UNIVERSITÀ DEGLI STUDI DI PADOVA

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Automatic processing of food in patients with restrictive Anorexia Nervosa: from attention to behaviour

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Abstract

Anorexia Nervosa (AN) is a severe psychiatric disorder, characterized by a relapsing and protracted course, with high mortality rates. One of the main symptoms of AN is an extreme restriction of calorie intake, which leads to a significantly low body weight. Over the years, with the aim of developing new and more effective treatments, several neurobiological models have been proposed to explain calorie restriction in AN. According to some of these models, alterations in the automatic responses elicited by food stimuli may play a role in the maintenance of the disorder as they could facilitate patients in resisting high-calorie food consumption and pursuing a low-calorie diet.

To test this hypothesis, the present project investigated the automatic responses elicited by both high and low-calorie foods in patients with restrictive AN, by looking at the process that goes from attention orientation to action preparation and execution.

In Chapter 3 is presented a study assessing the temporal course of attentional deployment toward food stimuli using an eye-tracking system. The results revealed that while healthy participants continued to look at food stimuli over the course of the trial, patients with AN avoided maintaining their attention on food stimuli. However, the fact that this difference was observed only in advanced stages of attentional processing suggests the involvement of more controlled rather than automatic mechanisms.

In Chapter 4, the interference effect elicited by different types of distractors (high-calorie foods, low-calorie foods and neutral objects) on participants goal-directed movements was assessed through an analysis of mouse trajectories. The results showed that healthy controls presented a similar deviation toward the three categories of stimuli. Patients with AN, instead, presented a greater deviation toward low-calorie foods and a reduced deviation toward high-calorie foods, compared to neutral objects.

Lastly, in Chapter 5, automatic approach-avoidance tendencies toward foods were assessed by means of a novel mobile approach-avoidance task. As a first step (paragraph 5.1), we developed and tested the mobile application in a sample recruited from the general population. The results of this study indicated the presence of a general approach bias towards food stimuli. Moreover, it was observed that this bias was influenced by other factor such as participants' BMI and hunger level. As a second step (paragraph 5.2), approach-avoidance tendencies toward foods were assessed in a sample of patients with restrictive AN. The analyses conducted on both reaction times and movements' force revealed that the natural tendency to approach food stimuli was reduced in patients with AN.

Overall, these results suggest that even if patients and controls do not differ in their initial attentional orientation toward foods, the motor programs that are automatically elicited by these stimuli are different. In particular, evidence is consistent in showing a reduced tendency to approach high calorie foods in patients with AN, a mechanism that may contribute to the maintenance of the disorder. The findings presented in this project can serve a starting point for a better understanding of the neurobiological correlates of AN and contribute to the development of new and more informed therapeutic strategies.

1 General Introduction

1.1 Anorexia Nervosa

Diagnosis and clinical characteristics

Anorexia Nervosa (AN) is a severe psychiatric disorder, characterized by an extreme restriction of calorie intake, which leads to a significantly low body weight, intense fear of gaining weight or becoming fat, and alterations in the way one's body weight or shape is experienced (American Psychiatric Association, 2013), see box 1.1.1. In the restrictive subtype, weight loss is primarily achieved through a reduction of food intake, in the binge-purging subtype, instead, purging behaviours (e.g., self-induced vomiting or misuse of laxatives/diuretics) and/or binging are also present.

CRITERIA DSM-5

Anorexia Nervosa 307.1 (F50.0)
A. Restriction of energy intake relative to requirements, leading to a significantly low body weight in the context of age, sex, developmental trajectory, and physical health. Significantly low weight is defined as a weight that is less than minimally normal or, for children and adolescents, less than that minimally expected.

B. Intense fear of gaining weight or of becoming fat, or persistent behaviour that interferes with weight gain, even though at a significantly low weight.

C. Disturbance in the way in which one's body weight or shape is experienced, undue influence of body weight or shape on self-evaluation, or persistent lack of recognition of the seriousness of the current low body weight.

Specify if:
(F50.01) Restricting type: During the last 3 months, the individual has not engaged in recurrent episodes of binge eating or purging behaviour (i.e., self-induced vomiting or the misuse of laxatives, diuretics, or enemas). This subtype describes presentations in which weight loss is accomplished primarily through dieting, fasting, and/or excessive exercise.

(F50.02) Binge-eating/purging type: During the last 3 months, the individual has engaged in recurrent episodes of binge eating or purging behaviour (i.e., self-induced vomiting or the misuse of laxatives, diuretics, or enemas).

Box 1.1.1 Diagnostic criteria for Anorexia Nervosa as reported in the DSM-5

Calorie restriction is one of the main symptoms of AN and probably its more evident behavioural manifestation. Patients adhere to extremely rigid diets, characterized by the avoidance of entire categories of foods, such as fats, carbohydrates, or sweets. Moreover, dieting is often accompanied by rigid rituals around food, including cutting food into tiny pieces, chewing for a specific number of times, eating very slowly, and hiding or throwing away foods (Calugi et al., 2019).

Another behavioural symptom that is often observed in patients with AN is excessive physical activity or restlessness, referred to as physical hyperactivity. It has been estimated that up to 80% of patients engage in excessive exercise routines, aimed at controlling their weight or alleviating feelings of guilt associated with eating (Davis et al., 1997). Importantly, a key characteristic of hyperactivity is its compulsive nature, as patients often report feeling obliged to exercise despite the negative consequences it has on their physical and mental health (Achamrah et al., 2016).

The other core aspect of AN psychopathology is represented by body dissatisfaction and disturbances in body image representation. Several studies highlighted the tendency of patients with AN to overestimate the size of their body and perceive themselves as overweight despite being underweight (Gardner & Brown, 2014; Hagman et al., 2015). Moreover, according to recent evidence, these disturbances are not limited to body image representation, but also extend to the body schema, which is the implicit sensorimotor representation of the body in the space, involved in motor preparation and execution (Gadsby, 2017; Meregalli et al., 2022). Over the course of the disease, preoccupations regarding body weight and shape might become obsessive and interfere with the life of the patient. This over-evaluation of shape and weight is also expressed in recurrent body-checking behaviours, such as frequent weighing or mirror checking, measuring body parts with tapes or hands, pinching or grabbing body parts to check for fat, and continuous comparing to others (Shafran et al., 2004). Beyond being expensive in terms of time and cognitive resources, body checking is also considered a maintenance factor of AN, as it seems to promote dietary restriction by increasing body dissatisfaction (Lavender et al., 2013).

As regards cognitive functioning, patients with AN often present a neuropsychological profile characterized by cognitive inflexibility, extreme attention to detail or poor central coherence, and perfectionism (Miles et al., 2020; Roberts et al., 2013; Tenconi et al., 2010). Although these aspects are not directly associated with eating disorder psychopathology, they can contribute to the maintenance of the illness and interfere with treatment. Rigidity might indeed promote ritualized habits/routines and enhance resistance to change, while poor central coherence may lead individuals to excessively focus on perceived flaws or imperfections, thus increasing body dissatisfaction (Tchanturia et al., 2013).

Illness denial and poor insight are other important cognitive aspects that often interfere with treatment, especially in the first phases of the disease. It has been estimated that more than 40% of patients with restrictive AN have impaired recognition of their illness and more than half of them believe that they do not need medical treatments (Konstantakopoulos et al., 2011).

Epidemiology

According to a review of 94 epidemiological studies, the lifetime prevalence