patients: their mean age (36.67 ± 6.05) and the relative new diagnosis of BED condition. From a personality point of view, the impairment of temperamental aspects but not characterial aspects, could corroborate the theory about the biological vulnerability to eating spectrum with differences in the evolution of different symptoms that would therefore be more correlated to the external environment and to the type of character development. This result could suggest that other factors could be considered in the pathogenesis of the disorder. In the past, our working group has shown, for example,

how patients with BED show alterations of other variables such as attachment dynamics and some relational impairments (Amianto et al., 2015).

In line with this interpretation, as concerning parental styles, measured by the Parental Bonding Instrument, BED subjects showed lower score in maternal care (CM) and higher score in paternal hyper protection (OP) respect to healthy subjects. These data are coherent with literature background and specifically reproduce what emerged from a previous research of our work group in which parental relationships also seem to be one of the determining factors in the differentiation between BED and subjects with obesity without BED (Amianto et al., 2015). In this sense, the family environment and the relational dynamics with caregivers could represent important factors in the pathogenesis of BED that act on specific temperamental and personality vulnerability.

With respect to eating indices, the group of BED subjects has significantly higher scores in drive of thinness, bulimia, body dissatisfaction, inefectiveness, interoceptive awareness and impulsivity with respect to the control group. It has been observed that high scores at the subscales drive of thinness, bulimia and interoceptive awareness are indicative of the severity of the eating disorder (Garner et al., 1982). BED patients have a greater tendency to weight control and high expectations on their body (Pratt et al., 2001), accompanied by a poor ability to discriminate the physical sensations of hunger and satiety. Eating impulsiveness, in part, is mediated by alterations in the component of interoceptive awareness, an element already largely related to eating disorders (Fassino et al., 2004). Confusion in emotional states, difficulty in recognizing certain visceral sensations as related to hunger and satiety could lead to eating impulsivity, which is unleashed when the subject has to face negative feelings or whose exact nature he does not perceive. It is interesting to note that eating alterations are intense exactly like those found in anorexia and bulimia nervosa with different clinical manifestations. It has been already demonstrated that participants with BED also show higher bulimia, higher ineffectiveness and higher impulsivity respect to obese subjects without BED confirming previous finding about the existence of a specific “psychopathologic core” of BED

patients (Segura-Garcia et al., 2014). These results, according to recent DSM 5 classification, underline that BED disorder it is a clear and distinct psychiatric condition characterized by dysfunctional eating behavior with different psychopathological features with respect to obesity alone (Amianto et al., 2016).

Another common pattern with more classic EDs is the high levels of alexithymia of BED patients in our study compared to controls. Alexithymia is defined as a difficulty in identifying and recognizing one's emotions (Taylor et al., 1996). Numerous studies have reported high levels of alexithymia in patients with eating disorders (Behar & Arancibia, 2014; Nowakowski et al., 2013). According to some recent studies, there is a strong correlation between alexithymia and negative affective alterations, such as anxiety and depression (Corcos et al., 2000; Marchesi et al., 2000) which are often associated with comorbid EDs.

A recent structural imaging work has correlated structural brain alterations with TAS-20 scores in patients with Anorexia and Bulimia nervosa and in healthy controls finding a significant correlation between TAS-20 and gray matter at the parietal lobe level in patients with Bulimia Nervosa but not in those with Anorexia Nervosa, both recruited at an early stage of disease (D'Agata et al., 2015). This correlation seems to corroborate the hypothesis that this relational function represents a pathogenetic factor linked to the disorder as well as a maintenance factor that contributes to the relational difficulties of these patients and not so much a consequence of the negative affective state of these patients. The data is even more interesting since it clearly distinguishes patients with Anorexia and with Bulimia scientifically confirming that these psychiatric pictures differ in the regulation of relational and emotional dynamics. No data are still known about BED.

Considering separately male and female healthy subjects, no differences were found concerning clinical and demographical data. However, for personality and psychopathology, male and female healthy subjects showed a gender related significant difference in Cooperativeness and Harm Avoidance as concern Personality. This result confirm some evidences about gender personality

related differences in healthy subjects (Huang et al., 2013). No gender related difference have been found in psychopathological and emotional indices confirming the role of personality trait in the constitution of our own identity (Fassino et al., 2002).

2.6.2 CONSIDERATIONS ABOUT DIFFERENCES IN RESTING STATE FUNCTIONAL ACTIVITY BETWEEN PATIENTS AND HEALTHY SUBJECTS

Resting state functional activity could be defined as the activity of the brain at rest measured trought fMRI. In contrast to having subjects perform a particular task, resting-state fMRI studies allow for the examination of temporal correlations between spontaneous fluctuations in blood-oxygen-level dependent (BOLD) activations in distinct brain regions. One commonly utilized network-based approach is independent component analysis, which isolates sets of regions showing the strongest levels of temporal synchronicity (Beckmann et al., 2005). Alterations in functional resting connectivity of different brain networks have been demonstrated in eating disorders (Pietrini et al., 2011; Collantoni et al., 2019; Spalatro et l., 2019). Literature evidences suggest that the executive network (Uher et al., 2004), the DMN (Cowdrey et al., 2014), the salience network (Lee et al., 2014) and the somatosensory one (Favaro et al., 2012) could play a role in the psychopathology of eating disorders. Several neuroimaging studies have also showed altered brain activation in brain regions that contribute to reward and anxiety processing in these subjects (Cowdrey et al., 2011; Frank et al., 2012 ; Holsen et al., 2012; Kaye et al., 2009; Uher et al., 2003; Wagner et al., 2008).

Results of the comparison between patients and control group in our study (considering female and male control subjects together) are coherent with literature evidences highlighting significant differences of the fusiform gyrus and post-central gyrus respectively in auditory sensori-motor network visual network. Specifically, we found a reduced activation of the fusiform gyrus and a greater activation of the post-central gyrus in BED patients with respect to the controls.

The fusiform gyrus is part of the temporal lobe and is typically involved in the executive functions of face recognition and processing of the linked emotional stimuli, while the post-central gyrus, part of

the parietal cortex, appears to be involved in the processing of proprioceptive stimuli (Beckmann et al., 2005).

Specifically, the fusiform gyrus together with the precuneum and the body extrastriatal area is involved in the processing of visual stimuli, in the process of shifting and in the perception of objects as well as body image processing (Gaudio et al ., 2012). The post-central gyrus is a region functionally connected to the insula in the functions of somatosensory and motor responses and in the emotionally and motor reaction to interoceptive stimuli.

Concerning more classical Eds differences from healthy subjects have been demonstrated in response to images of body shape (Gaudio et al., 2012). Moreover, Suda and collegues found that patients with AN had lower activation in the right fusiform gyrus suggesting a possible lateralization of some functions for this psychiatric condition. Another exploratory study highlighted lower activity of fusiform gyrus at rest in patients with BN respect to control subjects (Marsh et al., 2015) confirming that this area could be a transdiagnostic neurofunctional pattern within different EDs. No data are still available on BED even if some research suggest some similarity between BN and BED patients (Donnelly et al., 2018).

The fusiform gyrus, as mentioned above represents a fundamental site within self-monitoring networks (Steward et al., 2018). Nico and collegues (2010) demonstrated that stroke patients with focal left fusiform gyrus damage estimated body boundaries very accurately while patients with stroke of the right fusiform gyrus underneath their bodies, supporting this region is implicated in the impairment of body schema found in AN. Body size processing biases have been found to be present in BN but in this case no different lateralization has been shown (Mohr et al., 2011). Looking for some possible explanation about different results, it seems therefore that it could exist two differents interpretation about the role of fusiform gyrus in the context of EDs.

Using body image-specific stimuli across AN, BN and HCs, the fusiform gyrus, has shown more activation in response to body shapes when compared to control condition (Uher et al., 2005) but it

seems to be less active at rest in EDs respect to healthy subjects. A recent neuroimaging review on EDs suggests a possible model of body image distortion considering three neurobiologically based components (Steward et al., 2018):

1) a perceptive component mainly related to alterations of the precuneus, inferior parietal lobe and fusiform gyrus;
2) an affective component mainly related to alterations of the PFC, the insula and the amygdala;
3) a yet to be fully defined cognitive component focusing on beliefs concerning body shape and appearance.

Our evidence about fusiform gyrus emphasizes that even in BEDs there is a specific impairment in the areas responsible of the perception of the body image with neurobiological correlates common to anorexia and bulimia nervosa. It remains unclear how similar neurofunctional patterns are then expressed with very heterogeneous clinical manifestations.

Another significant difference in our sample concerns a greater activation of the post-central gyrus in patients with BED compared to control subjects. Many studies have shown an impairment of this region in the context of more classical EDs (Steward et al., 2018). McFadden and colleagues found reduced activity in the supplementary motor area and post-central gyrus in patients affected by Anorexia Nervosa respect to healthy subjects. This area has been identified as functionally involved in response to stimuli concerning the body of other subjects and processing of body stimuli related to self image (Vocks et al., 2010; McFdden et al., 2014). In this sense tasks involving visualization of images concerning body shapes showed a greater activation in patients affected by AN respect to healthy subjects. Conversely, resting state functional studies showed lower activity in patients with anorexia and grater activity in subjects with Bulimia Nervosa respect to healthy subjects.

Specifically, in bulimia nervosa, some research hightlighted a greater activation in areas associated with somatosensory and motor responses in the right insula cortex and post-central gyrus when asked

about food images (Brooks et al., 2011). The impairment of the sensory-motor network in the EDs has been discussed in literature with different hypotheses. An impairment of this area is hypothesized as an impairment both of the systems of interpretation of the interoceptive states and of their regulation in relation to their own behaviors. In our sample this area represents the most significant one in the comparison between patients and control subjects, both male and female, suggesting its independent importance in the context of BED. It therefore appears that this data is a reproducible, pathological-specific and reliable result.

2.6.3 CONSIDERATIONS ABOUT DIFFERENCES BETWEEN PATIENTS AND FEMALE HEALTHY SUBJECTS

The comparison between patients and female highlighted also a different activity within right fronto parietal executive network in the right caudate nucleus with a more activation in healthy subjects respect to BED patients. This difference regards specifically the right caudate.

The caudate nucleus is part of the dorsal striatum and has been implicated in the pathophysiology of many brain functions. Along with prefrontal and motor cortex, basal ganglia circuits, including the globus pallidus and striatal regions, facilitated and supports reward-motivated learning and habitual responding (Ashby,Turner, & Horvitz, 2010). Moreover, the caudate nucleus has been implicated in the fronto-striatal circuits involved in the inhibitory control processes.

The caudate nucleus, together with ventral striatum, represents also the region involved in reward process and in habit formation in the context of reward systems .Preclinical studies have reported that reward-motivated decision making and acquisition of new learned behaviours depend on striatal regions, such as the caudate, anterior putamen, and nucleus accumbens (Gruber, Hussain, & O'Donnell, 2009). Temporary deactivation or permanent destruction of these regions impedes the acquisition of new rewarded actions, but does not negatively impact execution of previously learned habitual behaviours (Schultz, 2016).

The caudate, anterior putamen, and accumbens are also sensitive to devaluation treatments, such as reduction in the expected value of outcome, and support extinction of non-rewarded actions (Trifilieff et al., 2013). The posterior putamen and globus pallidus, on the other hand, have been proposed to facilitate formation of rigid habits and automatic responses, which are resistant to devaluation treatments and persist irrespective of consequences (Sommer, Costa, & Hansson, 2014). These preclinical findings are in line with results from human studies (Boisgontier et al., 2016), which have activated a great deal of interest in exploration of these regions in compulsivity disorders.

Within psychiatric field, caudate structural and functional alterations have been highlighted in many conditions: from a structural point of view a decrease in the volume of this nucleus has been associated with schizophrenia (Ly et al., 2018). Follow-up studies on schizophrenic showed a reduction in atrophy of the caudate proportional to the outcome rates (Beckmann & Lauer, 1997; Jernigan et al., 1991). Structural alterations of the caudate have also been shown in obsessive compulsive disorders, attention deficit hyperactivity disorder (Canavero & Fontanella, 1998; Castellanos et al., 1994), autism (Haznedar et al., 2006) and substance abuse (Hanlon et al., 2015).

The involvement of the striatum in the pathophysiology of ADHD seems to be correlated with the pathogenesis of hyperactivity (Soros et al., 2019). Concerning ADHD, a recent review suggest that obesity and BED share with ADHD a common neural pattern involved in reward aspects, cognitive inhibition and emotional regulation and striatum represents one of major pattern of these functions (Seymour et al., 2015).

In the context of EDs, the neurofunctional approach has shown many evidences about the role of the caudate in the neurobiology of these disorders. Neverthless, results are still debated: if on one hand the impairment of the caudate has been reported in numerous studies, the direction of this alteration is still unclear. Concerning Anorexia Nervosa, some studies shown an atrophy of the caudate in patients with EDs when compared to control subjects, other studies show a greater volume of this nucleus (specifically the left one), suggesting a a possible hemispheric lateralization of different functions (Boghi et al., 2011; Leppanen et al., 2020). However, concerning Bulimia Nervosa,

literature appears more coherent in the sense of a general and more clear atrophy of the caudate compared to the control subjects. One of our previous studies, showed that the right caudate represents an important region in the neurobiological differentiations between AN and BN (Amianto et al., 2013). From a functional point of view, the literature highlights a common impairment of the striatum and of the regions involved in the executive control in subjects affected by AN and BN compared to healthy controls (Berner & Marsh, 2014; Steward et al., 2018) although the two pathologies are characterized by different functional alterations between them. Caudate impairment therefore could represent a common neurobiological marker in EDs.

Concerning BED patients, evidences are still limited. However, it has been shown that also in BED there is both a morphological and functional impairment of the caudate nucleus, specifically to the reward and inhibitory control circuits common to Bulimia (Donnelly et al., 2018). Some evidence shows a lower activation of the right caudate in BED patients compared to obese subjects without BED and compared to healthy subjects (Voon et al., 2015;) showing an intermediate profile between healthy subjects and subjects with Bulimia Nervosa (Seitz et al., 2016).

Our result is therefore consistent with preliminary data reported in the literature about the impairment of the caudate as a "common trait" in the neurobiology of EDs. The data is even more interesting if we observe the analogy of common lateralization to Bulimia Nervosa and opposite to Anorexia Nervosa in subjects with BED. In the literature, in fact, some theories proposed a different role of different hemispheres in emotional regulation within different EDs (Shobe, 2014).

It has been observed that a functional fragility of the right hemisphere can lead to different levels of disease severity with different compensatory strategies (Uher & Treasure, 2005). In our sample the observed hemispheric lateralization would be consistent with that observed in the literature for BN and with some characteristics that the two disorders share. In some recent studies conducted on BN patients, a reduced activation of the frontostriatal circuits and reduced caudate function would seem to correlate with both the severity of B / P symptoms and the outcome rates of these subjects (Balodis et al., 2013; Skunde et al., 2016; Seitz et al., 2016). Correspondingly, Skunde et al., observed

diminished dorsal striatum activity during a go / no-go task in patients with BN with high symptom severity compared to controls. Curiously, these differences were specific to the general go / no-go paradigm but not to the food-specific go / no-go paradigm, which is suggestive of a more generalized impairment of behavioral inhibition rather than a disorder-specific impairment.

2.6.4 CONSIDERATIONS ABOUT DIFFERENCES BETWEEN MALE AND FEMALE HEALTHY CONTROLS

Given the number of healthy control subjects in our study, we decided to carry out a specific functional analysis as a corollary to the previous ones already discussed. The aim of this further analysis was to highlighting any specific gender related differences with respect to the discriminating networks between control subjects and BED patients even also as an indirect test of reproducibility about our results. Specific studies about gender related difference of the resting state functional activity are very few.

One of this specific research showed that healthy male subjects have a higher normalized clustering coefficient in the left hemispheric network but a lower clustering coefficient in the right hemispheric network, suggesting a gender-hemisphere interaction (Tian et al., 2011). Tian and collegues observed a significant difference in the regional nodal characteristics in various brain regions, such as the frontal and occipital regions (leftward asymmetry) and the temporal regions (rightward asymmetry). Author uderlined that these evidenced suggested that a topological organization of human brain functional networks is associated with gender and hemispheres providing insights into the understanding of functional substrates underlying individual differences in behaviors and cognition. Other studies showed some gender related differences in resting-state functional connectivity in specific brain regions such as the amygdala, the insula and within the sensorimotor network (Kogler et al., 2016). Moreover, men showed stronger connectivity in parieto-temporal regions, and within cognitive and sensory networks while women revealed stronger connectivity in fronto-temporo-cerebellar regions, and within attention and memory-related networks (Hausmann et al., 2017).

Our results replicated these evidences, showing significant differences in the aforementioned regions: our male healthy subjects are characterized by a greater activation of the parieto-occipital areas (occipital lobe, calcarine cortex and angular gyrus), of the thalamus and of the paraippocampal areas with a predominant left lateralization compared to female healthy subjects. Female healthy subjects, on the other hand, were characterized by greater activation of the insula and the precuneus with a right predominant lateralization.

An interesting fact about gender related difference emerges from the comparison between subjects with BED and male healthy controls. In addition to the differences described above and related to gender and not to the condition of disease (precuneum, calcarine cortex and parieto-temporal areas), it exist a significant difference in the post-central gyrus, an area previously discussed as significantly associated with the BED pathology in the comparison of BED female patients and healthy female subjects.

Therefore, this difference, unlike the difference at the level of the caudate and fusiform gyrus more typical of the BED pathology and common to the female sex, seems to represent a pattern really strongly correlated to the BED pathology and resistant also to the comparison with different sex control subjects. We could hypothesize that they exist specific neurobiological pattern for the predisposition to certain psychiatric pathologies. For example, the specific sex prevalence of anorexia nervosa could be explained by specific neurobiological pattern rather than cultural or personological factors. Similarly, the explanations of a substantial equality in the prevalence of BED between females and males could find its explanation also through different gender related neurobiological patterns. This hypothesis could open new conceptual models but needs numerous replication studies in order to evaluate its credibility and reproducibility within scientific field.

2.7 CONCLUSION

The results of our study confirm the few emerging data in the literature on the neurobiological bases of BED, recently encoded as a new diagnosis within Eating Disorders and with increasingly specific and scientifically relevant characteristics in the context of psychiatry research.

First of all, our study confirms that BED subjects share a complex but specific personality and psychopathological profile with AN and BN subjects, characterized by biologically predisposing personality traits (such as Harm Avoidance) while character personality traits may be more affected by different relational factors than the more classical Eds. In our sample the lack of significance of self directedness, a central character personality trait, differently from other studies on BED subjects, has been discussed as a mirror of a less "defined" pathogenesis with respect to the more classical EDs, in which the role of family dynamics and the way in which these subjects manage their own emotions may insist differently on a common vulnerability to eating psychopathology.

The presence of alexithymic traits, already highlighted in literature also in BED subjects, confirms a common pattern of difficulty with respect to the management of more properly relational and affective aspects. The evaluation of the eating psychopathology, investigated by EDI-2, confirms that BED subjects show a similar impairment as that found in Anorexia and in Bulimia Nervosa confirming the same severity in terms of prognostics, classifiers and therapeutic possible approach.

Even from a neurobiological point of view our results appear to be in line with the few evidences of the literature to which they add some scientific evidences in a context still little explored. Our results demonstrate that patients with BED show a neurobiological profile characterized by greater resting functional activity in the post-central gyrus (temporal region) within visual network. BED subjects are characterized also by reduced functional activity at rest in the fusiform gyrus (parietal region) in the auditory sensori-motor network and in the right caudate nucleus in the right fronto parietal network. The pattern highlighted by our study suggests a greater activation of the parietal regions

combined with a lower activation of deep temporal and ventral regions in subjects with BED compared to healthy controls.

If on one hand BED shows neurobiological characteristics more similar to other psychopathological conditions (such as addictions and ADHD) and some researchers hypothesize a transdiagnostic pattern called “reward deficiency syndrome” based on the impairment of the reward and caudate system, on the other this hypothesis must be integrated. Our evidence suggests that BED is also characterized by neurobiological patterns more typically shared with Anorexia and Bulimia Nervosa and involved in the processing of body image and in the elaboration of proprioceptive and emotional stimuli. The same impairment of the caudate nucleus typical also of the most classical EDs, constitutes a further demonstration of the possibility of existence of a sort of "eating endophenotypes" which then give rise to different symptoms and clinical manifestations. The scientific evidence regarding the impairment of the caudate in the Eds supports also the concept of the "impulse control model" of eating disorders, in which the alterations of mesolimbic reward response mechanisms could explain the lack of control and the impulsivity that are often present in these subjects. In this sense, the hypothesis that a brain specific area corresponds to a specific function or a dysfunction is now largely outdated and the functional organization with different networks presumably represent a pattern of vulnerability on which different environmental factors subsequently act.

From a therapeutic point of view our results on resting state functional activity of BED patients open some questions and confirm some previous ideas:

- Complex neurobiological patterns and different resting state functional connectivity also appear in BEDs as well as in more classical EDs when compared to healthy subjects;
- These patterns on one hand seem more similar to other psychiatric conditions different from the EDs while our study suggests how such interpretations can be integrated: impairment of brain area functionally assigned to the processing of body image and proprioception are typical of eating disorders;

- BED seem to be characterized by more serious aspects of impulsiveness and reward than more classical EDs: some studies suggest a possible greater impairment of reward and inhibitory control systems or even just a different organization of these specific functions.

Some recent findings suggest many advantages in detecting and treating adolescent with Anorexia and Bulimia Nervosa in specialistic community based child and adolescent eating disorders services accessible from primary care in order to reduce health service cost and to work synergistically on different aspects of EDs (Anderson 2017). During the past, residential treatments or communities for EDs were considered as a last choice only for too severe patients or for patients with psychiatric comorbidities due to health costs and to the impact on quality of life. Recently, due to drop out rates, low outcome percentages of remission and chronicity highlighted in the literature for outpatient treatments or different approach, some authors suggest many possible advantages in long term programs.

The same type of evaluation should be considered for BED? Evaluation studies in terms of outcome should be evaluated in this regard.

Limits

Limits of our study are mainly 3:

- the small sample size in particular concerning patients group;
- the lack of two groups of patients with different gender didn't allow us to divide them and to compare these two different groups with the two control groups in order to evaluate any possible gender related differences in neurofunctional aspects of BED;
- the lack of significant correlations between neurofunctional patterns and clinical and psychopathological measures probably due to the low number of patients.

PART III

OTHER SCIENTIFIC CONTRIBUTION IN THE FIELD OF EATING DISORDERS, OBESITY AND NEUROIMAGING APPLICATIONS DURING PHD COURSE IN NEUROSCIENCE

3.1 NEURONAL VARIABILITY OF RESTING STATE ACTIVITY IN EATING DISORDERS: INCREASE AND DECOUPLING IN VENTRAL ATTENTION NETWORK AND RELATION WITH CLINICAL SYMPTOMS

[SEE SEPARATED FILE 3.1]

3.2 NATURALISTIC FOLLOW-UP OF SUBJECTS AFFECTED WITH ANOREXIA NERVOSA 8 YEARS AFTER MULTIMODAL TREATMENT: PERSONALITY AND PSYCHOPATHOLOGY CHANGES AND PREDICTORS OF OUTCOME

[SEE SEPARATED FILE 3.2]

3.3 CHILDHOOD EMOTIONAL ABUSE AND NEGLECT IN OBESE PATIENTS WITH AND WITHOUT BINGE EATING DISORDER: PERSONALITY AND PSYCHOPATHOLOGY CORRELATES IN ADULTHOOD

[SEE SEPARATED FILE 3.3]

3.4 PERSONALITY AND PSYCHOPATHOLOGY DIFFERENCES BETWEEN BARIATRIC SURGERY CANDIDATES, SUBJECTS WITH OBESITY NOT SEEKING SURGERY MANAGEMENT, AND HEALTHY SUBJECTS

[SEE SEPARATED FILE 3.4]

3.5 THE SONG OF ANOREXIA NERVOSA: A SPECIFIC EVOKED POTENTIAL RESPONSE TO MUSICAL STIMULI IN AFFECTED SUBJECTS

[SEE SEPARATED FILE 3.5]

PART IV

CONCLUSION

4.1 CONCLUSIONS AND FUTURE DIRECTIONS

Binge Eating Disorder (BED) was introduced as an autonomous diagnostic category only in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM5), released in May 2013, becoming one of the three major Eating Disorders (EDs) classified in the scientific community (Vo et al., 2017). BED has been often associated with obesity but differs from this condition in many domains: comparative studies between obese subjects with BED and those without BED show extremely different personality, behavioral and psychopathological profiles (Amianto et al., 2011). Group differences have been also extended to non-food stimuli: BED is associated with psychiatric comorbidity and the phenomenon of binge eating explains many differences This complexity is reflected by a difficulty in the therapeutic approach to the BED disorder: despite the existence of multidisciplinary interventions of different orientations, one of the major problems in the treatment of BED today remains the strong resistance to treatments and the high percentage of drop- out, also typical of other EDs (Abbate Daga et al., 2013; Fassino & Abbate Daga, 2013; Fassino et al .; 2009). According to this model, many authors focus also on neurobiological common patterns in EDs trying to find any similiraties or differences of BED respect to AN or BN that could be used as trans-diagnostical model for develop new therapeutic approach on EDs.

One of the most important findings in this context concerns the evidence that commonalities in specific neural network alterations are present across EDs and endorse the potential advantages of using a dimensional approach to elucidate the neurobiology of specific behavioral constructs The identification of neural targets for effective brain based treatments is ultimately one of the goals of

neuroimaging research but more research is needed to first develop comprehensive models of the behaviors that underpin EDs.

Literature background and results of my different PhD researches confirm that a possible neurobiological model of ED could be represented by an imbalance in information processing between ventral limbic and dorsal executive circuits (Wagner et al., 2008). These circuits are primarily implicated in inhibitory cognitive processes and reward-related behavior, which are altered in ED (Favaro et al., 2013; Amianto et al., 2015; Spalatro et al., 2019).

The aim of my principal phD research in the context of Eds was to explore through fMRI the neurofunctional circuits of patients affected by BED with particular attention to the areas involved in impulsivity and cognitive control. We focused also on possible gender related difference highlighting on one hand any differences from healthy subjects and on the other hand possible similarities to classical EDs, such as Anorexia and Bulimia Nervosa in order to help clinicians to identify more specific short or long term therapeutic protocols.

This study (together with the others presented in part III) is part of a set of exploratory studies using Neuroimaging tools in the context of Eds and specifically on BED with the aim of understanding and discussing its clinical implications in EDs therapeutic strategies and in their possible improvement. Results of this research confirm that BED shows typical neurofunctional patterns of EDs, even with its own specific characteristics and clinical different manifestations. Specifically, it appears that subjects with BED show a functional pattern characterized by an impairment of the circuits involved in body image and interoceptive processing and in reward and inhibitory control processes. The impairment of inhibitory control, recently highlighted through different functional analysis techniques, appears to be a common marker between Anorexia Nervosa, Bulimia Nervosa and Binge Eating Disorder although mediated by different functional networks (Spalatro et al, 2019). In Anorexia this impairment seems to be more related to dysfunctional executive functions while in BED it seems to be related with an impairment of the reward system, as for Bulimia Nervosa.

Trying to connect research and clinic, our previous study on AN patients hypothesized that one of the possible implications about this finding, was that of supporting a sequential treatment of these disorders, considering the impairment of the cognitive dimension of EDs as one of the possible motives of the ED psychopathology (Spalatro et al., 2019). In that study we underlined as cognitive remediation therapy may become primary-line interventions in the early stages of the ED treatment, which may then be followed by more dynamic psychotherapeutic approaches. More recently, our results highlight that also patients with BED show a neurobiological pattern characterized by an imbalance in information processing between ventral limbic and dorsal executive circuits (Wagner et al., 2008) but clinical implications could be different because they must also take into account different evidences from those highlighted by neuroimaging studies.

The exploration of other different functions in the context of BED (see part III, section 3.3 for details) showed that BED patients reported higher emotional abuse and emotional neglect than obese without BED while sexual and physical abuse are not specifically related to BED (Amianto et al., 2018). These evidences suggest that also in BED like other EDs, traumatic experiences during childhood need to take into account when clinicians have to thinkabout different therapeutic protocols (Bomberg et al., 2017). In particular specific therapeutic interventions that focus on the elaboration of emotional components of traumatic experiences (e.g. EMDR therapy) need to be specifically explored for BED treatment even if these approaches have been very debated (Bloomgarden and Calogero, 2008)

The aim of our research group, using different tools including also Neuroimaging and its applications, is to try to provide a bridge between research and clinical implications in the context of Eds characterized by the highest dropout rates among psychiatric disorders.

Our different research suggest on one hand that BED represent a severe psychiatric condition with similar characteristics to more classical EDs but also with specific neurofunctional pattern and traumatic characteristics. From a neurobiologically point of view, BED subjects showed neurofunctional patterns common to the most classic Eds but also with trans-diagnostic features

common to other complex psychiatric disorders such as addictions. It seems therefore that BED is a complex disorder characterized by a marked impairment of the reward and inhibitory control systems as well as for a neurobiological impairment of network involved in processing emotional and interoceptive stimuli. Other evidences suggest that traumatic and development elements are also included in BED complexity, and the relationship between these and the neurobiological aspects is still unclear. In this sense the clinical attitude and the direction of public health interventions would benefit from an awareness towards BED, often considered a "minor" disorder in the context of EDs.

On one hand any research suggests possible therapeutic implications (for example specific therapeutic interventions that focus on the elaboration of emotional components of traumatic experiences or Cognitive Remediaton Therapy hypothesized as a possible primary-line interventions in the early stages of the ED treatment) but on the other hand the way in which these treatments could be integrated is not clear. In this sense, Neuroimaging becomes a useless and misleading tool when its applications were not translated into an integration with respect to the clinic and to the construction of therapeutic models that are not separated but integrated.

To sum up from data emerging from our studies, we could fix different levels of reflection:

- BED as well as the other EDs is characterized by traumatic aspects but also by aspects of impairment of the circuits assigned to inhibitory control and therefore to impulsiveness and reward.
- For the first time we confirm that this set of functional network involved in these process and hypothesized to be altered in the BED are really involved;
- one of the problems concerning therapeutic approach in EDs could depend on a multidisciplinary approach that is temporally out of phase and fragmented;
- to date the idea that long-term therapeutic interventions like residential programs may become fundamental for EDs represents a very debated point.

The choice of long term and residential program in the context of EDs, including the BED (now mostly treated with outpatient protocols) would open the possibility of treating EDs as complex and

multifactorial pathologies in which any type of intervention could be performed in synergistic and synchronous terms and not disjoint and at different stages of the disease.

Long-term and residential treatments with a multidisciplinary team would allow a trans-diagnostic approach to EDs but with specific focus also respect to neurobiological evidences. In this sense, it would be possible to reduce costs by carrying out more "invasive" interventions (like long term programs) but presumably reducing drop outs rates.

Multidisciplinary treatments in long-term contexts would allow specific work both on maintenance mechanisms and reward alteration processes in a more behavioral and educational sense then also on more psychological and traumatic aspects related to the body image perception and on emotional processing through more psychotherapeutic and relational interventions. In residential programs, even the most properly symptomatic aspects would find space with different and individualized nutritional protocols. Moreover, neuroimaging conceived as a methodology at the service of the clinic, could provide a basis for knowledge of some non-manifest neurobiological mechanisms, also providing the possibility of including some experimental functional treatments in these contexts (tdCS? TMS?).

The research needs longitudinal and follow-up studies in this sense as well as providing new evidences about the aforementioned hypotheses.

4.2 ACKNOWLEDGEMENT

I want to acknowledge Prof Fassino and Prof Amianto, my tutor, for the supervision and the opportunity to conduct my PhD activity during these years.

I want also to acknowledge Dott. D'Agata, my co-tutor during my PhD activity for the supervision of my projects concerning nurofunctional techniques.

I want also to acknowledge all the Multidisciplinary Equipe of Residenza Dahu (Brusson, AO) for the clinical and research activity we did together during these years.

Finally I want to acknowledge Alessandro, my family and all my closer friends for the support with which they accompanied me in this complex course.

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European Psychiatry 55 (2019) 10–17

Contents lists available at ScienceDirect

European Psychiatry

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Neuronal variability of Resting State activity in Eating Disorders: increase and decoupling in Ventral Attention Network and relation with clinical symptoms

Angela V. Spalatro[a], Federico Amianto[a,*], Zirui Huang[b], Federico D'Agata[a], Mauro Bergui[c], Giovanni Abbate Daga[a], Secondo Fassino[a], Georg Northoff[d]

[a] Department of Neuroscience, Psychiatry Section, AOU City of Health and Science of Turin, University of Turin, Via Cherasco 11, 10126, Turin, Italy
[b] Department of Anesthesiology, University of Michigan Medical School, Domino Farms Lby M Ste 3100, Ann Arbor, MI, 48105-5737, USA
[c] Department of Neuroscience, Neuroradiology Section, AOU City of Health and Science of Turin, University of Turin, Via Cherasco 11, 10126, Turin, Italy
[d] The Royal's Institute of Mental Health Research & University of Ottawa Brain and Mind Research Institute, Centre for Neural Dynamics, Faculty of Medicine, University of Ottawa, 145 Carling Avenue, Rm. 6435, Ottawa, ON, K1Z 7K4 Canada

ARTICLE INFO

Article history:
Received 19 June 2018
Received in revised form 14 August 2018
Accepted 27 August 2018
Available online 29 October 2018

Keywords:
Eating Disorders
Inhibitory control
Interoceptive awareness
Neuronal variability
Ventral Attention Network

ABSTRACT

Background: Despite the great number of resting state functional connectivity studies on Eating Disorders (ED), no biomarkers could be detected yet. Therefore, we here focus on a different measure of resting state activity that is neuronal variability. The objective of this study was to investigate neuronal variability in the resting state of women with ED and to correlate possible differences with clinical and psychopathological indices.
Methods: 58 women respectively 25 with Anorexia Nervosa (AN), 16 with Bulimia Nervosa (BN) and 17 matched healthy controls (CN) were enrolled for the study. All participants were tested with a battery of psychometric tests and underwent a functional Magnetic Resonance Imaging (fMRI) resting state scanning. We investigated topographical patterns of variability measured by the Standard Deviation (SD) of the Blood-Oxygen-Level-Dependent (BOLD) signal (as a measure of neuronal variability) in the resting-state and their relationship to clinical and psychopathological indices.
Results: Neuronal variability was increased in both anorectic and bulimic subjects specifically in the Ventral Attention Network (VAN) compared to healthy controls. No significant differences were found in the other networks. Significant correlations were found between neuronal variability of VAN and various clinical and psychopathological indices.
Conclusions: We here show increased neuronal variability of VAN in ED patients. As the VAN is relevant for switching between endogenous and exogenous stimuli, our results showing increased neuronal variability suggest unstable balance between body attention and attention to external world. These results offer new perspective on the neurobiological basis of ED. Clinical and therapeutic implication will be discussed.

1. Introduction

Eating Disorders (ED) represent the psychiatric disorder with the highest rate of mortality in adolescent and young women [1]. To date, the physiopathology of these disorders is only partially understood. Clinicians suggest a multifactorial approach, in which neurobiological factors can contribute to the vulnerability, onset and outcome of ED [2–4]. Recently a growing number of functional magnetic resonance imaging (fMRI) studies have contributed to clarify neuro-functional alterations in eating disorders [5]. Based on these studies, a neurobiological model of ED suggests that there could be an imbalance in information processing between ventral limbic and dorsal executive circuits [6]. These circuits are primarily implicated in inhibitory cognitive processes and reward-related behavior, which are altered in ED [7–9].

Several groups have used resting-state fMRI [10] that is thought to reflect internally oriented thinking and consciousness [11,12]. This method measures brain activity in absence of any stimulus and allows to calculate temporal correlations between different brain areas, i.e., functional connectivity [13,14].

Despite the different interpretations of the Resting State studies on ED, the results are generally overlapping in that they show

* Corresponding author.
E-mail address: federico.amianto@unito.it (F. Amianto).

http://dx.doi.org/10.1016/j.eurpsy.2018.08.005
0924-9338/

functional alterations in various networks and/or areas. Specifically, alterations in the fronto-parietal network (a brain network involved in cognitive control functions) were found in both patients with Anorexia Nervosa (AN) and participants recovering from AN [15]. These resting-state findings may underlie the impaired cognitive control of appetitive processes as well as ruminations concerning the self and body image [16,17].

Functional connectivity describes the relationship, i.e., synchronization, between different regions and their activities in the resting state. This leaves out the neuronal features of the region itself independent of its relationship to others. For that, one could investigate the variability of neural activity in the resting state as it has been introduced recently [18–21]. This approach, called "standard deviation (SD) of blood oxygenation level-dependent (BOLD) signal" describes the fMRI fluctuations of the BOLD signal in a specific cerebral region, resulting in a more direct measure of a brain region activity [19–21]. To date, studies conducted with this approach are still very limited. Studies on psychiatric subjects show that in depression and bipolar disorders [22–27], the analysis of neuronal variability allows us to emphasize more precisely the neuro-functional alterations in terms of specific regions or networks including their relation to behavior and clinical symptoms [28,29].

The aim of this study is to explore for the first time fMRI resting state neuronal variability in ED patients including both anorectic (AN) and bulimia (BN) subjects and to correlate any differences with psychopathological and clinical symptoms. As no previous studies investigated SD in ED, our study must be considered exploratory. Based on previous findings [7,9,12] we tentatively hypothesized changes in SD in specifically the attention networks like ventral attention network (VAN) in ED including their relationship to psychopathological measures.

2. Methods and material

2.1. Participants

Forty-one women who were consecutively assessed after their first contact at the Center for Eating Disorders of the University of Turin diagnosed respectively with Anorexia Nervosa (25) and Bulimia Nervosa (16) were recruited for this study between January 2012 and December 2014. A diagnosis of AN and BN was established by a psychiatrist following DSM-IV-TR criteria [30] and confirmed using DSM 5 criteria before the data elaboration. Inclusion criteria were: female sex; age of illness < 1.5 years; right-handed; BMI < 18 and > 14. Exclusion criteria were major medical illness, neurological disorders, use of psychotropic medications or psychotherapeutic treatments in the last 6 months, presence of other relevant psychiatric diagnosis, contraindication for MRI. Seventeen matched healthy women were enrolled for the study as control group.

2.2. Ethics

The study was approved by the Ethical Committee of the San Giovanni Battista Hospital, Turin. (CEI/17 0028836) according to the Helsinki Declaration as revised in Edinbourgh in 2000. All patients and controls gave their written informed consent to the study.

2.3. Measures

During a screening interview, an expert psychiatrist assessed every patient and control with the support of the SCID [31] and conducted a clinical evaluation to determine possible inclusion in the study. Clinical data such as length of disease, BMI, binge/purging episodes, physical hyperactivity and use of laxative per week were also collected. According to Clinical Global Index (CGI), the psychiatrist assigned a severity index for the disease for each patient. All the participants completed a battery of self-administered psychometric tests including Temperament and Character Inventory (TCI [32]), Eating Disorder Inventory-2 (EDI-2 [33]), Toronto Alexithymia Scale (TAS-20 [34]), Symptom Checklist-90 (SCL-90 [35]), Beck Depression Inventory (BDI-II [36]) and Attachment Style Questionnaire (ASQ [37]) to evaluate psychopathological symptoms and personality features.

2.4. fMRI data acquisition

Functional data were collected at the Neuroscience Department AOU San Giovanni Battista, Turin, Italy on a Philips Achieva 1.5 T scanner (Erlangen, Holland) equipped with dual gradient system (Quasar, Philips) of 40 mT/m and a Sense high-field, high resolution eight-channel head coil optimized for functional imaging. The resting-state scan comprised 200 continuous functional volumes (repetition time = 1966 ms, echo time = 50 ms, flip angle = 90°, 24 axial slices, matrix = 128 × 128, slice thickness = 5 mm, acquisition voxel size = 1.8 mm × 1.8 mm × 6 mm, field of view = 25 cm). The total acquisition time was 6 min and 33 s; the patients were scanned with their eyes closed. Foam pads were used to reduce head motion and scanner noise. All participants reported keeping their eyes closed and being awake during the scanning.

2.5. fMRI data processing

Preprocessing steps were implemented in Analysis of Functional NeuroImages (AFNI) software [38]. We discarded the first five volumes in each scanning using the AFNI command "3dTcat". The functional images from each scan were then slice-timing corrected (via AFNI's 3dTshift), aligned to the second volume using AFNI's "3dvolreg", transformed into Talaraich space (Talairach J and P Tournoux 1988) using and resampled to 3 × 3×3mm3 using AFNI's "adwarp", and then spatially smoothed with a 6-mm full width at half maximum Gaussian blur (AFNI's "3dmerge"). Subjects with head motion larger than ±3 mm translation or ±1° rotation were removed. Within our sample two subjects exceeded this threshold (they have been eliminated from the following analysis); data of all the other participants were used for the following analysis. Time series for six estimated parameters of head motion and mean time series from the white matter (WM) and cerebrospinal fluid (CSF) were regressed out from grey matter. According to previous literature, the data was then filtered with a band-pass filter preserving signals between 0.01 and 0.08 Hz, which was thought to reflect fluctuations of spontaneous brain activity [39–41].

2.6. Resting state analysis

Resting-state data analysis was performed using AFNI (https://afni.nimh.nih.gov/ afni) (38). First, the global signal variance was calculated to account for possible global changes in all subsequent analyses. Specifically, according to literature, we calculated the SD of BOLD signal changes, a measure of neuronal variability in the resting state.

Following Yang et al. [42,43] we choose to calculate the global signal using two measures, the mean of the global signal (GM) and the global signal standard deviation (GSD). This yielded no significant differences between groups and between GM and GSD. Because these measures did not reveal significant differences in each subgroups subject-level voxel-wise, SD maps ($p < .305$) were standardized and normalized onto subject-level z-score

maps per brain volume by subtracting the mean voxel-wise SD obtained for the entire brain (global mean of SD), then dividing by the SD across voxels [44]. That's the reason why our SD showed negative values within our sample (as reported in Fig. 1 and 2) and in all the analysis that we have done. Next, according to the literature, spherical regions of interest (ROIs) with a radius of 6 mm were placed in the Talairach coordinates of all cortical nodes of each network. We adopted a well-established node template from a previous study [45–47], containing 264 putative functional areas (10 mm diameter spheres, 32 voxels per sphere) across the whole brain. We extract 11 different networks: the Default Mode Network (DMN), the Somato Motor Network (SMN), the Salience Network (SN), the Auditory Network (AUD), the Visual Network (VS), the Dorsal Attention Network (DAN), the Ventral Attention Network (VAN), the Cerebellum Network (CB), the Frontal Parietal Temporal Network (FPTC), the Medial Regional Network (MR), the Cingular Operculum Task Control Network (COTC) and the Subcortical Network (SUB). We extracted the SD from all of the nodes and we then calculated the mean SD of all nodes within each resting-state network. Data were then filtered with two separate bands within the standard range of 0.01–0.10 Hz: Slow5 (0.01–0.027 Hz) and Slow4 (0.027–0.073 Hz) [22,23,26].

2.7. Statistical analysis

Firstly, Analysis of variance (ANOVA) and age/BDI-controlled Analysis of covariance (ANCOVA) were performed to compare all variables between AN, BN and controls and between the two groups of subjects distinguished in patients (AN + BN) and controls using one sample *t*-test. A Bonferroni correction for multiple comparisons was applied accepting only results with $p < 0.001$. Only the variables that significantly differed between groups at this step were considered in the further analysis.

Secondly the SD values of the mean in each network and the SD values in each frequency band (Slow5 and Slow4) were entered into a one way ANOVA to compare group-level differences in the variability between each subgroup: AN, BN and CN. The networks' SD that were significantly different between subgroups were entered into a post hoc test to detect differences in neuronal variability between the various subgroups (i.e., AN, BN and CN). A one sample *t*-test was then performed to study differences between the two groups of subjects distinguished in patients (AN + BN) and controls. Third, a Pearson correlation analysis was performed between SD and the clinical variables (BMI and hyperactivity) and TCI, EDI-2, TAS-20, ASQ, SCL-90 subscales which differed between probands and controls.

Unless otherwise stated, all resulting t-maps were thresholded at a corrected p-value of < 0.05. That is, the multiple-comparison error was corrected using Monte Carlo simulation as implemented in AFNI program AlphaSim, yielding a family-wise error rate (FWER) at $p < 0.05$ with a minimal cluster size of 97 voxels. The smoothness used in the AlphaSim was the average smoothness across subjects. The statistical analyses were performed using Statistical Package for Social Sciences (SPSS) software (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Psychopathological assessment

We observed significant differences between anorectic subjects, bulimic subjects and healthy controls in education [*F = 6.296;*

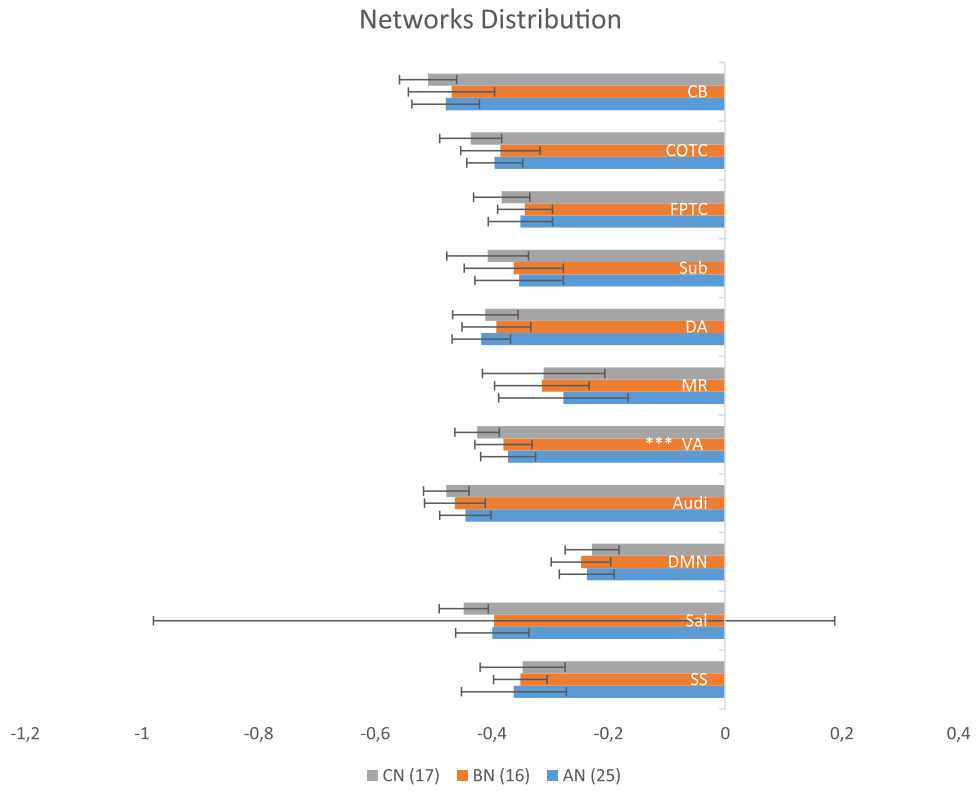

Fig. 1. Networks distribution across groups and differences between AN, BN and CN.
Legend: CN = control subjects; BN = bulimic patients; AN = anorectic patients. CB = Cerebellum Network; COTC = Cingular Operculum Task Control Network; FPTC = Frontal Parietal Temporal Network; SUB = Subcortical Network; DA = Dorsal Attention Network; MR = Medial Regional Network; (MR), VAN = Ventral Attention Network; AUD = Auditory Network; DMN = Default Mode Network; SAL = Salience Network; SS = Somato Sensitive Network.
***p < .05.

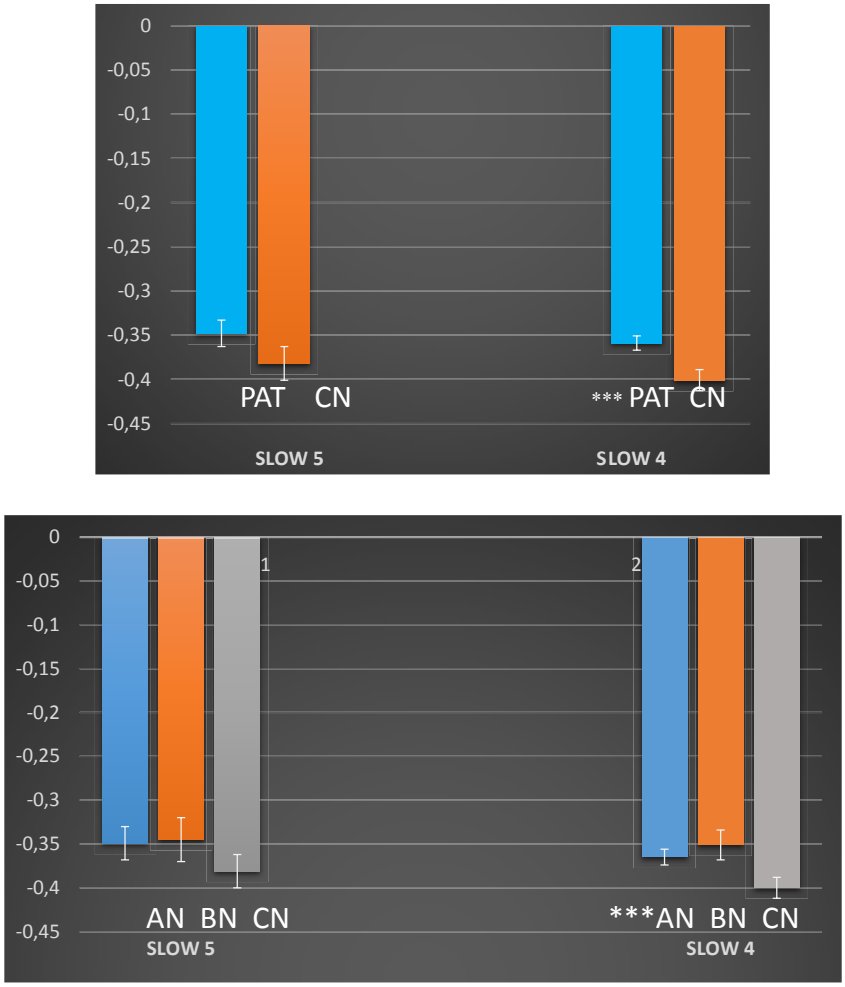

Fig. 2. SLOW 5 SLOW 4 differentiation between Patients (AN + BN) and Control (2a) and between AN, BN and CN (2b).
Legend: Fig. 2a. Comparison of Slow 5 and Slow 4 SD values between Patients (PAT = Anorectic patients and Bulimic Patients) and Controls (CN).
*** p < .05. Fig. 2b Comparison of Slow 5 and Slow 4 SD values between Anorectic patients, Bulimic Patients and Controls. AN = Anorectic patients; BN = Bulimic patients; CN = healthy controls.
*** p < .05

$p < 0.004$], in BMI [$F = 68.856$; $p < 0.000$] and physical hyperactivity [$F = 10.829$; $p < 0.000$]. (Table 1). Some subscales of the EDI-2 (drive to thinness [$F = 34.382$; $p < 0.000$], social insecurity [$F = 12.073$; $p < 0.000$], interpersonal distrust [$F = 10.652$; $p < 0.000$] and interoceptive awareness [$F = 16.220$; $p < 0.000$]) showed significant differences between the three groups with both anorectic and bulimic subjects scoring higher values than healthy subjects (Table 1). Moreover, both anorectic and bulimic subjects also

Table 1
Demographical, clinical and psychopathological characteristicsof the sample.

	AN (25)	BN (16)	CN (17)	F	p	Post hoc
Age	20.33 ± 4.42	21.56 ± 2.35	23.27 ± 2.19	2.382	.102	–
Education	13.57 ± 2.29	14.50 ± 2.09	16.13 ± 1.85	6.296	**.004**	CN > AN
BMI	15.99 ± 0.92	21.84 ± 2.35	21.42 ± 1.85	68.856	**.000**	BN, CN > AN
Physical hyperactivity	5.00 ± 3.31	4.86 ± 3.46	0.92 ± 1.16	10.829	**.000**	AN, BN > CN
EDI-2						
Drive of thinness	13.19 ± 6.72	16.50 ± 6.00	1.07 ± 1.33	34.382	**.000**	AN, BN > CN
Bulimia	3.19 ± 4.02	10.69 ± 5.49	1.20 ± 2.14	23.380	**.000**	BN > CN, AN
Body dissatisfaction	12.52 ± 6.71	20.62 ± 5.33	5.33 ± 5.34	23.618	**.000**	BN > AN BN, AN > CN
Impulsivity	7.23 ± 6.71	7.31 ± 5.39	0.67 ± 0.82	8.469	**.001**	AN, BN > CN
Social Insecurity	6.79 ± 4.95	7.87 ± 4.16	1.27 ± 1.83	12.073	**.000**	AN, BN > CN
Interpersonal distrust	6.47 ± 4.85	7.93 ± 4.52	1.47 ± 1.84	10.652	**.000**	AN, BN > CN
Interoceptive Awareness	9.47 ± 6.60	12.18 ± 7.02	0.87 ± 1.46	16.220	**.000**	AN, BN < CN
TAS-20						
Difficulty in identifying feelings	23.95 ± 6.13	23.31 ± 6.01	10.93 ± 4.11	27.916	**.000**	CN < AN, BN
Difficulty in describing feeling	17.82 ± 4.86	16.93 ± 5.64	11.07 ± 5.68	7.818	**.001**	CN < AN, BN
Externally Oriented Thinking	17.82 ± 4.86	16.93 ± 5.64	11.07 ± 5.68	7.818	**.001**	CN < AN, BN
Total	59.41 ± 9.57	60.38 ± 16.43	36.73 ± 10.41	19.150	**.000**	CN < AN, BN

AN = anorectic patients; BN = bulimic patients; CN = control subjects. BMI = Body Mass Index; EDI-2= Eating Disorder Inventory 2; TAS = Toronto Alexithymia Scale-20.

showed higher alexithymia scores compared with healthy subjects [*F = 19.150; p < 0.000*] (Table 1). Anorectic and bulimic patients showed higher scores in many other psychopathological scales and personality dimensions (Table 2). TCI scales (persistence, cooperativeness and self-transcendence) and ASQ subscales (second nature of relationships and discomfort about intimacy) were non-significantly different.

3.2. Head motion analysis

In order to exclude the possible bias of head motion, we firstly calculated the mean of motion shift and motion rotation of the whole sample (shift: 0.06 ± 0.03; rotation: 0.06 ± 0.02) and then we conducted an ANOVA to detect if there are any differences between groups. No significant differences were detected between AN, BN and healthy subjects in terms of motion shift (AN = 0.06 ± 0.02; BN = 0.07 ± 0.02; CN = 0.06 ± 0.03 p < . 319) and motion rotation (AN = 06 ± 0.02; BN = 0.06 ± 0.01; CN 0.06 ± 0.02; p < .320).

3.3. Global signal - global neuronal variability

In a first step, following Yang et al. [42,43] we calculated the global signal using two measures, the mean of the global signal (GM) and the global signal standard deviation (GSD). This yielded no significant differences between groups (for GM: F = .696; p < .503; for GSD: F = .871; p < .425) and between GM and GSD (t=-1.307; p < .305).

3.4. Neural networks - neuronal variability

We then investigated neuronal variability operationalized as standard deviation of BOLD signal changes (SD) in the resting state within the 11 networks of interest. ANOVA revealed that the SD differed significantly between anorectic subjects, bulimic subjects and healthy controls in specifically the Ventral Attention Network (VAN) [F = 7.311 p < 0.002] (Fig. 1). No other significant differences were found within the other networks (Table S1).

Following the literature, we also focused on Slow-5 and Slow-4 [22,23,48–51]. We first performed a two-sample test between patients (anorectic and bulimic subjects together) and healthy subjects for slow 5 and slow 4 (Fig. 2 a) followed by one way ANOVA between the three group separately for slow 5 and slow 4 (Fig. 2 b). This yielded significant SD differences in VAN specifically in slow 4 between patients (AN + BN) and CN: [*t=-2.754; p < .008*] and within the three subgroups (AN, BN and CN separately): [*F = 4.12; p < 0.02*]. No significant differences were found in slow 5. For details see also Table S2.

3.5. Neuronal variability in networks - relationship to psychopathology

In a final step, we correlated the neuronal data on VAN SD with psychopathological scores. Significant results showed that altered SD in VAN directly correlated with BMI [p < 0.01] and inversely correlated with TAS total [p < 0.01], physical hyperactivity [p < 0.04], drive of thinness [p < 0.03] and impulsivity [p < 0.03] (Table 3). Other correlation between SD and significantly different psychopathological scores (including some EDI-2 subscales interpersonal distrust, interoceptive awareness and interpersonal distrust, TAS-20 subscale difficulty in describing feelings, some TCI subscales novelty seeking, harm avoidance and self-directedness and ASQ subscales worry about relationship and need for approval) were non-significant.

4. Discussion

4.1. Main findings

We here investigated resting state activity in patients with Eating Disorders ED with a novel measure, that is, neuronal variability. Moreover we investigated for the first time the global signal as well as neuronal variability in specific networks. This yielded the following main findings: (i) no differences in global signal between ED and healthy subjects; (ii) increased neuronal variability in specifically the Ventral Attention Network (VAN) in

Table 2
Personality and general psychopathological assessment of the sample.

	AN (25)	BN (16)	CN (17)	F	p	Post hoc
TCI						
Novelty Seeking	17.05 ± 6.58	22.63 ± 5.19	16.67 ± 4.65	5.693	**.006**	BN > CN, AN
Harm Avoidance	21.29 ± 8.13	23.13 ± 5.66	14.93 ± 7.09	5.578	**.006**	AN > CN, BN
Self-directedness	23.38 ± 7.43	20.56 ± 8.14	32.20 ± 11.92	6.875	**.002**	AN, BN < CN
BDI-II	16.71 ± 9.69	17.81 ± 9.29	3.00 ± 2.10	16.348	**.000**	AN, BN > CN
SCL-90						
Total	140.95 ± 63.43	159.00 ± 49.33	49.33 ± 27.23	19.583	**.000**	AN, BN > CN
ASQ						
Trust	27.33 ± 4.83	25.44 ± 4.70	33.07 ± 5.09	10.356	**.000**	CN > AN, BN
Need for approval	35.00 ± 5.59	35.81 ± 8.60	27.47 ± 5.11	7.810	**.001**	CN < BN
Worry about relationships	27.62 ± 5.51	28.38 ± 6.68	19.13 ± 3.16	14.427	**.000**	CN < AN, BN

AN = Anorectic Patients; BN = Bulimic Patients; CN= Healthy Controls. TCI = Temperament and Character Inventory; BDI = Beck Depression Inventory II; SCL-90= Symptom Check List-90; ASQ = Attachment Style Questionnaire.

Table 3
Correlation between VAN and psychopathology in ED patients.

	VANα BMI	VAN α Physical hyperactivity	VAN α Drive of thinness (EDI-2)	VAN α Impulsivity (EDI-2)	VAN α Global Score (TAS-20)
Pearson	0.389	0.297	0.322	0.344	0.372
p	0.01	0.04	0.03	0.03	0.01

ED = Eating Disorders (Anorectic patients and Bulimic patients); VAN = Ventral Attention Network; TAS-20 = Toronto Alexithymia Scale-20.

ED; and (iii) correlation of increased neuronal variability in VAN with various psychopathological measures.

4.2. Global signal

We for the first time investigated the global signal (GS) in resting state of ED. Following Yang et al. [42,43], we applied two different measures of GS, that is GS mean and GS SD. Previous investigations yielded increased GS in schizophrenia on both a global level and a regional level [42,43]. In contrast, patients with bipolar disorder did not exhibit any change in the global component of GS [42]. However, a recent study showed that GS differed on the regional level in manic and depressed phases of bipolar disorder [25].

The present data investigate GS for the first time in ED. We here show no GS changes in ED on the global level. This suggests the GS to be different in ED when compared to the previous findings in schizophrenia and bipolar disorder. However, to further strengthen that claim future studies may want to directly compare ED, schizophrenia, and bipolar disorder within one and the same investigation. This perspective probably will confirm the hypothesis that GS could have a precise and clear role in the diagnostic classification of psychiatric disorders.

4.3. Neuronal variability in ventral attention network

Our main finding consists in increased neuronal variability in specifically the ventral attention network (VAN). The whole group of ED as well as both subgroups showed increased neuronal variability in specifically the VAN whereas no changes were observed in other networks. Moreover, we observed specific increase in slow 4, the faster frequency, whereas no such changes occurred in the slower frequency of slow 5. This means that in ED patients the faster frequency was affected and not the slower one concerning VAN. This result differs from what has been highlighted in bipolar disorder where the slow 5 is more compromised even if this impairment concerns different networks (posterior Default Mode Network and Salience Network) [25]. This difference in the involved frequencies of the VAN may represent a further specific marker for psychiatric disorders to be explored with further studies.

Our findings are partially in contrast with a previous investigation by Collantoni et al. [52] who observed reduced functional connectivity in this network in ED. Rather than applying functional connectivity, we here measured neuronal variability which was increased in VAN and which correlated with various psychopathological measures.

The VAN is involved in sudden shifts and redirection between different stimuli [53]. In this context, VAN works as a mediator between externally- and internally-directed stimuli with their respective activities. Especially the TPJ as core region of the VAN takes on a central role in encoding body-related stimuli and their discrimination form non-bodily-related stimuli [54–56]. The impairment of neuronal variability in VAN in ED thus suggests that these patients are less able to redirect and shift their focus from body-related stimuli to non-bodily-related environmental stimuli: their attention is thus fixed and “stuck” on the own body without being able to shift their attention away from the own body. This is certainly well in line with the clinical symptom of an “increased bodily-focus” (see [57,58] for such bodily-focus in the context of depression).

Moreover, the assumption of such deficit in internal-external shifting and re-direction is further supported by our findings of correlation. Increased neuronal variability in VAN was significantly correlated with various psychopathological measures like BMI, TAS, and typical eating disorder symptoms like physical hyper intensity, drive of thinness, and impulsivity. This suggests that an impaired neuronal variability in VAN could be the basis of some clinical symptoms of patients with EDs, even if the underlying neurobiological mechanisms should be confirmed in future research.

The psychopathological symptoms in ED may thus be traced to an abnormal temporal feature in VAN neural activity, i.e., increased neuronal variability: if the neuronal activity is less variable, the likelihood of shifting and re-directing attention between internal bodily-related and external, i.e., environmental non-bodily-related stimuli is decreased so that the patients’ focus remain on the internal bodily-related stimuli. That, in turn, induces the various symptoms one can observe in these patients [16,59]. Accordingly, psychopathological symptoms in ED may have temporal and spatial basis in abnormal spatiotemporal patterns of the resting state’s neural activity – this amounts to what has recently been introduced as “Spatiotemporal psychopathology” [12,60].

4.4. Conclusions

We here investigate for the first time global signal and neuronal variability in resting state in ED. While we did not find any changes in global signal in ED, our results demonstrated increased neuronal variability in a faster frequency, i.e., slow 4 in the ventral attention network in ED. Moreover, changes in resting state neuronal variability in VAN correlated with various psychopathological measures in ED. This further underlines the central relevance of VAN in ED and its altered capacity of shifting between internal body-related and external environmental non-bodily-related stimuli in ED as it can be observed in psychopathological symptoms. More generally, our findings support the recently suggested novel form of psychopathology, that is spatiotemporal psychopathology [12,54] to bridge the gap between neuronal and psychopathological levels.

Two mainstreams of clinical implications may derive from our findings. The first is the possibility to support a sequential treatment of these disorders considering the impairment of the cognitive dimension of EDs as one of the possible motives of the ED psychopathology. In fact neurocognitive impairment may represent a consequence of specific neurofunctional impairment on which both relational and emotional deficits are articulated. In light of this specific therapeutic protocols such as Cognitive Remediaton Therapy may become primary-line interventions in the early stages of the ED treatment, which can be then followed by more dynamic psychotherapeutic approaches.

The second regards the possibility to act on these specific neurofunctional alterations with primarily biological instruments such as TMS, tDCS or DBS in association with psychological and nutritional therapies. In both cases the study of neurofunctional markers of EDs offers the possibility to integrate in a multidisciplinary approach both biological and psychological treatments that have been considered separately from each other from a long time.

4.5. Limitations

The first limitation concerns the relatively short resting state which, based on a repetition time of 2 s, did not yield a high number of data points. Future studies may thus want to apply longer resting state with for instance 15 min and a lower TR (like 1 s).

The second limitation concerns the relative small sample of subjects. Future studies with the same approach need to be done to confirm our preliminary results in order to generalize our hypothesis and considerations on different neurobiological aspects of ED patients.

The third limitation concerns the use of a 1.5 T scanner. Future confirmatory studies should be conducted on scanners of at least 3 T power.

Declarations of interest

None.

Contributors

All the authors contributed to the paper. AVS contributed in sample recruitment, data collection and elaboration and in writing the paper. FA, ZH, FDA, MB, AB, GN, GAD and SF contributed in the data collection and elaboration and in the revision of the paper.

Disclosures

The lead author, AVS, affirms that the manuscript is honest, accurate, and transparent. Any discrepancies of the study have been explained within limitations.

Funding source

The present study was sponsored by the “Compagnia di San Paolo” Bank Foundation with the “Bando Neuroscienze” grant [code: 3929IT/PF 2008.2242] assigned in 2009 to Prof. Secondo Fassino and Dr. Federico Amianto and by IARPsrl generic [20BW320110719008513915033] Casale Monferrato “Resistenza ai trattamenti nei dca”

Acknowledgments

The authors thank Dr Carmen Settanta, Dr Caglio Marcella and Dr Paola Caroppo for their help in fMRI data acquisition and patients recruitment. The authors wish to acknowledge the fundings of San Paolo Bank Fundation and Cassa di Risparmio di Torino Bank Fundation given to the Professor Fassino for the support to the Pilot Centre for Eating Disorders in the years 2005–2015.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.eurpsy.2018.08.005.

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Psychiatry Research 269 (2018) 692–699

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

Childhood emotional abuse and neglect in obese patients with and without binge eating disorder: Personality and psychopathology correlates in adulthood.

Federico Amianto[a,*], Angela Valentina Spalatro[a], Miriam Rainis[a], Carla Andriulli[a], Luca Lavagnino[b], Giovanni Abbate-Daga[a], Secondo Fassino[a]

[a] Department of Neuroscience, Section of Psychiatry, Eating Disorders Centre, University of Turin, Turin 10135, Italy
[b] Department of Psychiatry and Behavioral Sciences, McGovern Medical School, The University of Texas Health Science Center at Houston, Texas, United States

ARTICLE INFO

Keywords:
Binge eating disorder
Obesity
Childhood traumatic questionnaire
Emotional abuse
Emotional neglect
Adulthood personality and psychopathology

ABSTRACT

The link between childhood traumatic experiences such as sexual and physical abuse and EDs in adulthood has been widely demonstrated. To date, however, little research focused on the association between emotional abuse and neglect in childhood and Binge Eating Disorder (BED) and obesity in adulthood.

We enrolled 127 patients [84 with BED and 43 obese] and 45 healthy controls (HCs). All participants were administered the same battery of psychometric tests. Between-group differences were explored and the relationship between emotional abuse and neglect in childhood and personality and psychopathology in adulthood was tested.

Obese patients showed higher scores in emotional abuse and neglect and sexual abuse when compared to HCs. Within obese participants, those with BED reported higher emotional abuse and emotional neglect than obese without BED and HCs; the BED group differed in physical and sexual abuse from obese participants.

The association between traumatic experiences in childhood and obesity in adulthood has been confirmed independently of the type of trauma. Therapists should take into account the traumatic etiology of BED, in particular psychological abuse, even in those patients who do not recall physical or sexual abuses. Specific techniques to approach traumatic experiences could be applied to BED or non-BED patients.

1. Introduction

Early childhood relationships determine humans' neurobiological organization; recent findings demonstrated that a pattern of positive experiences during the first years of life is an essential neurotropic factor for the proper development of the brain and its functions (Anda et al., 2006; Perry et al., 2009).

Traumatic experiences in childhood can predispose the individual to develop psychiatric disorders in adolescence and adulthood (Afifi et al., 2017; De Venter et al., 2013). Childhood trauma has been associated with the onset of different psychiatric conditions, namely: post-traumatic stress disorder (Cloitre et al., 2001), psychotic disorders (Mayo et al., 2017), depression and mood disorders (Sarchiapone et al., 2007), anxiety disorders (Sugaya et al., 2012), personality disorders and substance abuse (Dube et al., 2001) eating and dissociative disorders (Pignatelli et al., 2017) and affective and somatoform disorders (Kilpatrick et al., 2003). Traumatized subjects also show a higher prevalence of medical illnesses such as cardiovascular diseases (Moraitis and Ganesan, 2014), metabolic, immunological and sexual disorders (Kesebir et al., 2014; Maniglio, 2009), neoplastic, skeletal and liver diseases (Van Niel et al., 2014). Despite accumulating evidence on these effects of early traumatic events, the neurobiological and psychopathological patterns linking childhood trauma to obesity or to a specific psychiatric or metabolic disorders are still unclear.

With regard to eating disorders it has been observed that from 30% to 50% of affected indivuduals reported a physical or sexual abuse in childhood (Madowitz et al., 2015).

In particular, some studies showed a correlation between abuse and bulimic symptoms: higher rates of physical abuse, and sexual, physical and emotional neglect were found in patients with anorexia nervosa binge-purging subtype when compared to those with the restricting subtype (Caslini et al., 2016). A history of psychological or multiple types of abuse (Amianto et al., 2015; Léonard et al., 2003), as well as a parental neglect (Amianto et al., 2013) were found to be specific risk

* Corresponding author.
E-mail address: federico.amianto@unito.it (F. Amianto).

https://doi.org/10.1016/j.psychres.2018.08.089
Received 8 November 2017; Received in revised form 25 June 2018; Accepted 24 August 2018
Available online 05 September 2018

factors for bulimia nervosa.

As concerns obesity and Binge-Eating Disorder (BED), many studies demonstrated that traumatic events in childhood can lead to the development of this disorder in adulthood (Alvarez et al., 2007; Noll et al., 2007). With more detail, patients suffering from BED report high rates of child maltreatment with a wide range of traumatic experiences during childhood, regardless of gender, degree of obesity and binge-eating behaviors (Dunkley et al., 2010; Rohr et al., 2015). Although over the last years the relationship between childhood trauma and the development of BED in adulthood has been thoroughly investigated, to date little is known about some underlying mechanisms, particularly concerning the specific relevance of psychological traumas and emotional neglect in this regard.

The present study aims to assess childhood traumatic events in obese adults, using the Childhood Traumatic Questionnaire (CTQ) (Bernstein et al., 2003), with a specific focus on psychological abuse and emotional neglect, and to explore their correlations with psychopathological and personality characteristics in adulthood. Moreover, this study aims to compare obese patients with and without a diagnosis of BED to investigate specific mechanisms in these conditions. We hypothesize that different types or rates of childhood traumatic experiences may differentiate adult participants with obesity and BED from those without BED, and that this may relate to their different personality and psychopathology. Expanding the available knowledge of these differences may help clinicians to deliver more individualized treatments thus improving their efficacy.

2. Methods

2.1. Participants

One-hundred-fifty-three obese patients seeking treatment at the Regional Expert Centre for the Eating Disorder of University of Torino between October 2011 and June 2013 were enrolled in this study. All participants received a psychiatric examination to determine the presence or the absence of an eating disorder (specifically BED) using the Structured Clinical Interview for Diagnosis (SCID) for DSM-IV-TR, a tool that has fair to excellent inter-rater reliability on axis I and excellent on axis II diagnoses (Lobbestael et al., 2011). Inclusion criteria for the study were: 1) Age between 30 and 55 yo; 2) no intellectual disability or developmental or learning disorders; 3) no psychosis or neurological disorders (e.g., multiple sclerosis, stroke); 4) no history of dementia or severe head trauma; 5) no current acute psychotic condition or substance abuse; 5) duration of obesity > 1 year. The duration of obesity was not included in the database because the majority of subjects did not report it accurately and so it could have represented an unreliable datum.

From the initial sample, 26 participants were excluded according to the above criteria. The final group consisted of 127 obese patients (84 [females = 71; males = 13] suffering of BED and 43 [females = 33; males = 10] obese individuals without a diagnosis of BED).

A sample of 45 healthy controls [females = 30; males = 15] was recruited as control group. Inclusion criteria were the same of the participants' groups.

2.2. Ethics

All recruited participants provided written informed consent to this study. All the procedures were conducted according to the 1995 Declaration of Helsinky as revised in Edinburgh in 2000. Study was approved by the Ethics Committee of AOU City of Science and Health, Turin (protocol number: CS2/366).

2.3. Materials and methods

According to our aims all participants were administered the same battery of psychometric tests investigating personality and psychopathology characteristics: The Temperament and Character Inventory (TCI), The Eating Disorder Inventory-2 (EDI-2), The Binge Eating Scale (BES), The State-Trait Anger Expression Inventory (STAXI), The Symptom Checklist-90 (SCL-90), The Beck Depression Inventory-II (BDI-II), The Parental Bonding Instrument (PBI), the Attachment Style Questionnaire (ASQ) and the Childhood Trauma Questionnaire (CTQ).

2.3.1. The Temperament and Character Inventory

(TCI) (Cloninger et al., 1994) provides a clinical description and classification of different personality traits, relying on Cloninger's psychobiological model. There are four scales for temperament: Novelty Seeking (NS), Harm Avoidance (HA), Reward Dependence (RD, Persistence (P) and three scales for character: Self Directedness (SD; Cooperativeness (C) and Self-Transcendence (ST). According to literature, the percentile distribution above 67% and under 33% has to be considered abnormal (Cloninger et al., 1994). Concerning reliability and validity, its psychometric properties support its clinical usefulness in the assessment of personality psychopathology (Fossati et al., 2007).

2.3.2. The Eating Disorder Inventory-2

(EDI-2) (Garner, 1991) is a self-administered 91-item questionnaire that evaluated different psychological and behavioral characteristics, typical of eating disordered patients. It consists of 11 scales: Drive for Thinness, Bulimia, Body Dissatisfaction, Ineffectiveness, Perfectionism, Interpersonal Distrust, Interoceptive Awareness, Maturity Fears, Ascetism, Impulse Regulation and Social Insecurity. The examinee responds to 91 simple questions on a 6-point Likert scale ranging from *Never* to *Always*.

2.3.3. The Binge Eating Scale

(BES) (Gormally et al., 1982) focuses on the loss of control and the difficulty to adjust the relationship with food. It is a self-administered questionnaire comprised of 18 items, specifically designed for the assessment of binge-eating severity. Clinical cutoff is fixed at 16.

2.3.4. The State-Trait Anger Expression Inventory

(STAXI) (Comunian and Spielberger, 1992) provides a measure of the experience and expression of anger, evaluating their different components. It consists of six scales: State Anger, Trait Anger (divided into two subscales Trait Anger Temperament and Trait Anger Reaction), Anger Expression-In, Anger Expression-Out, Anger Expression Control and Anger Expression. Items are rated on a 4-point Likert response set, evaluating the intensity of angry feeling and frequency of anger experience, expression, suppression or control.

2.3.5. The Symptom Checklist-90

(SCL-90) (Derogatis, 1977) is a self-administered questionnaire consisting of 90 items, aimed at evaluation of psychopathology in psychiatric patients. It considers nine primary symptom dimensions (Somatization, Obsessive-Compulsive, Interpersonal Sensitivity, Depression, Anxiety, Hostility, Phobic Anxiety, Paranoid Ideation, Psychoticism). The examinee responds to 90 simple questions on a 5-point Likert scale ranging from *Never* to *Always*. It also provides an overall score indicating the overall level of psychopathology. According to literature, its psychometric characteristics are appropriate to be used as an instrument to assess a psychopathological profile (Rytilä-Manninen et al., 2016).

2.3.6. The Beck Depression Inventory-II

(BDI-II) (Beck et al., 1996) is a questionnaire that detects the presence of depressive symptoms and it's largely used to assess the severity of depression symptoms; it allows to distinguish the presence of Somatic and cognitive-affective symptoms. Clinical cutoff is fixed at 16.

2.3.7. The Attachment Style Questionnaire

(ASQ) (Feeney et al., 1994) proposes a series of 40 multiple-choice items. It is used for the evaluation of the current attachment style and allows to differentiate safe from insecure attachment. The parameters considered are represented by Confidence, Discomfort with closeness, Relationships as secondary, Need for approval, Preoccupation with relationships. The examinee responds to 40 simple questions on a 6-point Likert scale ranging from totally agree to totally disagree. ASQ shows adequate reliability and good validity according to Feeney et al. (1994).

2.3.8. The Parental Bonding Instrument

(PBI) (Parker et al., 1979) is a questionnaire comprised of two scales termed 'care' and 'overprotection' or 'control', and measure fundamental parental styles as perceived by the child. The measure is 'retrospective', meaning that adults (over 16 years) complete the measure for how they remember their parents during their first 16 years. The examinee responds to 25 simple questions on a 4-point Likert scale ranging from true to false concerning mother and father.

2.3.9. Childhood Trauma Questionnaire Short Form

(CTQ-SF) (Bernstein et al., 2003) is a self-administrated questionnaire that is used to evaluate childhood or adolescent abuse and neglect. The examinee responds to 28 simple questions on a 5-point Likert scale ranging from Never True to Very Often True. The questionnaire contains five subscales, three assessing abuse (Emotional, Physical, and Sexual) and two assessing neglect (Emotional and Physical). Each subscale ranges from a score of 5 (no history of abuse or neglect) to a score of 25 (very extreme history of abuse and neglect), four different severity levels have been considered for statistical purposes: 1) none to minimal; 2) low to moderate; 3) moderate to severe; 4) severe to extreme.

Reliability and validity of the CTQ, including good corroboration with independent data have been found (Bernstein and Fink, 1998).

2.4. Statistical analyses

The ANOVA test was applied to sociodemographic (e.g. age, years of education) and clinical (BED) variables, while the $\chi 2$ test was applied to gender distribution to explore the difference across participants with obesity, either with (BED) or without a diagnosis of BED (OB) and healthy participants (HS). A multiple comparisons with Tukey's HSD analysis was applied to significant variables. Results are shown in Table 1. Since unequal sample sizes can affect the homogeneity of variance assumption, the homogeneity of the variance was tested with the Levene's test performing the ANOVA analysis.

The ANOVA test was then applied only to CTQ subscales between OS (*whole group of patients with obesity)*, BED, OB and HS in order to evaluate differences across the different groups of obese individuals. A multiple comparisons with Tukey's HSD analysis was then applied to significant variables according to ANOVA. Results are shown in Table 2.

Since no sociodemographic variable differed between groups, the ANOVA test was then applied to psychopathological and personality variables across OB, BED and HS samples. A multiple comparisons with Tukey's HSD analysis was then applied to significant variables according to the ANOVA. Since very unequal sample sizes can affect the homogeneity of variance assumption, the homogeneity of the variance was tested with the Levene's test performing on all the ANOVA analysis. Variables were considered significant with $p \leq 0.001$ to avoid type II errors due to the high number of variables. Results are shown in Table 3.

Pearson's correlation was performed separately in OB and in BED to explore the relationship between psychopathological and personality characteristics with childhood traumatic experiences.

Based on the significant results obtained with Pearson's correlation two multiple linear regression analyses were performed respectively in OB and BED separately using emotional neglect and emotional abuse as independent variables and psychopathological and personality measures as dependent ones. Results are shown in Tables 3 and 4. In consideration of the variable reduction and of the explorative nature of the study the statistical significance was set at a value of $p \leq 0.01$.

Data analysis was performed with the IBM SPSS Statistics 21.0 (IBM Corporation, Armonk, New York) and Microsoft Excel (Microsoft Corporation, Redmond).

3. Results

3.1. Sociodemographic and clinical characteristics of the sample

No significant differences were found between OB, BED and HS as regards age ($p < 0.588$) and educational level ($p < 0.554$). Gender distribution did not differ significantly across OB, BED and HS (BED: 84% F, 16% M; OB: 77% F, 33% M; HS: 67% F, 33% M). BMI differed significantly across subgroups ($p < 0.000$) (Table 1).

3.2. CTQ differences between OS, BED, OB and HS

Comparing the whole group of obese participants (OS) with HS we found significantly higher emotional abuse ($p < 0.001$), higher physical abuse ($p < 0.030$), higher sexual abuse ($p < 0.001$) and higher emotional neglect ($p < 0.001$) in the group of obese patients (Table 2).

Fig. 1 displays the distribution of the two groups within the severity score levels for each CTQ subscale. Emotional abuse ($\chi^2 = 39.04$; df = 26; $p < 0.001$), sexual abuse ($\chi^2 = 27.01$ df = 26; $p < 0.001$) and emotional neglect ($\chi^2 = 34.02$; df = 26; $p < 0.001$) displayed the highest between-group differences; a barely significant difference was found with regard to physical abuse ($\chi^2 = 20.08$; df = 26; $p < 0.03$), while no significant difference was found as concerns physical neglect ($\chi^2 = 20.09$; df = 26; $p < 0.08$).

Fig. 2 displays the distribution of the two groups within the severity score levels for each CTQ subscale. Emotional abuse ($\chi^2 = 25.03$; df = 36; $p < 0.001$) and emotional neglect ($\chi^2 = 27.05$; df = 36; $p < 0.002$) displayed the higher between-group differences, while no significant difference was found as concerns physical abuse ($\chi^2 = 18.67$; df = 36; $p < 0.092$), sexual abuse ($\chi^2 = 19.08$; df36 = ; $p < 0.058$) and physical neglect ($\chi^2 = 13.45$; df = 36; $p < 0.195$).

Table 1
Sociodemographical and clinical characteristics of the sample.

	BED (84)	OB (43)	HS (45)	F	Tukey's HSD
Age	42.81 ± 13.01	43.71 ± 11.91	41.53 ± 7.98	0.542	–
Education	12.85 ± 3.03	12.03 ± 2.05	13.08 ± 3.76	0.547	–
BMI	37.61 ± 6.50	40.03 ± 8.43	21.61 ± 2.98	117.56*	a, b > c
Gender	84% F (71) 16% M (13)	77% F (33) 23% M (10)	67% F (30) 33% M (15)	–	–

BED = patients with Binge Eating Disorder; OB = patients with obesity without BED; HS = Healthy subjects.
a = BED; b = OB; c = HS.
* $p < 0.000$.

Table 2
Comparison of CTQ subscales' scores.

	OS (127)	OB (43)	BED (84)	HS (45)	F	Tukey's HSD
Emotional abuse	9.98 ± 5.32	7.12 ± 3.00	11.45 ± 5.65	6.96 ± 2.52	3.145*	a,c > b,d
Physical abuse	6.47 ± 3.44	5.56 ± 1.2	6.94 ± 4.07	5.84 ± 1.54	n.s.	-
Sexual abuse	6.28 ± 3.14	5.58 ± 1.99	6.63 ± 3.55	5.38 ± 1.34	2.943*	a,c > d
Emotional neglect	12.09 ± 4.71	10.09 ± 4.1	13.11 ± 4.7	9.27 ± 4.16	3.785*	a,c > b,d
Physical neglect	7.88 ± 3.09	7.09 ± 2.91	8.29 ± 3.12	7.58 ± 2.92	n.s.	-

OS = whole group of patients with obesity; HS = Healthy subjects; BED = patients with Binge Eating Disorder; OB = patients with obesity without BED.
a = OS; b = OB; c = BED; d = HS.
* $p < 0$ 0.000.

Table 3
Personological and psychopathological differences between BED, OB and HS.

	OB (43)	BED (84)	HS (45)	F	Tukey's HSD
Childhood Traumatic Questionnaire (CTQ)					
Emotional abuse	7.12 ± 3	11.45 ± 5.65	6.96 ± 2.52	21.451	b > a,c
Emotional neglect	10.09 ± 4.1	13.11 ± 4.7	9.27 ± 4.16	13.396	b > a,c
Binge Eating Scale (BES)	10.02 ± 6.19	25.17 ± 9.16	6.83 ± 5.29	101.710	b > a,c
Temperament and Character Inventory (TCI)					
Harm avoidance	19.05 ± 5.08	23.75 ± 5.94	17.13 ± 6.71	20.051	b > a,c
Self directedness	26.68 ± 7.51	20.64 ± 7.65	32.29 ± 8.3	33.035	c > a > b
Cooperativeness	31.2 ± 5.52	28.69 ± 6.88	33.09 ± 5.3	7.691	c > b
Eating Disorder Inventory-2 (EDI-2)					
Drive of thinness	8.24 ± 5.63	12.12 ± 5.67	1.67 ± 3.19	60.560	b > a > c
Bulimia	2.33 ± 3.15	8.41 ± 5.06	1.13 ± 2.61	57.534	b > a,c
Body dissatisfaction	16.26 ± 8.1	18.79 ± 6.29	5.09 ± 6.06	62.212	a,b > c
Inefectiveness	4.31 ± 4.43	10.04 ± 6.28	2.11 ± 2.72	40.228	b > a,c
Interpersonal distrust	4.38 ± 3.78	5.8 ± 4.63	2.2 ± 2.03	12.538	a,b > c
Interoceptive awareness	4 ± 4.1	9.21 ± 5.86	1.13 ± 2.14	46.707	a,b > c
Ascetism	4.69 ± 2.36	7.52 ± 4.04	2.98 ± 1.84	31.584	a,b > c
Impulsivity	2.52 ± 4.11	6.02 ± 5.33	1.07 ± 1.45	21.809	b > a,c
Social insecurity	4.67 ± 3.73	7.52 ± 4.49	2.27 ± 2.78	27.196	a,b > c
State-trait Anger Inventory (STAXI)					
State-anger	12.79 ± 5.47	17.08 ± 9.54	11.60 ± 2.25	8.554	b > a,c
Trait-anger	18.89 ± 6.98	25.52 ± 12.61	19.69 ± 4.26	7.112	b > a,c
Symptom chechlist-90 (SCL-90)	66.56 ± 31.76	132.67 ± 55.58	52.04 ± 34.48	57.039	b > a,c
Parental Bonding Instrument (PBI)					
Maternal care	27.12 ± 7.66	21.23 ± 9.21	31.51 ± 5.57	25.034	a,b < c
Maternal overprotection	17.14 ± 7.64	18.25 ± 8.53	12.78 ± 7.28	6.940	a,b > c
Paternal care	23.4 ± 9.21	20.01 ± 9.38	27.67 ± 8.45	10.177	b < c
Paternal overprotection	15.48 ± 8.88	16.37 ± 9.47	9.44 ± 7.76	9.208	a,b > c
Attachement Style Questionnaire (ASQ)					
Trust	32.56 ± 7.54	28.63 ± 5.25	30.8 ± 3.84	7.105	a > b
Worry about relationships	25.4 ± 7.34	30.89 ± 8.55	25.62 ± 5.67	10.517	b > a,c
Need for approval	19.81 ± 5.41	24.32 ± 6.74	20.58 ± 4.34	10.493	b > a,c

HS = Healthy subjects; BED = patients with Binge Eating Disorder; OB = patients with obesity without BED. a = OB; b = BED; c = HS; all $p < 0.001$.

Table 4
Linear regression analysis between emotional abuse and psychopathological measures and between emotional neglect and psychopathological measures in OB.

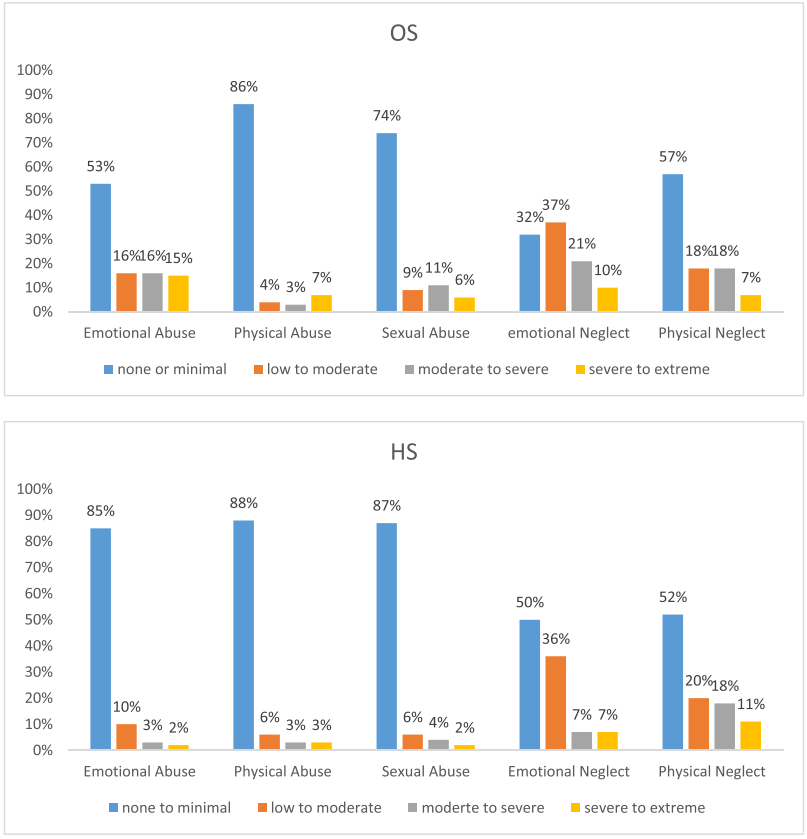
Independent variable **CTQ Emotional abuse**					
	Unstandardized coefficients		Standardized coefficients	*t*	***p***
Dependent Variables	B	Std. Error	Beta		
Symptom Check List-90 (SCL-90)	0.600	0.174	0.474	3.445	0.001
Maternal Care (PBI)	−1.160	0.356	−0.458	−3.257	0.002
CTQ Emotional Neglect					
	Unstandardized Coefficients		Standardized Coefficients	*t*	***P***
Dependent Variables	B	Std. Error	Beta		
Self Directedness (TCI)	−0.875	0.256	−0.480	−3.419	0.001
Symptom Check List-90 (SCL-90)	3.869	1.048	0.499	3.690	0.001
Maternal Care (PBI)	−0.994	0.250	−0.533	−3.982	0.000

CTQ = Childhood Traumatic Questionnaire.

3.3. ANOVA comparison of samples' characteristics

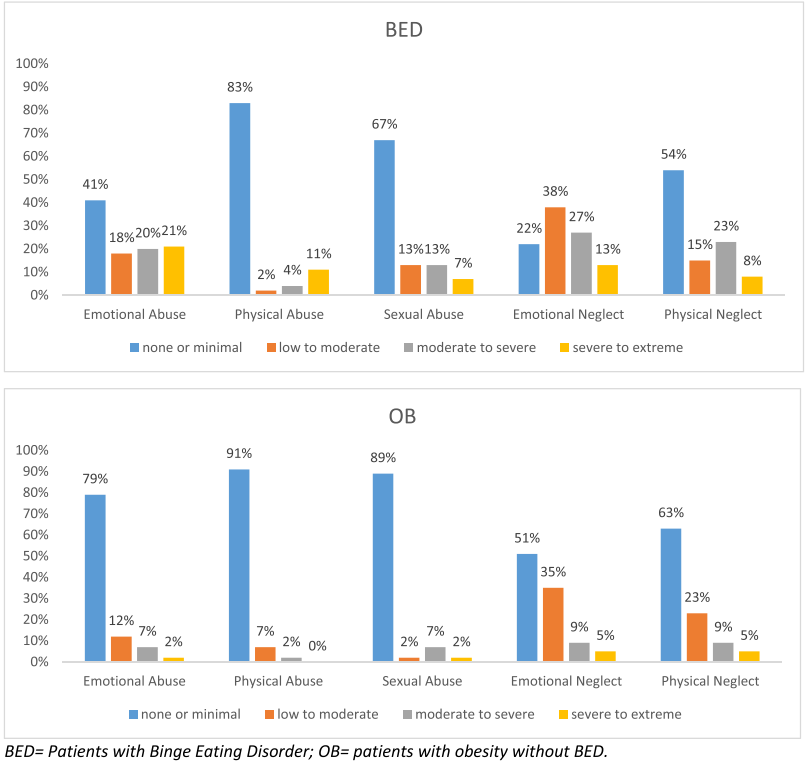
Table 3 shows differences in personality and psychopathological characteristics between OB, BED and HS. Concerning personality OB and BED showed lower self-directedness ($p < 0.001$) when compared to HS. BED group reported also higher harm avoidance ($p < 0.000$) and lower cooperativeness than HS and OB ($p < 0.001$)

Concerning eating psychopathology, as measured by the EDI-2, both OB and BED subgroups showed higher drive for thinness ($p < 0.001$), body dissatisfaction ($p < 0.001$), ineffectiveness ($p < 0.001$) and



OS= Whole group of patients with obesity; HS= healthy subjects.

Fig. 1. Distribution of the two groups (respectively OS and HS) within the severity score levels for each CTQ subscale.



BED= Patients with Binge Eating Disorder; OB= patients with obesity without BED.

Fig. 2. Distribution of the two groups (respectively BED and OB) within the severity score levels for each CTQ subscale.

interoceptive awareness ($p < 0.001$) when compared to HS. BED group showed also higher bulimia ($p < 0.001$), ineffectiveness ($p < 0.001$) and impulsivity than HS and OB groups ($p < 0.001$).

Concerning anger, as measured by the STAXI, no differences were found between OB and HS. Individuals with BED showed higher state anger ($p < 0.001$) and trait anger ($p < 0.0.001$) than HS and OB. The same result was found in general psychopathology, measured by SCL-90: subjects with BED were found to have higher levels of psychopathology than HS and OB ($p < 0.001$).

Concerning parental attitudes (PBI), BED and OB showed lower maternal care ($p < 0.001$), higher maternal overprotection ($p < 0.0.001$) and higher paternal overprotection ($p < 0.001$) when compared to HS. The BED subgroup also showed lower paternal care than HS ($p < 0.001$).

As concerns attachment (ASQ), participants with BED reported higher worry about relationships ($p < 0.001$) and need for approval ($p < 0.001$) than HS and lower trust than OB ($p < 0.001$).

3.4. Pearson's correlation between CTQ and significant differences between OB and BED

Concerning OB, emotional neglect was inversely related with self-directedness ($p < 0.001$) and maternal care ($p < 0.000$), and directly with body dissatisfaction ($p < 0.0.002$), and SCL-90 total score ($p < 0.001$). We found also an inverse correlation between emotional abuse and maternal care ($p < 0.002$).

Concerning the BED group we found a direct correlation between emotional abuse and interoceptive awareness ($p < 0.001$) and an inverse correlation between emotional neglect and maternal care ($p < 0.000$).

3.5. Multiple linear regression analysis between emotional neglect and emotional abuse subscales and personality and psychopathological variables in OB

Linear regression analysis with CTQ emotional abuse as independent variable showed the following significant results: a positive relation with SCL-90 total score (B = 0.474; $t = 3.445$; $p < 0.001$) and a negative relation with maternal care (B = −0.458; $t = -3.257$; $p < 0.002$) (Table 4).

Linear regression analysis with CTQ emotional neglect as independent variable showed the following significant results: a negative relation with self-directedness (B = −0.480; $t = -3.419$; $p < 0.001$) and with maternal care (B = −0.533; $t = -3.982$; $p < 0.000$) and a positive relation with SCL-90 (B = 0.499; $t = 3.690$; $p < 0.001$) (Table 4).

3.6. Multiple linear regression analysis between CTQ emotional neglect and emotional abuse and personality and psychopathological variables in BED

Linear regression analysis with emotional abuse as independent variable showed the following significant results: a positive relation with interoceptive awareness (B = 0.368; $t = 3.542$; $p < 0.001$) and with SCL-90 total score (B = 0.329; $t = 3.156$; $p < 0.002$) (Table 5).

Linear regression analysis with emotional neglect as independent variable yielded the following significant results: a positive relation with SCL-90 (B = 0.342; $t = 3.291$; $p < 0.001$) and a negative relation with maternal care (B = −0.539; $t = -5.649$ $p < 0.000$) (Table 5).

4. Discussion

As expected, a higher pattern of childhood traumatic experiences was demonstrated in obese participants compared to healthy controls. The total incidence and also the distribution of emotional and sexual abuses are significantly related to the clinical condition of obesity. These data confirm previous findings about the association between different types of abuse and obesity in adulthood suggesting that adverse life experiences during childhood may play a major role in the development of obesity (Hemmingsson et al., 2014).

4.1. Childhood traumatic experience, personality and psychopathology in obese patients

It has been proposed that adverse childhood experiences may play a role in favoring adult obesity inducing mental and emotional perturbations, maladaptive coping responses, stress and metabolic disturbances (Ehlert, 2013). Our results on psychopathology and personality characteristics of obese participants confirmed that obese individuals in general show more severe clinical profiles with respect to healthy population. Obese participants were also characterized by abnormal scores in personality profile, eating variables and psychopathological indices supporting the idea that obesity itself is a clinical condition that should be addressed by mental health professionals even if it is not yet considered a psychiatric condition (Fairburn et al., 2002). In particular obese patients showed lower self-directedness, a crucial character trait involved in the "core" personality diathesis of both eating and general psychopathology, further correlating obesity with mental disorders (Fassino et al., 2002, 2013; Gerlach et al., 2016).

Along with the emotional problems within obese participants both maternal and paternal care were significantly lower than those of healthy participants, while obese patients reported higher maternal and paternal overprotection. According to previous findings on obese and BED patients, these scores outline a type of 'affectionless control' parental behavior pattern which may be particularly risky for the development of obesity in the offspring (Amianto et al., 2016; Palmisano et al., 2017).

Our correlation analysis confirmed that in obese participants higher rates of childhood unfavorable emotional experiences are directly associated to lower maternal care, lower development of character, and with eating and general psychopathology. The fact that such a linear relationship is still detectable in adult obese participants may suggest a direct causal effect from emotional experiences in infancy to personality

Table 5
Linear regression analysis between emotional abuse and psychopathological measures and between emotional neglect and psychopathological measures in BED.

Independent variable CTQ Emotional abuse					
	Unstandardized coefficients		Standardized coefficients	*t*	***P***
Dependent Variables	B	Std. Error	Beta		
Interoceptive awareness (EDI-2)	0.381	0.107	0.368	3.542	0.001
Symptom check list-90 (SCL-90)	0.469	0.149	0.329	3.156	0.002
CTQ Emotional neglect					
	Unstandardized coefficients		Standardized coefficients	*t*	***P***
Dependent Variables	B	Std. Error	Beta		
Symptom check list-90 (SCL-90)	0.396	0.120	0.342	3.291	0.001
Maternal care (PBI)	−1.038	0.184	−0.539	−5.649	0.000

CTQ = Childhood Traumatic Questionnaire.

traits and psychopathology in adulthood, nevertheless the comprehension of the pathogenic mechanisms needs longitudinal studies.

4.2. The role of childhood traumatic experiences for BED expression

Our findings support the hypothesis that sexual abuse is not a specific risk factor for the development of BED; nevertheless, both emotional neglect and emotional abuse are more specific factors involved in the development of this eating disorder. Previous findings on individuals with BED showed higher levels of childhood trauma compared to controls but without significant differences with respect to different kinds of childhood trauma (Brewerton et al., 2014). Furthermore, studies focused on sexual and physical abuse showed that, within the BED population, an early onset of the disorder is associated with higher rates of molestation, physical assault and sexual abuse (Hymowitz et al., 2017). Other data in literature suggest that the rates of sexual and physical abuse in BED are more than two folds higher than in the general population, resembling those of the psychiatric population. Therefore, the contribution of sexual and physical abuse to the development and maintenance of BED *per se* is not completely clear, suggesting that they may represent nonspecific risk factors for mental suffering in general (Rohr et al., 2015).

Our findings confirm that childhood emotional abuse and neglect are linked to BED and obesity, and that the severity of emotional impairment represents a more specific risk factor for the development of BED than trauma itself. Notwithstanding, childhood emotional abuse and neglect are often not included in comprehensive explicative models of these health problems (Gluck et al., 2001). Recent researches investigated the utility to collect the history of emotional abuse for the prediction of BED incidence and the classification of individuals with and without BED (Dalle Grave et al., 2013). This study confirmed the importance of evaluating emotional abuse and self-perception as possible indicators of BED in individuals with emerging weight difficulties. Future studies should investigate whether these findings can be generalized to the clinical population, and the utility of addressing BED and self-perception in the therapeutic interventions for BED and obesity (Gluck et al., 2001).

4.3. Personality and psychopathology features of obese participants with and without BED in relationship with childhood traumatic experiences

Obese participants with BED showed higher harm avoidance, lower self-directedness and lower cooperativeness than OB. These data confirm previous results supporting a higher risk of personality disorders in BED individuals (Leombruni et al., 2014; Palmisano et al., 2017).

Participants with BED reported also higher bulimia, ineffectiveness and impulsivity than OB confirming previous research about the existence of a specific “psychopathologic core” of BED patients (Segura-Garcia et al., 2014). These results, according to recent DSM-5 classification, underline that BED is a clear and distinct psychiatric condition characterized by dysfunctional eating behavior with different psychopathological features with respect to obesity alone (Amianto et al., 2016).

According to previous findings on attachment in adult relationships, BED participants displayed less trust in others, more relational anxiety, more dependence in relationships and an excessive need for other's approval. Attachment style, in particular need for approval, combined with specific personality and psychopathology features has been demonstrated as one of the core element of eating disorders (Abbate-Daga et al., 2010; Turner et al., 2009). Some research suggested that self-criticism and need for approval are potential mechanisms through which certain forms of childhood maltreatment may be associated with body dissatisfaction in BED patients (Dunkley et al., 2010).

On the other hand obese participants with BED displayed lower maternal and paternal care. This datum is strictly related to the finding of higher emotional neglect in these participants confirming that careless parents may predispose to the development of obesity in general (Palmisano et al., 2017).

Taken together, these findings on personality and psychopathology features suggest that in non–BED obese patients a better family context characterized by less emotional traumatic experiences could act as protective factor for the development of character traits, severe general psychopathology and, definitely, act as a protective factor for the development of an eating disorder (Davis et al., 2013).

In BED patients, instead, the lower levels of parental care may have produced greater confusion and uncertainty in responding to the higher levels of unfavorable emotional experiences, thus favoring a lower character development, higher psychopathology expression and higher difficulty in identifying the sensations of hunger and satiety distinguishing them from other emotions. This confusion may represent the core of the typical binge eating behavior as discussed in a recent review on this issue (Kittel et al., 2015). It seems that emotional traumatic experiences could play a very specific role in BED pathogenic mechanism acting as a possible mediator between parental psychopathology and environmental risk factors for the development of an adult psychiatric condition (Sachs-Ericsson et al., 2012).

4.4. Conclusions

The present study confirms the association between all types of abuse and adult obesity, supporting that adverse emotional experiences during childhood play a major role in the development of obesity (Afifi et al., 2017).

To the best of our knowledge this is the first study that explores how the different types of childhood traumatic experiences may have played a different role not only with respect to obesity but also to BED. In particular, while most studies focused on the association between eating disorders and sexual and physical abuse this study revealed that emotional abuse or is more harmful than other forms of abuse. Indeed, our study points out that while obesity is related to childhood traumatic experiences in general, BED disorder is specifically related to emotional neglect and emotional abuse, and not to physical or sexual abuse.

Our results suggest that obesity itself is a condition which strictly resembles that of an eating disorder and hence needs a multidisciplinary therapeutic approach in which psychological and psychopharmacological treatments may heavily influence the prognosis of the disease and thus potentially reduce therapeutic costs (Amianto et al., 2011;Bomberg et al., 2017).

In particular specific therapeutic interventions that focus on the elaboration of emotional components of traumatic experiences (e.g. EMDR therapy) (Bloomgarden and Calogero, 2008) need to be specifically explored for BED treatment, in which these approaches have been the subject of much debate.

4.5. Limitations

A significant limitation of this study, which need future replications, is the relatively small number of patients and the predominance of female patients: a higher number of male participants would allow us to investigate gender differences in experiencing and processing emotional neglect and traumatic experiences. In addition, the clinical sample was selected among those referring to an eating disorders treatment center, therefore, may be not completely representative of the whole obese population. In fact, this explains the higher frequency of BED participants among recruited sample, which is inconsistent with the real incidence of BED respect to non-BED participants. Moreover, it could also be speculated that obese participants with childhood trauma experiences are more likely to seek psychiatric support than not abused patients. Finally, the research on traumatic experience was conducted on adult participants using self-report questionnaire, thus a recall bias of an effort-after meaning bias cannot be excluded.

Acknowledgements

The authors warmly thank Dr. Enrica Marzola for her help in draft revision.

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European Psychiatry 45 (2017) 198–206

Contents lists available at ScienceDirect

European Psychiatry

journal homepage: http://www.europsy-journal.com

Original article

Naturalistic follow-up of subjects affected with anorexia nervosa 8 years after multimodal treatment: Personality and psychopathology changes and predictors of outcome

F. Amianto *, A. Spalatro, L. Ottone, G. Abbate Daga, S. Fassino

Department of Neuroscience, Psychiatry section, AOU Cittá della Salute e della Scienza di Torino, Turin, Italy

ARTICLE INFO

Article history:
Received 6 April 2017
Received in revised form 20 July 2017
Accepted 21 July 2017
Available online 3 August 2017

Keywords:
Anorexia nervosa
Multimodal treatment
Personality
Psychopathology
Psychotherapy
Predictors of outcome

ABSTRACT

Background: Eating disorders (EDs) are serious mental illnesses of growing clinical and social impact. Despite their severity, there is still no satisfactory evidence-based treatment. Follow-up investigations are the most reliable studies to enlighten long-term outcome predictors and modifiers.
Methods: In total, 59 subjects affected with anorexia nervosa were assessed 8 years after their admission into an outpatient multimodal treatment program for eating disorders. The follow-up changes in diagnostic criteria were compared with Chi-square test. Improved and not-improved subjects were compared. Clinical, personality and psychopathology features between T0 and T1 were compared with *t*-test for repeated measures. Correlation between T0 features and changes at T1 in personality and psychopathology features were assessed.
Results: The rate of complete remission was 42%, an overall rate of 67.8% improved, a rate of 18.6% worsened. Concerning personality, a significant decrease of harm avoidance and increase in self-directedness were evidenced. Interoceptive awareness, drive for thinness, bulimia were significantly reduced at follow-up. Many T0 personality facets were related to personality and psychopathology improvement at follow-up.
Conclusion: Multimodal treatment encompassing psychiatric, nutritional and psychological approaches is at the moment the most reliable approach for the treatment of moderate to severe anorexia nervosa with a discrete rate of improvement. Some personality and psychopathology characteristics may represent specific factors which favor resistance and impair improvement. Future approaches should consider the personalization of therapeutic approach according to these features.

1. Introduction

Anorexia nervosa (AN) is a group biologically-based serious mental illness of growing clinical and social impact due to its increasing prevalence in general population, and to its long and severe course, associated to high rates of chronicity, mortality and relapse [1–4].

Current follow-up studies on AN are limited in number, hampered by dropout rates, sample width, and heterogeneity, and also affected by a lack of consistence about definitions of recovery, remission and relapse [5]. According to literature studies published in the last ten years, AN course and outcome show a huge heterogeneity [6]. Remission rates appeared to be related with follow-up duration, with global EDs remission rates around 48.7% at 2.5 years follow-up [7]. Nevertheless, it is frequent the diagnostic crossover, and there is a heavy influence of complicating factors on outcome [8].

The AN shows the highest time to obtain remission among other eating disorders (EDs) [7,8]. Remission rates for AN are 37.1% after 2.5 years, with partial remission but favorable outcome in 68.6% of patients [7], and from 52.1% to 53.9% after 6 years [9]. These results are maintained at 12 years follow-up [10]. Binge-purging subtype of AN showed lower recovery rates than restricter subtype [7]. Studies with more restrictive criteria, that consider remission as stable absence of any eating symptom and maintenance of normal BMI for almost 3 years, showed considerably lower remission rates, around 15% in AN at 12 years follow-up [5]. Transitions from AN to full criteria BN are less frequent (cumulative probability across studies around 2:1) and crossover from BN to AN are unlikely (cumulative probability around 13:1) [8].

* Corresponding author. Neurosciences Department, Via Cherasco, 11, 10126 Turin, Italy.
E-mail address: federico.amianto@unito.it (F. Amianto).

http://dx.doi.org/10.1016/j.eurpsy.2017.07.012
0924-9338/

In addition to the heterogeneity of the findings, a major limit of follow-up studies is that they are mostly based on objective symptoms and body weight [11–13] while emotional and behavioral aspects are often neglected, despite evidences that residual emotional and psychosocial impairments increase relapse risk [14–17].

To provide an overall assessment of the functioning of the patients along with the comorbidities of their eating disorders may be relevant to the evaluation of its therapeutic needs, and in determining its course and outcome [11,18].

Personality traits have proven to influence EDs onset, maintenance and prognosis [4,17,19–22]. Nevertheless, the study of their changes in time has been largely neglected by current follow-up studies [23]. According to Cloninger's model, EDs are characterized by peculiar personality profiles. The dimensional approach of Cloninger's model investigates seven personality traits and the Temperament and Character Inventory is an instrument of evaluation that has been used previously to deepen the knowledge about personality traits of different psychiatric patients with great reliability in the scientific field [24]. AN patients show lower Novelty Seeking (NS) and Cooperativeness (C) and higher Persistence (P) than general population [21,24,25] and with respect to healthy siblings of the same family [26]. Psychological treatments modify personality traits, driving EDs patient's closer to healthy controls [21,27]. HA, P, SD and ST significantly change after psychological treatments, independently from ED diagnosis and BMI changes [28], with an overall reduction of HA and ST and an increase of RD, SD and C [29,30]. Nevertheless, recovered patients with AN still show higher HA and higher P [31] and lower SD [32] than healthy controls.

Our study provides a prospective 8-years investigation on a sample of AN patients treated with an integrate treatment model. As an adjunct to clinical outcome variables (e.g. the modification of eating attitudes and behaviors, and of diagnostic criteria), the assessment of the present research also encompasses the changes in TCI personality traits, in EDI-II eating psychopathology, along with in general psychopathology. Finally, the present research also explores the relationship between changes in personality traits and those in eating and general psychopathology. The hypothesis is that personality changes may play a role in the long-term outcome of the disease. Clinical and therapeutic implications of our results in the context of eating disorders treatment will be discussed.

2. Methods

We recruited a sample of 264 female outpatients from Eating Disorder Pilot Center of the Department of Neuroscience (CPR DCA), University of Turin, first evaluated between January 1st, 2003 and December 31st, 2005 (T0 time of this study) who received a full diagnosis of AN according to DSM-IV or DSM-IV-TR. The diagnosis was established by a psychiatrist during the first examination at the intake in the center (T0) and at the follow-up point 8 years later (T1) using the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition (SCID-I) [33]. Other inclusion criteria were (1) the absence of previous or current full criteria comorbidities assessed both at T0 and between T0 and T1 with the SCID-I; (2) the lifetime absence of a psychosis or another major psychiatric diseases; (3) patients have been treated for at least 2 years at Regional Pilot Center for Eating Disorders with full adherence to standard therapeutic protocol: psychiatric visits once/month; diet-therapy follow-up once/month and Brief-Adlerian Psychodynamic Psychotherapy (B-APP) of 20 sessions (once/week) according to the manualized model of Fassino and coworkers [34].

All patients gave their informed written consent. The Institutional Review Board of "AOU Città della Salute e della Scienza di Torino" approved this study.

Among 264 eligible subjects, 121 were contacted to be enrolled in research while 143 were out of reach. Among these 33 refused to take part in the study for personal reasons and 29 they did not gave back the package of tests or filled them incorrectly. Finally, 59 subjects with AN participated into the study.

2.1. Outcome measures

Clinical data (height, weight, BMI and minor psychiatric symptoms) of participants were collected at their first access into the center (T0) and at the time of follow-up (T1), and in both time points they were assessed with a battery of psychometric tests including: Temperament and Character Inventory (TCI) [35]; Eating Disorder Inventory-2 (EDI-2), [36]; The Body Shape Questionnaire (BSQ) [37]; The Binge Eating Scale (BES) [38]; Beck Depression Inventory (BDI) [39].

2.2. Statistical analysis

The sample recruited for the follow-up study was compared with the whole sample of patients admitted in the Outpatient Service in the period of the follow-up using the ANCOVA corrected for age, age of onset and years of study to evidence the level of representativeness of the final follow-up sample. A $P < 0.001$ level of significance was applied to this analysis.

The rates of each diagnosis at T0 and at T1 were compared with the χ^2 test.

The *t*-test for repeated measures was applied to the clinical measures, personality traits, eating psychopathology of whole sample. The diagnostic subgroups were not considered separately because of the numeric exiguity. The personality dimensions showing significant changes at follow-up were referred to the percentile distribution of the normative sample [35].

Based on the clinical evolution the subjects were subgrouped into four groups: (1) "healed" group (i.e. who did not display the DSM 5 criteria for an eating disorder at T1); (2) "improved" group (rise of the BMI higher than 1 point with respect to T0); (3) "stable" group (those who did not worsen); (4) "worsened" group (those who displayed a worsening of the BMI).

The four groups were compared at T0 with one-way ANOVA to evidence possible prognostic factors. A *t*-test for repeated measures between T0 and T1 was performed separately between the not-worsened (healed + improved + stable) and the worsened groups to evidence risk factors for long-term worsening.

In order to evidence the relationship between the changes in personality and psychopathology traits and baseline features they were computed the delta scores (T1 minus T0 score) for each variable which displayed a significant change at follow-up. They were performed two linear regression analysis: first they were used the T0 personality traits as independent variables and the deltas as dependent ones. Second they were used the deltas of personality traits as independent variables and the deltas of clinical and psychopathology measures as dependent ones.

Statistical analysis were carried out with SPSS 17 for Windows. In consideration of the explorative and naturalistic nature of the follow-up study it was considered a $P < 0.05$ for significance threshold.

3. Results

No significant difference was found with ANCOVA between the follow-up and the sample recruited at T0.

3.1. Clinical course and diagnostic migration

Fig. 1 displays the diagnostic distribution of the sample at T0 and the diagnostic distribution at T1. In total, 42.4% of the sample reaches a healthy condition. Eating disorder not otherwise specified emerged at the follow-up. The rate of ANR diagnosis is stable while the ANP and ANBP diagnoses significantly reduced. In total, 67.8% of subjects improved, 81.4% of subjects did not worsen, and 18.6% had an unfavorable outcome.

Fig. 2 shows the courses of the different diagnostic groups. Chi-square test evidences that they are significantly different ($\chi^2 = 14.041$; df = 6; $P < 0.029$). ANR subjects display the highest rate of worsening but also of healing. Purging subjects improve more than the other groups but reach the healthy condition less frequently than ANR subjects. Bingeing-purging subjects display a pattern similar to that on ANR subjects but with less healthy outcomes.

Table 1 displays the evolution of each diagnostic subgroup. The Chi-square analysis did not reach the significance, nevertheless the initial diagnosis tend to migrate more frequently towards remission for ANR subjects, and towards ANR subtype for ANP and ANBP. ANR subjects more frequently maintain the same diagnosis after 8 years, followed by the ANBP.

3.2. Changes between T0 and T1 among clinical, personality and psychopathology measures in the whole group

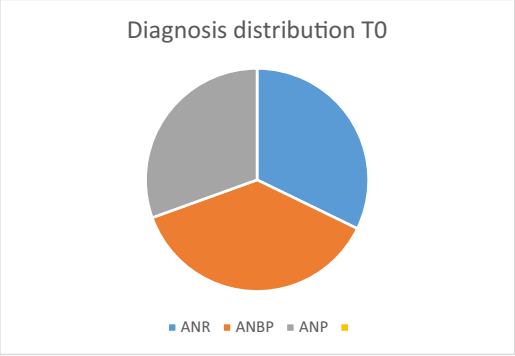
Table 2 displays the clinical, personality and psychopathology changes at follow-up. They are evident significant improvement of overall BMI ($P < 0.000$), purging behavior ($P < 0.000$) and also laxative use ($P < 0.004$).

The sample evidenced an improvement in Harm Avoidance ($P < 0.005$; form 95° to 85° percentile), and Self-directedness ($P < 0.000$; form 9° to 25° percentile), with particular improvement of Resourcefulness ($P < 0.001$), Purposefulness ($P < 0.005$), Responsibility ($P < 0.008$) and Fear of Uncertainty ($P < 0.01$).

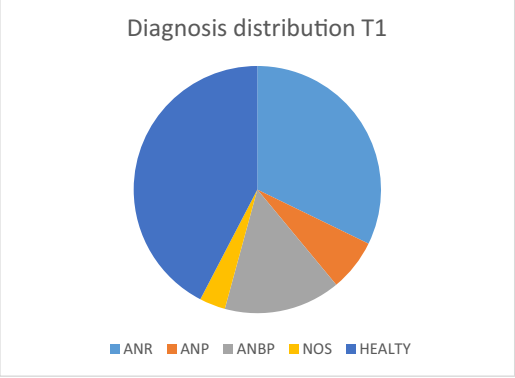
Four psychopathology traits improved: interoceptive awareness ($P < 0.000$), drive for thinness ($P < 0.001$), bulimia ($P < 0.001$), impulsiveness ($P < 0.004$), and interpersonal distrust ($P < 0.005$). Both the BSQ ($P < 0.004$) and the BES ($P < 0.009$) evidenced a significant improvement.

3.3. T0 comparison between the four outcome subgroups

Table 3 displays the T0 comparison between the four outcome subgroups. The healed group displays lower anticipatory worry and pessimism ($P < 0.011$), harm avoidance ($P < 0.006$), body



Diagnosis at T0	N°	Rates
Restricter Anorexia (ANR)	19	32.2 %
Purging Anorexia ANP (ANP)	18	30.5 %
Binge-Purging Anorexia (ANBP)	22	37.3 %
Total	59	100%



Diagnosis at T1	N°	Rates
Restricter Anorexia (ANR)	19	32.2%
Purging Anorexia ANP (ANP)	4	6.8 %
Binge-Purging Anorexia (ANBP)	9	15.3 %
Eating Disorder NOS	2	3.4%
Healthy	25	42.4%
Total	59	100%

Clinical Course	N°	Rates
improved	40	67.8 %
stable	8	13.6%
worsened	11	18.6%
Total	59	100%

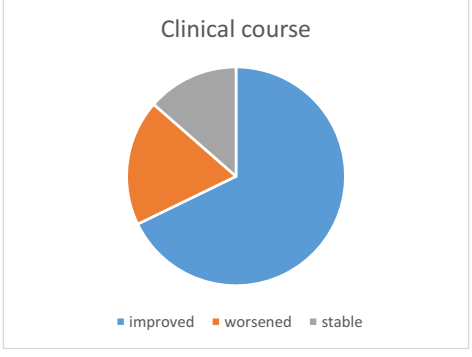
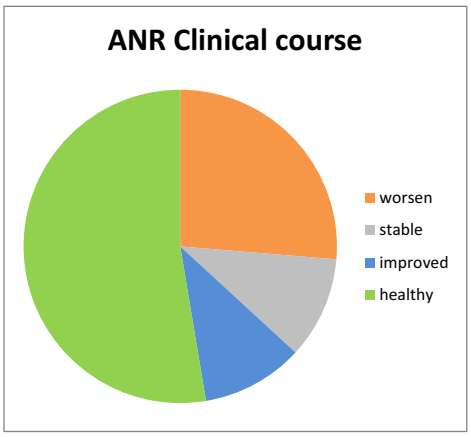
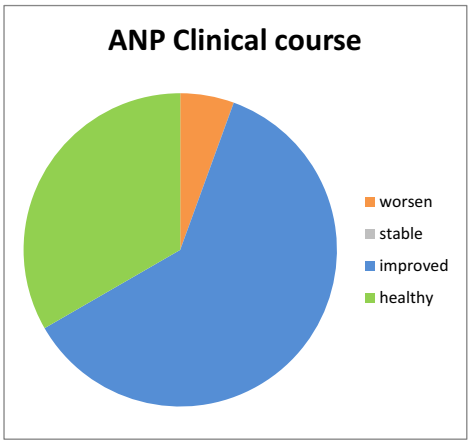


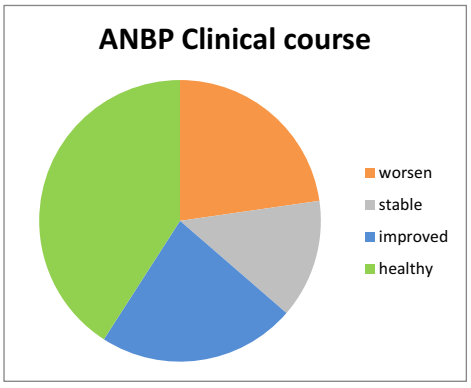
Fig. 1. Diagnosis at T0 and follow-up with clinical course.



ANR Clinical Course	N°	Rates
healthy	10	52.6%
improved	2	10.5%
stable	2	10.5%
worsen	5	26.3%
Total	19	100%



ANP Clinical Course	N°	Rates
healthy	6	33.3%
improved	11	61.1%
stable	0	0.0%
worsen	1	5.6%
Total	18	100%



ANBP Clinical Course	N°	Rates
healthy	9	40.9%
improved	5	22.7%
stable	3	13.6%
worsen	5	22.7%
Total	22	100%

Fig. 2. Distribution of the original diagnoses among improvement categories.

Table 1
Distribution of the anorectic subtypes at follow-up.

Diagnosis at T0	Diagnosis at T1 (follow-up)					Total
	Healed	ANR	ANP	ANBP	ED NOS	
Restricter anorexia						
No.	10 (52.6%)	6 (31.6%)	1 (5.3%)	2 (10.5%)	0 (0.0%)	19 (100.0%)
% of the total	16.9%	10.2%	1.7%	3.4%	0.0%	32.2%
Purging anorexia						
No.	6 (33.3%)	8 (44.4%)	2 (11.1%)	2 (11.1%)	0 (0.0%)	18 (100.0%)
% of the total	10.2%	13.6%	3.4%	3.4%	0.0%	30.5%
Binge-purging anorexia						
No.	9 (40.9%)	5 (22.7%)	1 (4.5%)	5 (22.7%)	2 (9.1%)	22 (100.0%)
% of the total	15.3%	8.5%	1.7%	8.5%	3.4%	37.3%
Total						
No.	25 (42.4%)	19 (32.2%)	4 (6.8%)	9 (15.3%)	2 (3.4%)	59 (100.0%)

ANR: restricter anorexia nervosa; ANP: purging anorexia nervosa; ANBP: bingeing-purging anorexia nervosa; EDNOS: eating disorder not otherwise specified.

Table 2
Comparison between T0 and T1 variables in the whole group.

Clinical variables	T0 ($n = 59$) Mean ± SD	T1 ($n = 59$) Mean ± SD	t	P
Age	30.20 ± 8.89	37.46 ± 8.56	−30.69	0.000
BMI	16.06 ± 0.94	17.54 ± 2.16	−5.58	0.000
Purging behavior (per day)	3.70 ± 5.51	0.69 ± 2.14	4.94	0.000
Laxative use (per day)	0.31 ± 0.46	0.09 ± 0.28	3.03	0.004
TCI				
Harm avoidance (HA)	24.24 ± 6.99	21.48 ± 6.95	2.94	0.005
Fear of uncertainty (HA1)	7.94 ± 2.98	7.06 ± 2.60	2.75	0.010
Self-directedness (SD)	21.12 ± 8.17	26.47 ± 7.98	−5.36	0.000
Purposefulness (SD1)	3.76 ± 2.42	4.97 ± 2.41	−2.98	0.005
Responsibility (SD2)	3.73 ± 1.93	4.65 ± 1.92	−2.83	0.008
Resourcefulness (SD3)	2.06 ± 1.63	2.90 ± 1.77	−3.79	0.001
EDI-2				
Drive for thinness	10.25 ± 8.17	7.08 ± 6.53	3.49	0.001
Bulimia	4.29 ± 5.41	2.51 ± 4.10	3.49	0.001
Interpersonal distrust	6.29 ± 4.86	4.49 ± 4.26	2.94	0.005
Interoceptive awareness	10.12 ± 7.01	5.54 ± 6.40	5.01	0.000
Impulsiveness	6.68 ± 6.05	4.08 ± 4.29	3.11	0.004
Social insecurity	7.61 ± 4.84	6.10 ± 4.47	2.636	0.011
BES	17.64 ± 12.13	12.96 ± 11.51	2.807	0.009
BSQ	102.76 ± 43.32	76.96 ± 53.81	3.11	0.004

dissatisfaction ($P < 0.029$) and binge eating ($P < 0.006$) with respect to the stable group. It also displays higher attachment with respect to improved subgroup ($P < 0.016$).

3.4. t-test at T0 and t-test for repeated measures in the not-worsened VS worsened subgroups

Higher levels of drive to thinness ($t = 2.207$; df = 57; $P < 0.031$) and body dissatisfaction ($t = 2.278$; df = 57; $P < 0.026$) and higher levels of BSQ scores ($t = 2.168$; df = 57; $P < 0.039$) characterized the worsened group.

The changes between T0 and T1 evidence a non-significant improvement in bingeing-purging behaviors coupled with a non-significant improvement in Self-directedness and at the BSQ are characteristic of the worsened group (Table 4).

3.5. Regression analysis between T0 personality features and delta scores of changed variables

Table 5 displays the linear regression analysis between the T0 personality features and the deltas of personality and psychopathology at T1. Many improvements in personality and psychopathology features are related with T0 personality features.

3.6. Regression analysis between delta scores of personality and clinical variables

BMI increases with the reduction in harm avoidance (HA) (B = 0.480; $t = 2.251$; $P < 0.033$), and the increase in resourcefulness (SD3) (B = 0.579; $t = 2.719$; $P < 0.011$). Vomiting decreases with the reduction in harm avoidance (HA) (B = 0.536; $t = 2.192$; $P < 0.037$); bulimia decreases with the increase in resourcefulness (SD3) (B = 0.514; $t = 2.071$; $P < 0.048$); body dissatisfaction decreases with the increase in responsibility (SD1) (B = 0.538; $t = 2.220$; $P < 0.035$); inadequacy decreases with the increase in purposefulness (SD2) (B = 0.518; $t = 2.159$; $P < 0.040$), interoceptive awareness decreases with the increase in responsibility (SD1) (B = 0.478; $t = 2.387$; $P < 0.024$).

4. Discussion

The present research followed-up 59 patients affected with anorexia nervosa enrolled in the Pilot Center for Eating Disorders eight years before for a multidisciplinary treatment. The direct comparison of the follow-up sample with the whole initial sample evidenced a good representativeness of the first with respect to clinical, personality and psychopathology measures.

4.1. Clinical course and diagnostic migration

The follow-up sample in its complex evidences a significant change in the diagnostic distribution after 8-years from the intake in the program for eating disorder treatment. A high rate of the sample displayed a complete remission of the anorexia nervosa, an in general about 70% of the subjects were improved compared to only the 19% which are worsened. This result is in line with the best outcomes reported by previous literature [7,9,40], and it underlines that the current standards of care, even though far from being optimal, gained a significant degree of effectiveness in the last ten years [41].

As concerns the diagnostic migration the most relevant evidence concerns the high number of subjects who become healthy (42.4%) with a complete absence of symptoms at follow-up. Another interesting result is the stability of the number of ANR diagnoses between T0 and follow-up, coupled with and the significant decrease of ANP and ANBP diagnoses. This datum apparently suggests a strong resistance of the subjects affected with ANR to healing. Instead, when the course of the disease is considered, it is evident that the subjects affected with RAN are both the subjects that more frequently heal but also worsen, while those who were affected with the purging form of AN display the higher resistance to a complete remission but also the lower rate of stability or worsening. In its complex the picture of the follow-up concerning the diagnostic migration and the rate of improvement related to initial diagnosis in our sample suggests that initial diagnosis does not represent a relevant prognostic factor as concerns the long-term improvement. This partially contrasts with recent literature which suggest that a diagnosis of bingeing-purging type of anorexia nervosa [42,43] or higher rate of bingeing-purging behaviors in general [44] represent negative prognostic factors for treatment outcome. This suggests that, more than being a specific negative prognostic factor for treatment outcome, the diagnosis of bingeing-purging behaviors needs a specific adjustment of treatment strategy with respect to the RAN diagnosis [45].

Table 3
T0 ANOVA comparison among outcome subgroups.

	Healed ($n = 25$) Mean ± SD	Improved ($n = 18$) Mean ± SD	Stable ($n = 5$) Mean ± SD	Worsened ($n = 11$) Mean ± SD	F	P	Post-hoc
HA1	6.3 ± 3.2	8.8 ± 2.0	10.8 ± 0.5	9.1 ± 2.0	4.415	0.011	Healed < stable
HA	21.4 ± 7.4	24.4 ± 6.8	32.0 ± 2.4	26.7 ± 4.1	4.589	0.006	Healed < stable
RD2	5.0 ± 1.9	1.2 ± 0.8	4.5 ± 2.4	4.1 ± 2.8	4.007	0.016	Healed > improved
BD	8.5 ± 7.4	8.7 ± 8.3	8.8 ± 8.2	11.6 ± 7.8	3.231	0.029	Healed < stable
BES	11.2 ± 7.3	23.0 ± 15.4	30.7 ± 10.1	25.0 ± 11.4	5.202	0.006	Healed < stable

HA1: anticipatory worry and pessimism; HA: harm avoidance; RD2: attachment; BD: body dissatisfaction; BES: Binge Eating Scale.

Table 4
t-test for repeated measures among non-worsened vs. worsened anorectic subjects.

Variable	Non-worsened ($n = 48$)				Worsened ($n = 11$)			
	T0 Mean ± SD	T1 Mean ± SD	*t*	*P*	T0 Mean ± SD	T1 Mean ± SD	*t*	*P*
Age	29.60 ± 7.92	36.94 ± 7.68	−40.89	0.000	32.91 ± 12.41	39.72 ± 11.85	−6.65	0.000
BMI	16.04 ± 0.95	18.18 ± 1.68	−8.92	0.000	16.01 ± 0.93	14.72 ± 1.75	4.07	0.000
Binge behavior	0.35 ± 0.48	0.12 ± 0.33	0.31	0.003	0.45 ± 0.52	0.55 ± 0.52	−0.43	0.676
Purging behavior	3.71 ± 5.72	0.56 ± 2.27	0.47	0.000	3.63 ± 4.71	1.27 ± 1.34	1.54	0.156
TCI								
Self-directedness	20.89 ± 8.53	26.46 ± 8.53	−5.02	0.000	22.09 ± 6.61	26.45 ± 5.24	−1.85	0.094
EDI-2								
Interoceptive Awareness	10.02 ± 7.14	5.90 ± 6.87	3.94	0.000	10.55 ± 6.71	4.00 ± 3.55	3.85	0.003
BSQ	95.95 ± 40.39	69.86 ± 52.51	3.08	0.005	128.83 ± 47.92	104.17 ± 54.44	0.97	0.377

Table 5
Regression analysis between T0 personality features and delta scores of changed variables.

Independent variables	Dependent variables	B	*t*	*p*
⋀ Vomiting	Compassion (C4) T0	2.068	2.771	0.039
	Total cooperativeness (C) T0	6.984	2.943	0.032
⋀ Anticipatory worry and pessimism (HA1)	Extravagance (NS3) T0	1.746	2.743	0.041
	(Disorderliness) NS4 T0	1.667	2.657	0.045
	Persistence (P) T0	1.015	2.891	0.034
	Attachment (RD3) T0	2.519	2.719	0.042
	Uninterested conscience (C5) T0	1.460	2.777	0.039
	Shyness with strangers (HA3) T0	1.739	2.942	0.032
⋀ Harm avoidance (HA)	Extravagance (NS3) T0	1.907	2.748	0.040
	Fear of uncertainty (HA2) T0	2.003	2.740	0.041
	Sentimentalism (RD1) T0	1.532	2.996	0.030
⋀ Purposefulness (SD2)	Attachment (RD2) T0	0.600	3.003	0.030
	Persistence (P) T0	0.554	2.931	0.033
	Purposefulness (SD2) T0	3.149	4.202	0.008
	Helpfulness (C3) T0	1.775	3.561	0.016
⋀ Resourcefulness (SD3)	Explorative activity (NS1) T0	0.830	2.718	0.042
	Extravagance (NS3) T0	1.518	3.350	0.020
	Persistence (P) T0	0.812	3.250	0.023
⋀ Drive to thinness	Highlighted second nature (SD5) T0	8.335	2.634	0.046
⋀ Inadequacy	Fatigability (HA4) T0	1.490	3.500	0.017
	Responsibility (SD1) T0	8.685	3.316	0.021
	Purposefulness (SD2) T0	5.374	3.470	0.018
	Self-acceptance (SD4) T0	9.677	3.435	0.019
	Highlighted second nature (SD5) T0	9.186	3.263	0.022
	Self-directedness (SD) T0	8.113	3.411	0.019
⋀ Interpersonal distrust	Extravagance (NS3) T0	1.661	2.821	0.037
	Disorderliness (NS4) T0	1.847	3.181	0.025
	Anticipatory worry and pessimism (HA1) T0	2.491	3.507	0.017
	Fear of uncertainty (HA2) T0	1.730	2.788	0.039
	Shyness with strangers (HA3) T0	1.796	3.283	0.022
	Fatigability (HA4) T0	1.250	3.530	0.017
	Sentimentalism (RD1) T0	1.275	2.938	0.032
	Persistence (P) T0	0.879	2.705	0.043
	Empathy (C2) T0	3.541	3.212	0.024
	Self-forgetfulness (ST1) T0	5.004	2.750	0.040
⋀ Interoceptive awareness	Extravagance (NS3) T0	1.666	2.830	0.037
	Disorderliness (NS4) T0	1.604	2.764	0.040
	Anticipatory worry and pessimism (HA1) T0	2.060	2.901	0.034
	Fatigability (HA4) T0	1.102	3.114	0.026
	Highlighted second nature (SD5) T0	6.327	2.702	0.043
	Empathy (C2) T0	3.811	3.458	0.018
	Transpersonal identification (ST2) T0	2.065	2.895	0.034
⋀ Impulsivity	Transpersonal identification (ST2) T0	2.126	2.974	0.031
⋀ Social insecurity	Fatigability (HA4) T0	1.644	3.453	0.018
	Responsibility (SD1) T0	7.673	2.619	0.047
	Empathy (C2) T0	3.866	2.609	0.048

4.2. Changes at follow-up in clinical, personality and psychopathology measures

Among the clinical variables considered at follow-up the BMI, the daily purging behaviors and the use of laxatives were significantly reduced in the whole sample. More resistant to change was the bingeing attitude which did not decrease significantly. This confirms the relevance of bingeing as a factor related to resistance as already evidenced by literature [44]. The mean BMI of AN subjects has significantly improved reaching the cutoff for the diagnosis of anorexia nervosa, while purging behaviors and the use of laxatives were reduced to levels near to the zero. This underlines that the multimodal treatment on the sample considered as a whole was effective to produce a remission

of the diagnosis of anorexia nervosa even in severely affected subjects (BMI = 16) [46], and that this change may be long-lasting in time [7,9].

The change in clinical symptoms was coupled with changes in both personality dimensions and psychopathology. In particular, both Self-directedness and three of its facets and Harm Avoidance significantly improved with treatment. These two features have been described as core personality traits of many axis I mental disorders [22,47] and also supposed to be related to frailty in personality structure [48] and they represent a core feature of the personality profile in anorexia nervosa.

4.3. The relationship between personality improvement and psychopathology changes

According to one of the hypothesis of the paper it is thus possible that at least partly the overall improvement of ED symptoms may be due to a development of the core personality features which have been evidenced at follow-up. The better adjustment produced by the change in these traits may reduce the suffering of the individual and his/her need for the expression of eating symptom. The correlation analysis partly supports this hypothesis. In fact, the correlation between T0 personality features and the follow-up improvement in clinical and psychopathological measures is very extensive. As an hypothesis, according to the conception of the anorexia nervosa as a disorder of the self [49–51] which is conceived as the integrating function between cognitive, emotional, relational, body and somatosensory functions of the individual [52] we may argue that the improvement in these personality traits may represent the expression of a better integration of the self which is accompanied by a better interoceptive awareness and reduced drive to thinness and bulimia.

4.4. Predictors of change and resistance

When the four outcome groups have been compared some personality and psychopathology features significantly distinguished each other, thus representing specific outcome predictors. In particular, the harm avoidance and the fear of uncertainty along with the binge eating scale were significantly lower in healed subjects when compared with stable ones. This suggests that the high harm avoidance represents a specific factor which obstacles the progression of the multimodal treatment towards healing. This dimension has been evidenced as a core trait in eating disorders [21] but also in a large range of other mental disorders [22,47]. It was already demonstrated a negative outcome predictor for depression [53] and present data seem to confirm its negative relevance also for the course of eating disorders. Since the present study, narcissistic personality traits were evidenced as the strongest predictors of stability in the short-term treatment in eating disorders [54], future research should explore the possible relationship between harm avoidance and narcissistic traits in this population.

The meaning of the BES scores as predictor of stability is more difficult to interpret, even though it may be related to the above mentioned literature evidences about the worse evolution of subjects affected with binge-purging anorexia with respect to those affected with restricter type [42–44]. A lower attachment distinguishes the healed and the improved subgroups, being a predictor of a more complete long-term resolution of the eating episode. Attachment has been claimed as a major component of the complex relational and intrapsychic dynamics affecting eating disorders [50]. Nevertheless, it is possible that during the multimodal treatment the differences in this feature may be vicariated by the attitudes of therapists who actively support patients to therapeutic alliance [55,56] until the reaching of an improvement. Finally, the rates of body dissatisfaction are the only predictors of worsening with respect to healing. Body dissatisfaction is a psychopathologic core feature of eating disorder, and it has been demonstrated as independently related to attachment [57]. Recently Grenon et al. [58] proposed a complex model relating this feature to parental bonds mediated by attachment anxiety and media internalization. The present finding suggests that this feature may represent the most relevant target for therapies addressing resistances in ED treatment [59], and that these may be centered on attachment dynamics [48].

When follow-up changes were compared between the non-worsened and the worsened subjects it emerged that only three changes between T0 and T1 were related to the different outcome. In the worsened group the purging behavior and the body shape score did not reduce significantly, while the self-directedness did not rise. This finding is very new and difficult to explain, nevertheless it could be related to the evidence of a better outcome for early onset anorexia nervosa with respect to late onset one [60] since the worsened sample displays a relatively lower age at intake. This issue deserves future exploration, since the meaning of relatively high self-directedness for eldest patients could be significantly different with respect to that which is gained during a multimodal treatment by younger subjects.

5. Conclusion

The present study presents some data concerning the outcome of multimodal treatment on a relatively small sample of anorectic subjects. It evidences an outcome which resembles that already presented by literature. The improvement in harm avoidance and self-directedness, along with many eating psychopathology features also supports the relevance of these already known core personality features in eating disorders. Nevertheless the wide but weak correlation between personality traits and clinical and psychopathology features suggests that the dynamics linking personality changes and clinical outcome are complex and possibly mediated by factors which should be further objects of study.

As new findings some predictors of outcome have been evidenced both as regards psychopathology and personality features. Moreover, the role of attachment as a personality trait, but also as a possible underlying factor to body dissatisfaction may represent a new suggestion for future research and psychotherapeutic approaches to overcome resistances.

5.1. Limitations

The main limitations of the present study concern the relative small number of subjects which reduces the possibility of further statistical exploration concerning clinical subgroups and may have reduced the strength of some performed analysis. Moreover, due to the follow-up nature of the study possible recruitment biases may have affected the recruited sample. The absence of a specific assessment of the relapse episodes during the period of follow-up reduced the information about clinical course of the subjects. Nevertheless, the assessment of personality and psychopathology features of recruited subjects with the same assessment instruments of the intake permitted a follow-up of personality and psychopathology features which adds some new evidences to existing literature.

Disclosure of interest

The authors declare that they have no competing interest.

Acknowledgements

The authors thank Dr. Barbara Iazzolino and Dr Carmen Settanta for their help in assessing the follow-up subjects.

The authors wish to acknowledge the fundings of San Paolo Bank Fundation and Cassa di Risparmio di Torino Bank Fundation given to the Professor Fassino for the support to the Pilot Center for Eating Disorders in the years 2005–2015.

Professor Amianto wish to acknowledge the National Eating Disorder Association (NEDA) for the "Charron Family" Grant given in 2005 for the research on families of subjects affected with eating disorders.

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Eating and Weight Disorders - Studies on Anorexia, Bulimia and Obesity (2019) 24:623–631
https://doi.org/10.1007/s40519-019-00690-z

ORIGINAL ARTICLE

Personality and psychopathology differences between bariatric surgery candidates, subjects with obesity not seeking surgery management, and healthy subjects

Amianto Federico[1] · Angela Valentina Spalatro[1] · Ilari Giorgio[1] · Marzola Enrica[1] · Giovanni Abbate Daga[1] · Fassino Secondo[1]

Received: 11 April 2018 / Accepted: 9 April 2019 / Published online: 6 May 2019

Abstract

Purpose To explore personological and psychopathological characteristics in individuals with obesity presenting for bariatric surgery compared with individuals with obesity not seeking bariatric surgery and healthy individuals to help clinician decision for surgical treatment.

Methods 379 participants [160 candidates for bariatric surgery (B) vs 219 not seeking bariatric surgery (NB)] and 304 healthy subjects (HS) were assessed with a battery of well-validated psychometric tests.

Results The B group showed an intermediate personality profile between HS and NB. They also exhibited lower depressive and anxiety scores. Eating and attachment impairment were found lower in the B group with respect to the NB.

Conclusions Candidates for bariatric surgery display advantageous personality features and lower rates in psychopathology compared to other participants with obesity. These features may represent both traits facilitating the search for a bariatric treatment, and the preferred ones selected by the surgeon. Implications for clinicians addressing obese participants towards bariatric surgery and limitations concerning "impression management" are discussed.

Level of evidence Level III, case-control analytic study.

Keywords Obesity · Bariatric surgery · Personality · Psychopathology · Treatment choice

Introduction

Bariatric surgery is considered the most effective treatment for patients with severe obesity in case of failure of conservative weight loss therapies [1]. In the past, psychiatrists and surgeons thought that the surgical risk linked to this invasive type of surgery had to be reserved only for patients with severe obesity who would encounter an equally high risk of morbidity and mortality without surgical approach [2]. Recently, the concept of "last option" is completely exceeded: bariatric surgery is considered as one of the first-line treatments in patients with severe obesity, because it is an effective treatment and, concerning long-term weight loss, it reduces overall mortality and incidence of metabolic comorbidity [3]. Since the beginning of the new century, there has been a significant increase in bariatric surgery request reaching the considerable number of half a million bariatric interventions carried out worldwide already in the 2013 [4]. There is a lot of interest in identifying which factors could be considered as predictors of good outcome

This article is part of topical collection on Personality and eating and weight disorders.

✉ Amianto Federico
federico.amianto@unito.it

Angela Valentina Spalatro
angelaspalatro@gmail.com

Ilari Giorgio
giorgio_ilari@yahoo.it

Marzola Enrica
enrica.marzola@unito.it

Giovanni Abbate Daga
giovanni.abbatedaga@unito.it

Fassino Secondo
secondo.fassino@unito.it

[1] Neurosciences Department, Psychiatry Section, University of Turin, Via Cherasco 11, 10126 Turin, Italy

with respect to bariatric surgery. General outcome predictors associated with bariatric surgery are demographic variables, preoperative weight, motivation and expectations, eating behavior, psychosocial functioning, and personality and psychiatric comorbidities [5].

Concerning psychiatric comorbidity, some research shows that bariatric surgery candidates have higher rates of psychopathology compared to other individuals with obesity [6]. According to a recent meta-analysis, among patients that underwent bariatric surgery, the most common psychiatric diseases were depression (19%) and binge-eating disorder (17%) [7]. Moreover, both depression and binge-eating disorder have been associated with more frequent weight recovery following surgery [8]. Conversely, 1 and 3 year follow-up studies regarding weight outcomes showed that neither depression nor binge-eating disorder was consistently associated with differences in weight outcomes, and some research suggests that patients with bipolar disorder and schizophrenia achieve comparable weight loss to controls without mental illness [9]. Such opposite evidences suggest that a clear scientific model to address clinical choices in this area is still far from being defined. It seems that difficulty and opposite results in highlighting good outcome predictor factors are due to the limited kind of approach of current strategies, which use different scales and focus on mental health diagnoses according to DSM-5 rather than to psychosocial, personality, and psychopathological features of these candidates [10].

Some studies suggest that personality traits should be included in the comprehensive assessment of individuals with obesity, since personality seems to be the strongest predictor for the development of Binge-Eating Disorder (BED) among subjects with obesity and some personality traits, as self-directedness, demonstrated lower scores in subjects with obesity compared to controls [11].

The Temperament and Character Inventory (TCI) may be one of the most important psychometric tests able to give information on the way in which people perceive themselves and the environment, providing possible personality patterns involved both in the onset of obesity and in the compliance with the post-bariatric surgery indications [12]. Sullivan and colleagues [13] showed that TCI dimensions are able to distinguish, within the subjects with obesity, those who will effectively enroll in a weight management program.

The aim of this study is to explore psychopathology traits, eating behavior, personality, and attachment characteristics in a sample of participants with obesity that choose to undergo bariatric surgery, in participants with obesity that do not choose this approach and in healthy subjects. To find out, differences in these measures could be useful for the management of these patients. A better knowledge of personality and psychopathology profile of these patients may represent a guide for programming therapeutic interventions (eventually included psychiatric or psychological support) to favor the best possible outcomes.

Materials and methods

Subjects

Two groups of participants with obesity have been enrolled between November 2011 and March 2016. All the patients consecutively admitted at the Outpatients Service who met inclusion criteria were enrolled in each branch of the study. In the first group, they were included 160 subjects ($M = 24$; $F = 136$) consecutively presented and requesting for bariatric surgery at the outpatients service of the Bariatric and General Surgery Service of the City of Health and Science of Turin. These participants were all those who had been found suitable for bariatric surgery after a consultation with an expert surgeon who selected and managed them on the basis of the 1992 US National Institutes of Health (NIH) consensus statement guidelines for bariatric surgery as revised in 2005 [14]. In particular, bariatric surgery candidates should have attempted to lose weight by nonoperative means, including self-directed dieting, nutritional counseling, and commercial and hospital-based weight loss programs, but should not be required to have completed formal nonoperative obesity therapy as a precondition for the operation. Requested BMI is 40 or at least 35 if accompanied by such comorbidities as diabetes, hypertension, arthritis limiting daily function, and cardiopulmonary failure. Other inclusion criteria include the patient's ability to understand the surgery and the consequences of the treatment, to comply with long-term follow-up, to agree to maintain vitamin and mineral supplementation, and to report problems promptly to specialists familiar with the complications of bariatric surgery. According to the present protocol, the contraindications represented by uncontrolled emotional disorders and drug or alcohol abuse were demanded to the psychiatric evaluation. These did not exclude the subjects form the present research, but only form the surgical intervention. The obese participants referred to the psychiatric visit represented the 85% of all patients asking for a surgical consultation ($n = 188$), since 28 subjects (15%) were judged inidoneous for the intervention by the surgeon, based on physical conditions.

The enrollment of the participants for the present study was done at the Outpatient Service of the Expert Centre for Eating Disorders of the City of Health and Science of Turin where the patients were sent by the surgeons to perform the psychiatric assessment after the first surgical visit. The psychiatric visit was meant to assert possible psychiatric disorders potentially interfering with bariatric surgery management [e.g., acute bulimia nervosa (BN), major depression, acute psychosis, drug or alcohol dependence, etc.]

and to establish adequate treatments (e.g., prescription of a drug treatment or psychotherapy) or exclusion from surgery. For the aims of the study, bariatric participants selection was made according to the following inclusion criteria: (1) age > 20 and < 50; (2) no intellectual disability or developmental or learning disorders; (3) no psychosis or neurological disorders (e.g., multiple sclerosis, stroke); (4) no history of dementia or sequelae of severe head trauma. The age limits (20–50 years) were chosen because of the high number (more than 95%) of requests for surgery within this age range and the need to produce a relatively homogeneous "adult" group for psychometric tests (in particular, the personality tests display a progressive modification with age). The other criteria were chosen to grant the highest possible validity for personality and psychopathology self-assessment. The psychiatric visit included accurate anamnesis, SCID-I administration [15], and psychometric testing. According to the psychiatric evaluation, four participants (2.5%, 1 with BN, 2 affected with severe cluster B personality disorder with alcohol abuse and one with schizotypal personality disorder) were excluded from bariatric surgery, but included in the database of our Outpatients Service because eligible form a medical point of view. Instead, 32 participants (20%, 24 with BED and the others with mild to moderate depression or anxiety disorders) received a prescription of antidepressant drugs and/or psychotherapy for their symptoms, and then proposed for surgery after recovery from psychiatric symptoms. These subjects were also included in the present database. Conversely, the participants that were not surgical candidates (i.e., not eligible from a medical point of view) were excluded from the present analyses.

The second group consisted of 219 ($M = 35$; $F = 184$) individuals with obesity coming from general population and searching for non-surgical obesity treatment and consecutively admitted for a psychiatric evaluation at the outpatients service of the Expert Centre for Eating Disorders of the City of Health and Science of the University of Turin. This group of participants with obesity may also include some subjects excluded from the bariatric surgery after the surgical examination (but not the subjects excluded from surgery after the psychiatric evaluation) who did not declare their previous surgical assessment. In fact, this would have been an exclusion criterion from this branch of the study. We applied the same psychopathological inclusion criteria for the study which were applied for the bariatric group to avoid a recruitment bias. A total of 11 subjects (7 subjects younger than 20, 3 subjects with intellectual disability, and 1 subject with acute psychosis) were selected out of the initial group of 231 subjects admitted to the assessment procedure, and thus, they were not included in the present study.

The control group was represented by 304 healthy subjects ($M = 80$; $F = 224$) selected on the basis of the above-mentioned age range (20–50 years) from a database of the Neuroscience Department, Psychiatry Section including healthy subjects of both sexes, voluntarily enrolled at school lessons, medical or cultural meetings, or using personal contacts from general population, with an age range from 16 to 70 years old. These subjects have been screened for psychiatric disorders, intellectual disability, developmental or learning disorders, or neurological disorders (e.g., multiple sclerosis and stroke), history of dementia, or sequelae of severe head trauma at the moment of recruitment. These participants were selected in different time frames for different study purposes as "healthy subjects" (HS), this granted the higher possible heterogeneity and representativeness of general population. According to DSM-IV-TR (2000) criteria, no specific selection was made as concerns body weight. Nevertheless, the screening for eating disorders excluded BN and BED or even ED NOS (Eating Disorder not otherwise specified) overweight subjects. Healthy controls were not included if they had an ED according to DSM criteria.

Procedure

All participants followed the same procedure. During the psychiatric evaluation, the semi-structured interview with the SCID-I explored the presence of an eating disorder or other psychiatric disorders according to DSM-IV-TR (2000). To collect clinical data of the sample during this first evaluation, anthropometric parameters were measured: weight, height, and body mass index (BMI). A battery of specific tests was then administered to the participants and to the control group to collect psychopathological, personality, and attachment characteristics of the sample; this battery includes the following.

- The Temperament and Character Inventory (TCI; [16]) is an instrument for the dimensional assessment of personality. It is divided into seven dimensions, four of which assess temperament: Novelty Seeking; Harm Avoidance; Reward Dependence and Persistence. The other three dimensions assess character: Self-directedness; Cooperativeness and Self-transcendence.
- The Attachment Style Questionnaire (ASQ; [17]) is a 40-item self-report questionnaire on attachment style. The measure includes five dimensions: confidence, discomfort with closeness, need for approval, preoccupation with relationships, and relationships as secondary.
- The Beck Depression Inventory-II (BDI-II; [18]) is used to measure the presence and severity of depressive symptoms. Clinical cut-off is generally fixed at 16.
- The Symptom Checklist-90 (SCL-90; [19]) is a multidimensional inventory designed to evaluate a wide spectrum of psychopathological symptoms. It is composed of 90 items organized into nine primary symptom subscales: somatization, obsessive–compulsive, interper-

sonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, and psychoticism.

- The Eating Disorder Inventory-2 (EDI-2; [20]) is a self-report inventory that measures disordered eating attitudes, behaviors, and personality traits common to individuals diagnosed with Eating Disorders.
- The Binge-Eating Scale (BES; [21]) investigates psychological variables related to binge eating. The cut-off is generally fixed at 18 to discriminate the presence or the absence of a binge-eating attitude.
- The Toronto Alexithymia Scale (TAS-20; [22]) is a measure of deficiency in understanding, processing, or describing emotions. The total score is the sum of three subscales: Difficulty Describing Feelings; Difficulty Identifying Feelings, and Externally Oriented Thinking.

Ethics

All recruited participants and controls provided written informed consent to this study. All the procedures were conducted according to the 1995 Declaration of Helsinki as revised in Edinburgh in 2000. The self-administration of the psychometric tests used for this research is a routine assessment practice with patients affected with obesity, and thus, according to guidelines of the Ethical Committee of the AOU City of Health and Science of Turin, the approval for this study was not requested.

Statistical analysis

The ANOVA test was applied to continuous socio-demographical and clinical variables (e.g., age, BMI, and BDI-II), while the Chi-square test was applied to categorical variables (e.g., gender distribution) to evaluate the difference between participants with obesity that choose to undergo bariatric surgery (B), and participants with obesity that do not choose this approach (NB) and healthy subjects (HS). Bonferroni post hoc analysis was then applied. Due to the high number of variables considered, to avoid type II errors, it was considered significant a $p \leq 0.001$.

To discriminate the role of the age and depression on the differences between groups (since both have shown a significantly difference between groups), we applied a multivariate analysis (ANCOVA) using age and BDI as covariate on the analysis of the differences in psychometric indices between B, NB, and HS. A post hoc analysis was applied to detect any differences between the three groups.

A logistic regression analysis between the two groups of participants with obesity was applied to the variables which significantly differentiated the groups to evidence the variable which independently predicted the belonging each group, thus reducing the variables for the regression analysis. The outcome variable was the searching of bariatric surgery or not.

Two separate multiple linear regression analyses were performed within each obese group looking for the relationship between the dimensions which predicted group membership and the variables which characterized each group.

All statistical analyses were performed using the Statistical Package for Social Sciences (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp). In consideration of the explorative nature of the study, it was considered a $p < 0.05$ for significance threshold in the analysis following the ANOVA.

Results

Socio-demographical and clinical characteristics of the sample

Table 1 displays the ANOVA comparison of socio-demographical and clinical characteristics between bariatric surgery candidates (B), participants with obesity not seeking for surgery (NB), and healthy subjects (HS). Concerning socio-demographical characteristics, B and NB showed higher age with respect to HS. Concerning clinical characteristics, NB showed intermediate BMI between B and HS. B showed an intermediate profile between NB and HS also with respect to BDI-II score.

Table 1 Demographical and clinical characteristics of the sample

	B (160)	NB (219)	HS (304)	χ^2	*P*	*df*
Gender	F 15% (24) M 85% (136)	F 16% (35) M 84% (184)	F 26% (80) M 74% (224)	12.08	0.002	2
				F	*P*	Post hoc
Age	42.30 ± 11.50	43.29 ± 13.96	27.11 ± 3.77	210.40	.001	B, NB > HS
BMI	42.24 ± 7.74	36.82 ± 8.71	24.03 ± 1.89	510.93	.001	B > NB > HS
BDI II	17.77 ± 12.52	23.18 ± 11.96	3.37 ± 3.03	43.57	.001	NB > B>HS

B bariatric candidates, *NB* non bariatric obese subjects, *HS* healthy subjects, *BMI* body mass index, *BDI II* beck depression inventory II

Multivariate analysis (ANCOVA) of psychopathological, personality, and attachment characteristics of the sample using age and BDI as covariates

Table 2 displays differences in psychopathological, personality, and attachment variables between the three subgroups using age and BDI as covariates.

Concerning personality, participants with obesity showed higher harm avoidance ($p < 0.001$) and lower self-directedness with respect to HS. At post hoc analysis, B showed an intermediate profile between B and HS and they showed a higher reward dependence with respect to HS ($p < 0.001$).

Concerning eating behavior, participants with obesity showed higher scores in bulimia ($p < 0.001$) and social insecurity ($p < 0.001$) with respect to HS as measured by EDI-II. Post hoc analysis showed that B have an intermediate profile between NB (higher score) and HS (lower score). Participants with obesity showed also higher BES score with respect to HS ($p < 0.001$). Post hoc analysis revealed an intermediate score of B with respect to NB (higher) and HS (lower).

Concerning psychopathology, participants with obesity showed higher scores as measured by SCL-90 total score ($p < 0.001$) with respect to HS. Post hoc analysis showed that B have an intermediate profile between NB (higher score) and HS (lower score).

Concerning attachment and alexithymia assessment, participants with obesity showed higher scores in need for approval ($p < 0.001$) and higher scores in all the subscales of TAS-20: difficulty describing feelings ($p < 0.001$), difficulty identifying feelings ($p < 0.001$), and externally oriented thinking ($p < 0.001$) and in TAS-20 total score ($p < 0.001$). Post hoc analysis revealed no significant differences between NB and B. No intermediate profile has been shown.

Logistic regression analysis between B and NB obese groups

Logistic regression analysis allowed the identification of two variables as possible predictors for seeking bariatric surgery: harm avoidance ($p < 0.005$) and bulimia ($p < 0.049$). Statistical features and level of significance were reported in Table 3.

Table 3 Logistic regression analysis using the allocation in the of bariatric surgery group as dependent factor

	B (160)	NB (219)	Logistic regression analysis		
			B	*T*	*P*
Harm avoidance (TCI)	17.62 ± 6.67	21.63 ± 6.75	0.938	−0.64	0.005
Bulimia (EDI-2)	4.69 ± 4.74	7.49 ± 5.86	0.931	−0.72	0.049

B bariatric candidates, *NB* non-bariatric obese subjects

Table 2 ANCOVA of personality, psychopathology, and attachment characteristics of the sample using AGE and BDI as covariates

	B (160)	NB (219)	HS (304)	*F*	*P*	Post hoc
Temperament and character inventory (TCI)						
Harm avoidance	17.62 ± 6.67	21.63 ± 6.75	15.60 ± 7.58	45.73	0.001	NB > B>HS
Reward dependence	15.11 ± 3.63	14.20 ± 3.69	13.64 ± 4.26	7.34	0.001	B > HS
Self-directedness	26.00 ± 8.27	22.59 ± 8.13	29.24 ± 8.41	40.88	0.001	NB < B<HS
Eating disorder inventory-2 (EDI-2)						
Bulimia	4.69 ± 4.74	7.49 ± 5.86	2.66 ± 4.37	24.07	0.001	NB > B>HS
Social Insecurity	5.72 ± 4.45	7.26 ± 4.56	2.45 ± 2.75	4.82	0.001	NB > B>HS
Symptom check list-90 (SCL-90)						
SCL-90 total score	102.65 ± 67.55	119.35 ± 63.22	53.67 ± 42.07	69.23	0.001	NB > B>HS
Attachment style questionnaire (ASQ)						
Need for Approval (ASQ3)	33.53 ± 10.17	34.71 ± 9.01	26.44 ± 9.27	35.86	0.001	B, NB > HS
Toronto alexithymia scale-20 (TAS-20)						
Difficulty describing Feelings	16.68 ± 8.04	18.77 ± 8.34	11.54 ± 4.92	52.16	0.001	B, NB > HS
Difficulty Identifying Feelings	12.48 ± 5.61	13.57 ± 5.39	11.00 ± 5.29	41.49	0.001	B, NB > HS
Externally Oriented Thinking	18.31 ± 6.27	19.34 ± 6.68	16.25 ± 5.77	12.64	0.001	B, NB > HS
Total score	47.48 ± 16.44	51.69 ± 17.08	38.87 ± 10.82	37.70	0.001	B, NB > HS
Binge-eating scale (BES)	17.22 ± 11.06	22.40 ± 11.05	3.24 ± 3.05	42.56	0.001	NB > B>HS

B bariatric candidates, *NB* non-bariatric obese subjects, *HS* healthy subjects

Multiple linear regression analysis within each obese group

In the NB group, harm avoidance evidenced an inverse association with the self-directedness, while bulimia displayed a direct association with BES and an inverse association with cooperativeness (Table 4). No significant association was found between harm avoidance and bulimia for the B group.

Discussion

Differences between obese participants and HS

Consistent with the previous findings, participants with obesity of our study were characterized by psychopathological suffering and attachment troubles. Obesity itself, and not only the BED, results as a clinical condition carrying psychopathological problems that require a multimodal therapeutic approach including psychiatric and psychological care [6].

Obese participants, regardless from the clinical subgroup, differed from the healthy subjects for the higher need for approval, difficulty in describing and identifying feelings, and difficulty in externally oriented thinking, showing a possible impairment of emotional functioning. These evidences support the existence of a psychosomatic core for the obesity syndrome and possible common roots with the eating disorders. Obese subjects may be vulnerable because of unmet needs of approval which have been already evidenced as core elements of eating disorders [23]. On the other hand, they display difficulties in managing their unpleasant emotions using thought and verbalization oriented towards others, possibly because of their high levels of alexithymia. Therefore, they may not express their requests explicitly, but may somatize them as "concretized metaphors", similarly to what happens in eating disorders [24].

The relationship between alexithymia and eating behavior in obesity has been sparsely studied and poorly understood. Nevertheless, some empirical evidence suggests a relationship between alexithymia and obesity [25]. Although other studies do not support this hypothesis [26], some evidence suggest that alexithymia could be a primary factor involved in obesity, independent of mood factors and eating attitudes [27].

The above described interpretation connecting the core relational deficits (attachment and management of emotions) of participants with the obesity is not only consistent with the recent literature [28], but also permits a correlation with some recent biological findings on obesity. An altered attachment pattern in obesity may result in an alteration of physiologic and behavioral responses to psychological stress mediated by neuroendocrine pathways, such as those involving cortisol, insulin, leptin, and neuropeptide [29]. Recent findings sustain that people with a secure pattern of attachment are more easily comforted in stressful situations and are more able to regulate negative emotions [30]. Secure attachment may, thus, reduce the risk for obesity by preventing frequent or exaggerated stress responses from disrupting the normal functioning and development of physiologic systems that affect energy balance and body weight [31].

Taken together, our results suggest that attachment and alexithymia represent distinctive features of subjects with obesity: their insecure attachment style and difficulty in emotional management could have a strong impact on the relationship with the therapist and the surgeons [32]. In the long-term a possible goal will be to identify how the attachment style and the quality of the patient-clinician relationship may be prognostic factors for weight reduction, either with nutritional or surgical approaches. These features may suggest more specific therapeutic indications for each patient [33].

Differences between B and NB

From a psychiatric point of view, a major issue for bariatric surgery is represented by the interference of psychiatric disorders with the management of the surgical intervention

Table 4 Multiple linear regression analysis within NB group

	Beta	*t*	*P*
Dependent variable			
Self-directedness (TCI)	−0.345	−4.696	0.001
Cooperativeness (TCI)	0.128	2.215	0.028
	Beta	*t*	*P*
Bulimia (EDI-2)			
Cooperativeness (TCI)	−0.119	−2.525	0.012
Binge-eating scale (BES)	0.689	12.585	0.001

TCI temperament and character inventory, *EDI-2* eating disorder inventory, *BES* binge-eating scale

[5]. This issue can be viewed from two standpoints: "Do the motivations that drive subjects to choose bariatric surgery represent a signal of a worse psychopathological and clinical condition or, conversely, do they represent a marker of a greater awareness of the disease?" [34]. Some authors hypothesized that subjects who choose surgery are less willing to follow a dietary regimen and less aware of the risks associated with the surgical choice. Other authors hypothesized that these participants are more aware of their disease and of consequent physical complications, and then, their choice of surgery represents a way to start an effective treatment with a self-conservative motivation instead of a self-punitive and aggressive attitude towards an unsatisfying body [35].

Our research gives a substantial support to the second hypothesis. The comparison between surgical and non-surgical participants with obesity shows that participants seeking for bariatric surgery have intermediate personality features between participants with obesity not seeking for bariatric surgery and healthy subjects. This coincides with a lower degree of anxiety and avoidance of frustration, a greater self-determination and awareness about their own goals, and a greater capacity to rely on others in a mature and self-conservative way (e.g., better self-care, research of treatments, and surgery choice) [36].

This "resilient" personality profile is supported by psychopathological indices and eating measures. In fact, bariatric candidates appeared to be less affected by depressive and anxiety symptoms. They also showed less inclination towards uncontrolled eating behavior. These evidences together support the idea that our bariatric population is a healthier and well-functioning sub-population of participants with obesity, thus, presenting positive outcome indices which support the indication towards a bariatric intervention from a psychiatric point of view [5].

This evidence is in contrast to previous results that describe higher rates of psychiatric disorders and dysfunctional eating attitudes in candidates for bariatric surgery [7]. A possible interpretation of this discrepancy is that the high amount of psychopathology reported in earlier studies may not describe the current bariatric surgery population that may differ from the past also because of the current better perception of bariatric surgery [3, 4]. Thus, bariatric candidates of our sample might have been more prone to the surgical option thanks to the minor influence of depressive thoughts (like pessimism and discouragement) and anxious symptoms (as worries about consequences of their choices). The lower harm avoidance (TCI) and bulimia (EDI-2) might influence participants' attitudes towards the surgical choice through different but convergent patterns. The first feature represents a genetic disposition towards lower anticipatory worry and pessimism and higher confidence with the unknown [36]. The other is a specific indicator of lower eating psychopathology and eating suffering.

The clinical evaluation performed by the surgeon before addressing the subject to the psychiatric examination was explicitly not addressed to identify psychopathologic problems. Nevertheless, the surgeons may have involuntarily selected the participants in the bariatric group on the basis of personality or other "presentation" features. Moreover, the uncontrolled eating behaviors which are generally associated with concurrent psychopathology [9] might have involuntarily pushed the surgeons to discourage the surgical option for the obese participants with binge-eating, even though recent literature does not discourage, or even encourages, surgical treatment also for the obese subjects affected with the BED [10]. Alternatively, surgeons may have involuntarily excluded psychiatric subjects among those which they supposed to display lower ability to cooperate with post-surgical management [5]. This undeclared selective attitude reported by Fabricatore and coworkers [37] was described as prospective of "impression management" in bariatric surgery candidates; nevertheless, due to the low rate of exclusion from surgery, it should not have had a great influence in the final characteristics of the bariatric sample. On the other hand, it is more probable that the more anxious or depressed obese individuals adequately informed (e.g., by general practictioner or Internet) about the surgical risks and requests for post-surgical management spontaneously refrained to ask for bariatric surgery visit.

Conclusion

Both surgery candidates and obese participants not searching for surgery display attachment troubles and high alexithymia compared to healthy controls. These may interfere in their relationship with caregivers and should be considered by treatment programs.

Nevertheless, two separate populations of participants with obesity emerged from the present study. Our findings suggest that bariatric population is a subgroup which displays less personality or psychopathology disturbances with respect to non-bariatric participants. Thus, in our sample, the demand for bariatric surgery may represent a "marker of a greater awareness of the disease" in subjects with self-conservatives attitudes who do not display self-aggressive intentions [34].

Even though our methodology tried to reduce recruitment biases, the bariatric participants may have undergone some kind of selection as "impression management". If so, our findings evidence that this impression widely corresponds with personality and psychopathology features identifying a "resilient" profile among subjects with obesity. It would be important for future studies to consider

assessing and controlling for a measure of underreporting to rule out potential impact on this point.

According to the NIH guidelines, a pre-surgical psychometric evaluation coupled with a psychiatric assessment represents an easy, quick, and more objective instrument to explore participants' personality and psychopathological features, avoiding unduly exclusion from bariatric surgery [38].

Further follow-up research is needed to support the predictive value of the present finding of a "resilient" personality and psychopathology profile as a specific indication for bariatric surgery, to improve assessment targets and optimize treatments [7].

Limits

Limitations of this study include some methodological aspects. In the present investigation, the psychiatric interview and test administration follow the first surgical assessment and precede the admission to surgery. As discussed before, the surgeons may have involuntarily deselected some participants asking for surgery because of their bad general functioning. The authors and the cooperating surgeons estimate that it should be low, since the subjects excluded by the surgeons were few and only physical problems were considered. Nevertheless, the high risk of comorbidity between physical and psychopathological problems may produce an underestimation of the bias. Some limits are consequent to the use of self-administered tests: the subjects with obesity requesting a surgical intervention may have answered in a more social desirable way given that their answers will be used to decide whether they can be operated or not. In fact, studies with an independent evaluation interview show a higher prevalence of psychiatric disorders and then studies that did not have an independent assessment process [34]. The assessment was conducted using the DSM-IV criteria which not completely overlap with current DSM 5 criteria. Moreover, the cross-sectional nature of the research and the limited number of males does not allow to generalize our finding to all population of subjects with obesity. Moreover, exclusion criteria may have impacted findings in terms of making this population appear healthier when compared to other literature.

Future longitudinal research is necessary to confirm the relevance of our findings for the good outcome of treatments on this surgical population.

Acknowledgements The authors wish to thank Prof. Mauro Toppino for his cooperation in the recruitment of bariatric subjects and Dr. Luca Arletti for the English revision of the text.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards (Protocol number: CEI/17 0,028,836).

Informed consent Informed consent was obtained from all individual participants included in the study.

Data availability The data sets analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

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Eating and Weight Disorders - Studies on Anorexia, Bulimia and Obesity

The song of Anorexia Nervosa: a specific evoked potential response to musical stimuli in affected subjects

--Manuscript Draft--

Manuscript Number:	
Full Title:	The song of Anorexia Nervosa: a specific evoked potential response to musical stimuli in affected subjects
Article Type:	Original Article
Funding Information:	
Abstract:	Purpose: Research applying the EEG to AN is still limited, even though in other psychiatric disorders it permitted to find out the allmarks of the disorder. The aim of the study was to explore whether EEG recorded basal activity and reactivity to musical stimulation differs in anorexia nervosa (AN) as compared to healthy subjects (HS). Methods: Twenty female subjects (respectively 10 with AN and 10 HS) were administered a battery of psychometric tests and underwent EEG under three different conditions: 1) at baseline; 2) after a generic music stimulation; and 3) after a favorite music stimulation. EEGs of AN patients showed higher absolute amplitude of cortical slow waves (theta) in the parieto-occipital and temporal derivations, as far as for a deficit in the beta band. Results: They showed a higher N100 latency and a reduced P300 latency compared to HS. While N100 and P300 latency was sensitive to the musical stimulus in HS group, the AN group showed no difference after music stimulation. Conclusion: These data suggest that AN is accompanied by a state of brain hyperarousal with abnormal reactivity to environmental which is similar to the state of control subjects after musical stimulation. If confirmed, this finding may have treatment implications.
Corresponding Author:	Federico Amianto, M. D., Ph. D. University of Torino Torino, ITALY
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	University of Torino
Corresponding Author's Secondary Institution:	
First Author:	Angela Spalatro
First Author Secondary Information:	
Order of Authors:	Angela Spalatro
	Marco Marzolla
	Sergio Vighetti
	Giovanni Abbate Daga
	Secondo Fassino
	Benedetto Vitiello
	Federico Amianto, M. D., Ph. D.
Order of Authors Secondary Information:	
Author Comments:	Dear Editor-in-Chief Massimo Cuzzolaro, my colleagues and I are pleased to send you our manuscript titled “The song of Anorexia Nervosa: a specific evoked potential response to musical stimuli in affected subjects” to be evaluated for publication on the Eating and Weight Disorders-Studies on Anorexia, Bulimia and Obesity Journal. Experimental approaches of neurophysiological and neurofunctional neuroimaging,

	such as EEG or fMRI, have been applied to improve the understanding of psychopathology of anorexia nervosa. Neuroimaging studies have provided many important information while the research applying EEG to AN is still limited. The present study explores whether EEG recorded basal activity and reactivity to musical stimulation differs between anorexia nervosa and healthy subjects. Twenty female subjects (aged 16-26 years, respectively 10 with AN and 10 HS) were administered a battery of psychometric tests and underwent EEG under three different conditions: 1) at baseline without stimuli; 2) after a general music stimulation; and 3) after a favorite music stimulation. AN patients differed from HS in EEG characteristics both at baseline and after exposure to acoustic stimuli. These data suggest that AN is accompanied by a state of brain hyperarousal with abnormal reactivity to environmental stimulation which produces an effect on evoked potentials which is similar to that of the musical stimuli in healthy controls. This finding suggests that the brain activity of AN subjects is impaired by a functional activity which distorts the perception of external environment. If confirmed, this finding may have treatment implications, in particular for the use of brain stimulation techniques and the application of music therapy to the treatment of the disorder. We hope you will be interested in our contribution, submitted solely to Eating and Weight Disorders-Studies on Anorexia, Bulimia and Obesity, neither in part nor completely submitted for publication or published elsewhere. The authors declare no financial disclosure or conflict of interest with the present paper. We also declare our complete availability and willingness to make any changes requested for publication. We are looking forward to hearing from you, Best regards. Turin, July 15th, 2019Federico Amianto, MD, PhD

The song of Anorexia Nervosa: a specific evoked potential response to musical stimuli in affected subjects

Authors:

Angela Valentina Spalatro, MD[a], Marco Marzolla, MD[a,c], Sergio Vighetti, MD,PhD[b], Giovanni Abbate Daga, MD,PhD[a], Secondo Fassino MD[a], Benedetto Vitiello, MD, PhD[c], Federico Amianto, MD,PhD[a,c]*

Affiliations:

[a]Department of Neuroscience, Section of Psychiatry, Eating Disorders Centre, Via Cherasco 11, University of Turin, 10135, Turin, Italy

[b]Department of Neuroscience, Section of Neurophysiology, Via Cherasco 15, University of Turin, 10135, Turin, Italy

[c]Department of Public Health and Pediatric Sciences, Child and Adolescent Neuropsychiatry, P.zza Polonia 94, University of Turin, 10126, Turin, Italy

***Corresponding author:**

prof. Federico Amianto

Department of Neuroscience, University of Torino

Via Cherasco 11, 10126 Turin, Italy

Tel: +39-011-3135248, Fax: +39-011-3135439

E-mail: federico.amianto@unito.it

Acknowledgments

The authors thank Prof. George Northoff for helping in the conception of the study and dott. Matteo Martini for his contribution in editing the manuscript.

Abstract

Purpose: Research applying the EEG to AN is still limited, even though in other psychiatric disorders it permitted to find out the allmarks of the disorder. The aim of the study was to explore whether EEG recorded basal activity and reactivity to musical stimulation differs in anorexia nervosa (AN) as compared to healthy subjects (HS).

Methods: Twenty female subjects (respectively 10 with AN and 10 HS) were administered a battery of psychometric tests and underwent EEG under three different conditions: 1) at baseline; 2) after a generic music stimulation; and 3) after a favorite music stimulation. EEGs of AN patients showed higher absolute amplitude of cortical slow waves (theta) in the parieto-occipital and temporal derivations, as far as for a deficit in the beta band.

Results: They showed a higher N100 latency and a reduced P300 latency compared to HS. While N100 and P300 latency was sensitive to the musical stimulus in HS group, the AN group showed no difference after music stimulation.

Conclusion: These data suggest that AN is accompanied by a state of brain hyperarousal with abnormal reactivity to environmental which is similar to the state of control subjects after musical stimulation. If confirmed, this finding may have treatment implications.

Keywords: *Anorexia Nervosa; EEG activity; slow waves; p300; hyperarousal; music therapy.*

Level of Evidence: Level III, Evidence obtained from well-designed cohort or case-control analytic studies

1. Introduction

According to the biopsychosocial model, Anorexia Nervosa (AN) results from the interaction of different factors, including biological, psychological and environmental ones [1]. The ever-increasing prevalence of the disease prompts more investigations in the search of innovative and more effective therapeutic strategies [2,3]. Experimental approaches of neurophysiological and neurofunctional neuroimaging, such as EEG or fMRI, have been applied to provide evidences for a greater understanding in the pathogenesis and evolution of these disease [4,5]. EEG studies in other psychiatric conditions, like schizophrenia, have shown some specific hallmarks of neuronal activity, such as an increased presence of delta (1-3 Hz) and theta (3.125-8 Hz) activity compared to the unaffected population [7]. Moreover, patients suffering from Major Depression showed a significant correlation between the subdomain of the motor slowdown and the presence of slow electroencephalographic activity, specifically alpha1 and theta 2 [8].

The evidence that some alterations in the frequencies of neuronal activity are specifically related to psychopathological alterations of mental disorders [9] may suggest that external stimulation that can interfere with these frequencies, like through TMS or tDCS, might be effective in modifying neuronal activity and possibly clinical symptoms [10, 11].

In recent years, the use of EEG methods has also been associated with experimental therapeutic protocols investigating the rationale for the use of music-therapy in patients with schizophrenia and major depression [12]. Specifically, the musical administration could have a therapeutic effect on the synchronization of encephalic rhythms and on the prefrontal-hippocampal plasticity involved in psychoticism and anxiety [13].

Concerning ED, research linking EEG with music-therapy is still limited. Some preliminary EEG studies in AN revealed theta waves patterns in frontal hemispheres of

these subjects, suggesting a cortical slow wave pattern in AN [14]. This alteration could be consequent to malnutrition as suggested by previous electroencephalographic studies [15]. Nevertheless, other authors hypothesized that the detection of low values in parieto-occipital delta waves and frontomedian alpha activity in AN patients compared to healthy controls may represent a specific neurobiological characteristic of this disorder and not exclusively a consequence of malnutrition [16]. This pattern could be connected to a slight frontal dysfunction or to a state of increased attention-vigilance [17]. Studies on Event-Related Potentials (ERPs) recording techniques showed second rate amplitudes and latency alterations in early and late ERPs evoked components among anorectic people [18], suggesting deficits in environmental stimuli categorization and selective attention shifting [19].

On the other hand, the evidence for therapeutic effects of music therapy in AN, is still limited even though there have been encouraging preliminiary reports 20). In particular, the use of music therapy in the treatment of AN may represent an useful adjunctive treatment to overcome resistances to treatment in these patients [2].

The aim of this preliminary study is to explore the EEG characteristics in a sample of female patients suffering from AN and to compare these features with those of healthy subjects. The second aim was to explore the effect of music stimulation on EEG activity in AN and healthy subjects and to examine the possible association between EEG and psychopathology characteristics.

2. Methods

2.1.Participants

Thirty female subjects (20 affected by AN and 10 healthy subjects) were enrolled for this study. Patients were recruited at the Outpatient Service of the Regional Expert Centre for the Eating Disorder of the University of Torino, AOU Città della Salute e della Scienza di Torino, between December 2016 and June 2017. All participants received a psychiatric examination to determine the presence or the absence of an eating disorder (specifically Anorexia Nervosa) using the Structured Clinical Interview for Diagnosis (SCID) for DSM-IV-TR, a tool that has fair to excellent inter-rater reliability on axis I and excellent on axis II diagnoses [21,22]. Inclusion criteria for the study were: 1) female sex; 2) BMI between 14 and 17; 3) age between 16 and 26 years; and 4) duration of illness < 1.5 years. Exclusion criteria were: a) intellectual disability, developmental or learning disorders; b) psychotic or neurological disorder (e.g., multiple sclerosis, stroke); c) history of dementia or severe head trauma; d) current acute psychotic condition or substance abuse; and e) history of hearing problems. The final group consisted of 10 patients affected by Anorexia Nervosa. A sample of 10 healthy controls matched for age and sociodemographic characteristics was recruited as control group.

Ethics

All recruited participants provided written informed consent to this study. All the procedures were conducted according to the 1995 Declaration of Helsinki as revised in Edinburgh in 2000. Study was approved by the Ethics Committee of AOU City of Science and Health, Turin (protocol number: 0089968).

2.2. Measures

All the participants completed a battery of self-administered psychometric tests including:

Toronto Alexithymia Scale (TAS--20) [23]: a 20-item questionnaire used to assess the level of alexithymia. This scale had a strong support for its reliability and factorial validity [24].

Barratt Impulsiveness Scale (BIS) [25]: used as a measure of the degree of subject's impulsivity. It showed good validity and reliability.

BDI-II [26]: this test is composed of two different scores, respectively related to the "Somatic--Affective" and to the "Cognitive" area of depressed mood. It shows a high internal consistency and content validity.

SCL-90 [27]: it is composed of 90 items assessing the presence and the severity of mental distress symptoms in different domains. Its psychometric properties support its validity as an instrument to assess the psychopathological profile [28].

Temperament and Character Inventory (TCI) [29]: this questionnaire provides an estimate of the personality structure of the subject, according to the neurobiological model proposed by Cloninger (1994). Its psychometric properties support its clinical usefulness in the assessing of personality psychopathology [30].

Emotion Regulation Questionnaire (ERQ) [31]: a 10-item questionnaire that evaluates the emotion regulation modalities implemented by the subject. It has shown acceptable validity and reliability.

Difficulty in the Emotion Regulation Scale (DERS) [32]: 36-item questionnaire measuring individual patterns of emotional regulation. It has shown excellent internal consistency and good test-retest reliability and construct validity.

2.3. EEG data acquisition

With the participant comfortably seated at a semi-recumbent position in a sound and light attenuated room, 40-minutes eyes-closed EEG recordings were obtained using a 19-channel EEG Analysis Station according to the Jasper International 10-20 System (33). According to this System, electrodes were placed at Fp2, F8, T8/T4, P8/T6, O2, F4, C4, P4, Fp1, F7, T7/T3, P7/T5, O1, F3, C3, P3, Fz, Cz, and Pz through a self-adhesive conductive paste.

First, a quantitative electroencephalographic (qEEG) recording was performed. Quantitative EEG (qEEG) is a method of analyzing electrical activity of the brain to derive quantitative patterns that may correspond to diagnostic information and/or cognitive deficits [33]. The peculiarity of qEEG is that it takes into account frequency and amplitude in a simultaneous and independent way. The qEEG allows 6 main frequency bands to be obtained, one for each electrode used, according to a Fourier spectral analysis. The electrodes record and transmit the surface potentials to a computer, which converts them (using an analog digital method) into graphic values and quantifies them (with spectral analysis on successive epochs of 2 sec) [34]. The qEEG recording was obtained in three different situations:

- at rest, with no musical stimuli;
- while listening to a standardized music, the same one for patients and controls [35];
- while listening to an individually selected track.

Prior to data analysis, artifact detection was performed to exclude eye-movements, head-movements, muscle-movements, and segments of decreased alertness. EEG recordings

were then exported using ELMIKO's EEG DigiTrak Analysis Software to the ASCII format for later processing.

2.4. P300 analysis

The P300 wave is an event related potential (ERP) component elicited in the process of decision making. It is considered a possible index of attention and processing capacity. According to literature, Odball Paradigm Method has been used to elicit event related potentials (ERP) [36]. According to this method, mix low-probability target items are mixed with high-probability non-target (or "standard") items: a P300 wave manifests itself in response to rare stimuli, called targets, dispensed in a random sequence that sees them alternated with more frequent stimuli, called non-target. The detection of P300 evoked potentials was performed in basal conditions, after listening to the standard musical stimulus, and finally after the individualized musical stimulus, using the Oddball Paradigm method.

2.5. Statistical Analysis

A parametric comparison of sociodemographic, clinical, personality and psychopathological characteristics was carried out with Student's t test to test for differences between patients with Anorexia Nervosa (AN) and Healthy Subjects (HN).

A nonparametric test using independent Mann-Whitney analysis was then performed on the qEEG variables, assuming as a null hypothesis the non-variation within the distribution between the absolute amplitude averages in patients and controls. A global measurement survey was initially carried out, including the set of measurements taken at

baseline, during standard musical stimulus and during individual musical stimulus. With regard to the event-related evoked potentials (p300), we conducted a Student's t test between patients and healthy controls concerning p300 in three different conditions according to our aim: 1) at baseline; 2) after a common musical stimulus; 3) after preferred individual musical stimulus. The intra-group variability was verified separately for both patients and controls using Student's t test for repeated measurements, in the three different phases of detection in order to verify a variation that should confirm or refuse the normalization observed in the intergroup comparisons. Finally, we performed a Pearson linear correlation between psychometric, clinical and EEG variables in order to detect possible correlations.

We considered the significance threshold of $p < 0.001$ for psychometric measures and $p < 0.05$ for EEG analysis.

3. Results

3.1. Clinical and psychopathological variables

Table 1 shows significant differences between patients and controls in cinical and psychopathological indices.

[Insert Table 1 here]

3.2. Quantitative EEG (qEEG) analysis and comparison between patients and controls

Significant differences in qEEG were found between AN and HS with higher values reported in AN regarding the following electrodes and waves: T3 (wave theta: $p<0.02$), T5 (wave alpha: $p<0.02$ and beta: $p<0.02$), P3 (wave theta: $p<0.05$), T6 (wave beta: $p<0.04$) e O1 (wave theta: $p<0.03$ and wave beta 1: $p<0.02$). (see Table 2).

[insert Table 2 here]

3.3. ERPs comparison between AN patients and controls in different conditions

ERPs comparison between AN and HS showed significant differences (see Table 3) at baseline in Lat Fz N1 ($t=3.18$; $df=2$; $p<0.000$) and p300 ($t=-1.99$; $df= 2$; $p<0.05$), after standard musical stimuli in Lat Fz N1 ($t=4.65$; $df= 2$; $p<0.01$) and p300 ($t=-2.54$; $df=2$; $p<0.02$) and after Individual Preferred musical stimulus in Lat Fz N1 ($t=3.36$; $df=2$; $p<0.001$).

[insert Table 3 here]

3.4. ERP intragroup comparison after musical stimulum

ERP intragroup comparison of different conditions showed significant differences between baseline condition and individual stimuli condition in HS group specifically in LatP3 Fz (t= 2.32; df=2; p<.0.03), Cz (t=2.40; df=2; p<0.03) and Pz (t=2.03; df=2; p<0.05), no significant difference was found in AN group (see Table 4).

[Insert Table 4 here]

3.5. Correlation between ERPs and psychopathological characteristics of the AN group.

A significant correlation was found between ERPs (see Table 5) and some psychopathological variables: TAS-20 (r=0.60; p<0.001), Expressive Suppression (r=0.60; p<0.000), Cognitive Instability (r=0.60; p<0.000), Impulsivity (r=0.56; p<0.01), and SCL-90 (P=-0.46; p<0.04).

[Insert table 5 here]

4. Discussion

4.1.Electroencephalographic baseline quantitative features of AN patients

Participants with AN differed from healthy controls for a higher absolute amplitude of cortical slow waves (theta) diffused in the parieto-occipital and temporal derivations, as far as for a deficit in the beta band. These may be a sign of brain suffering possibly due to reduced blood perfusion with respect to controls [37]. According to previous studies, this may be due to the low BMI [38], which has also be related to deficits in executive functions as reduced perfusion of temporal cortical areas has been associated with performance in visual-spatial executive tasks [39]. Neuroimaging studies have highlighted functional alteration of parieto-temporal regions in subjects with AN at the level of the left parahippocampal gyrus and the left fusiform gyrus [40]. Moreover, recent studies suggested a role of the parietal lobe in the development and maintenance of body image [41, 42]. Thus, as sustained by Smeets and Kosslyn [43], the temporal-parietal asymmetry observed in our AN sample may relate to distorted body image perception.

4.2. The baseline differences in N100 latency and the musical effect on N100 wave

Participants with AN displayed a significantly greater N100 latency at baseline, which may be related to a deficit in selective attention [44, 45] or to an increased state of arousal [46]. The latter interpretation would be consistent with the correlation of higher N100 latency to a dysfunction in the catecholamine production as evidenced by literature [47]. The basic between-group difference is maintained throughout the experiment and it is not significantly affected by the two musical stimulations, thus indicating that higher N100 latency is a stable characteristic of this population. This is consistent with the evidence of

high harm avoidance in our AN participants, which is a typical marker of trait-hyperarousal related to stable temperament features [48, 49].

The concomitant presence of time distribution differences and of a left asymmetry index supports the hypothesis of a difference in the processing of emotional information related to the musical stimulus in the AN participants. This would be consistent with the evidence of alterations in the functional limbic circuits involved in the processing of emotional information in anorexia nervosa [50]. A previous reports suggests that, in healthy subjects, musical stimuli produce an intense activation of the reward system at the limbic level [51]. Recent evidence ascribes this action to the recruitment of the accumbens nuclei [52], an area involved in the pathogenesis of affective manifestations of patients with AN [53]. However, in our study, the intra-group comparisons refutes the hypothesis that such activation can be effective in re-approaching the latency of N100 of the AN participants to that of controls by reducing their arousal level. The lack of pre- and post-stimulus differences also within the control group suggests a poor sensitivity of the N100 latency to the musical stimulus per se and reducing its relevance as a distinctive marker of AN participants emotional elaboration anomalies.

P300 wave between group differences

The latency of the P300 is significantly reduced in AN participants, in contrast with what found with the N100 latency. Multiple reports has linked this finding with hyper-arousal in cortical state and increased obsessiveness [54], traits which are both associated with AN. Indeed, some researchers have suggested that high obsessiveness and Increased vigilance constitute true and proper endophenotypes of the anorexic pathology that are present early at the subclinical level [55]. This means that healthy subjects in baseline conditions display low levels of vigilance and pay attention to different stimuli in a

different manner, proportionate to their relevance [56]. Instead, AN patients, and possibly also at-risk but not yet affected youngsters, tend to process stimuli with faster categorizations due to an increased state of vigilance. Their high alert levels bring their functioning closer to that of patients with Compulsive Obsessive Disorder and Panic Attack Disorder [54, 57].

AN subjects, therefore, would be more efficient in the categorization of external stimuli, but, in the long term, this increased level of activation could lead to a reduction in their ability to discriminate stimuli [58]. This discriminative deficit may include the subjects with AN in the ADHD spectrum, a frequently comorbid diagnosis which shares the hyperactivity as a common symptom [59].

4.3. Musical effect on P300 wave

The musical stimulus, therefore, seems not to act on AN participants who maintain the left hemispheric filter as general operation [60]. The absence of any specific response to individualized musical stimuli is further evidence of a poor discrimination ability in AN participants [58]. This alteration of the self-related functioning has been correlated to an altered resting-state activity in schizophrenic subjects. In particular the lack of sensibility to a stimulus related to the self supports the hypothesis of a poorer self-development in these subjects [61–63]. Possibly, therefore, the individual musical stimulus do not produce relaxation in subjects with AN, because of their high levels of alert. As a difference from controls, AN participants are more efficient in categorizing external stimuli as they are hypersensitive, not more relaxed. This could explain why in the long run the increased level of activation leads to a reduction in the ability to discriminate

between the external stimuli according to the neuropsychological theories that correlate the deficit in shifting selective attention to prolonged hyperstimulation conditions [5].

4.4. Correlation between the event-evoked components and AN features

Participants with AN showed a strong positive correlation between the latency of the N1 component at the frontal level and both the overall alexithymia and cognitive instability. The latency of the N1 component also positively correlates with increased impulsivity and emotional suppression. This supports the evidence that in eating disordered subjects the altered control of the selective attention is related with troubles in the management of emotional states [61]. Subjects affected with AN display a lack of confidence in managing and modulating negative emotions because of their deficit mechanisms of regulation and containment of negative affects [64]. Subjects with AN suppress the external manifestations of their emotions displaying a dysfunctional emotional regulation strategy. This is also consistent with the findings concerning the left asymmetry in quantitative analysis and in the typical characteristics of neurocognitive rigidity [65].

4.5.*Conclusions*

Our study reveals differences in the functioning of the left hemisphere of AN participants compared to healthy controls confirming the presence of some type of asymmetry in this population [60]. In parallel, the differences in N100 and P300 latency of the event-related evoked acoustic potentials assimilate the functioning of patients with AN to psychiatric disorders such as OCD because of the alterations in the shift of selective attention to external stimuli [2]. Such procedural dysfunction may represent an endophenotype of the AN that evoked potentials may precociously detect before diagnosis and track after treatments [55]. Their generalized hyperarousal and hypersensitivity that we called "the song of anorexia nervosa" may impair the responsiveness to those positive relational stimuli within the therapeutic relationship which should increase their self-esteem and favor the development of their self [61].

The combination of a higher latency of N100 and a low latency in P300 in front of the musical stimulus may represent a specific diagnostic marker for AN disorder. If further studies will confirm this result, it may potentially be used in prevention and early diagnosis and in addressing therapeutic approaches identifying subjects at risk of resistance or relapse [2].

Finally, the present results provide some neurophysiologic evidence to support the use music therapy to enhance traditional therapies in AN patients, but also point to some objective difficulties. Some recent report suggest a possible anxiolytic role of music therapy in AN patients [20]. Music therapy stimulates the frontal and limbic areas in the processing of the musical stimulus, activates the emotional and cognitive functions related to the reward system and may increase the inter-hemispheric connectivity [37].

Nevertheless, resistance mechanisms related to the hyperarousal and the difficulty in selective attention may oppose these effects. Thus it could be necessary to use specific frequency stimulation to overcome them.

4.6.Limitations

Our study is exploratory and preliminary. The results are promising, but a number of limitations must be taken into account, including the small sample size, uncertainty of localization and interpretation, which are typical of surface methods. Similarly, the lack of reference about electroencephalographic studies in psychiatry, and in the study of AN in particular, increases the interpretative difficulties of the findings. The study does not investigate the therapeutic effects of music therapy on AN or the possible beneficial implications of the addition of music therapy with respect to conventional psychotherapeutic or psychopharmacological methods. Future more structured research projects are needed to further test the efficacy of this adjuvant therapy. However, this is the first study exploring the effects of the music stimulation from a neurophysiologic point of view and correlating cognitive evoked potentials to psychopathology in participants affected by AN.

Author contribution

FA and AVS contributed to the conception and design of the study, patients' recruitment and data collection. FA, AVS, MM and SV contributed to the acquisition and to the analysis of data. FA, MM, BV, GAD and SF and contributed to the draft and revision of the manuscript.

Disclosure statement

The authors declare no conflict of interest.

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Table 1. Sociodemographical, clinical and psychopathological assessment of the sample

	AN (10) m ± sd	CN (10) m ± sd	t	p
BMI	13.97 ± 1.28	16.16 ± 1.33	-3.74	0.001
Age	20.45 ± 4.32	23.27± 1.73	2.38	ns
TAS-20	66.80 ± 6.84	36.50 ± 12.51	6.72	0.000
Cognitive Instability (BIS)	6.80 ± 1.98	4.90 ± 0.99	2.70	0.05
SCL-90	153.50 ± 61.54	46.10 ± 26.44	5.07	0.000
Emotion Suppression (ERQ)	18.80 ± 6.16	6.40 ± 2.41	5.93	0.000
Impulsivity (DERS)	18.30 ± 5.53	9.20 ± 2.34	4.74	0.000

AN=Anorexia Nervosa; CN= Controls; BMI= Body Mass Index; TAS-20=Toronto Alexithymia Scale-20; BIS= Barrett Impulsivity Scale; SCL-90= Symptom CheckList-90; ERQ= Emotion Regulation Questionnaire; DERS= Difficulty in Emotion Regulation Scale; m=mean value; sd=standard deviation.

Table 2. Quantitative EEG (qEEG) analysis and comparison between patients and controls using Mann-Whitney test.

Electrode	Wave	AN (10) m ± sd	CN (10) m ± sd	p
T3	Theta	0.66±0.20	0.38±0.17	0.02
T5	Alpha	0.43±0.41	0.21±0.16	0.02
	Beta	0.64±0.32	0.32±0.21	0.02
P3	Theta	1.01±0.86	0.68±0.41	0.05
T6	Beta	1.07±1.55	0.37±0.26	0.04
O1	Theta	1.22±0.90	0.58±0.38	0.03
	Beta1	2.01±1.70	1.69±1.38	0.02

AN=Anorexia Nervosa; CN= Controls; T3=left temporal electrode; T5=left temporal electrode; P3=left parietal electrode; T6=right temporal electrode; O1=left occipital electrode; m=mean value; sd=standard deviation.

Table 3. ERPs comparison between anorectic patients and healthy controls

	AN (10) m ± sd	CN (10) m ± sd	t	p
Baseline Lat Fz N1	116.20 ±20.19	94.10 ±8.55	3.18	0.02
Standard musical stimulus Lat Fz N1	108.50 ±6.55	90.03 ±10.70	4.65	0.01
Individual musical stimulus Lat Fz N1	109.70 ±14.23	93.35 ±5.73	3.36	0.02
Baseline P300 Fz	310.80 ±32.02	335.50 ±22.79**	-1.99	0.03
Standard musical stimulus P300 Fz	302.80 ±20.51	330.58 ±27.73	-2.54	0.03
Individual musical stimulus P300 Fz	297.50 ±31.44	310.54 ±25.21**	1.02	ns

AN=Anorexia Nervosa; CN= Controls; Fz=frontal midline sagittal plane; N1=left nasion; m=mean value; sd=standard deviation.

Table 4. ERPs Student's T-test intragroup comparison of different conditions (baseline and after individualized stimulus).

	Baseline mean ± sd	Individualized stimulus mean ± sd	t	p
AN sample (N=10)				
Lat P300 Fz	310.80 ± 32.02	297.50 ±31.44	0.93	-ns
Lat P300 Cz	314.30 ± 28.84	298.60 ±34.52	1.10	ns
Lat P300 Pz	316.70 ± 30.80	301.30 ±34.07	1.06	ns
CN sample (N=10)				
Lat P300 Fz	335.54 ± 22.79	310.54 ±25.21	2.32	0.04
Lat P300 Cz	337.60 ± 22.94	311.13 ±26.27	2.40	0.04
Lat P300 Pz	334.53 ± 24.48	278.20 ±34.14	2.03	0.05

AN= Anorexia Nervosa; CN= controls; Fz= frontal midline sagittal plane; Cz=central midline sagittal plane; Pz= parietal midline sagittal plane; m=mean value; sd=standard deviation.

Table 5. Correlation between ERPs and psychopathological characteristics of the AN group.

	Lat FzN1 α TAS-20	Lat FzN1α Exp Suppression	Lat FzN1 α Cognitive Instability	Lat FzN1 α Impulsivity	Lat FzP300 α SCL-90
r	0.60	0.60	0.60	0.56	-0.46
p	0.000	0.000	0.000	0.010	0.04

Fz=frontal midline sagittal plane; N1=left nasion.

***TURIN UNIVERSITY** NEUROSCIENCES DEPARTMENT*
Via Cherasco 15 - 10126 Torino – Italy
Tel +011-6634848; Fax +011-673473

To Editor-in-Chief of the *EAWD Journal*
Prof. Massimo Cuzzolaro

Paper: "The song of Anorexia Nervosa: a specific evoked potential response to musical stimuli in affected subjects"

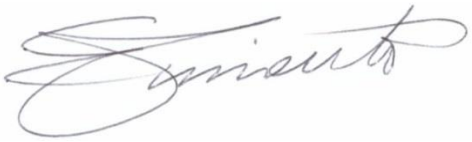
Authors:
Angela Valentina Spalatro, MD[a], Marco Marzolla, MD[a,c], Sergio Vighetti, MD,PhD[b], Giovanni Abbate Daga, MD,PhD[a], Secondo Fassino MD[a], Benedetto Vitiello, MD, PhD[c], Federico Amianto, MD,PhD[a,c]*

The authors declare no financial disclosure or conflict of interest with the present paper.

On behalf of all co-authors:

Turin, July 15th, 2019

Federico Amianto, MD, PhD



*Correspondence to: **prof. Federico Amianto**
Neurosciences Department, Psychiatry Section, University of Turin, Via Cherasco 11, 10126 Turin, Italy
*e-mail: federico.amianto@unito.it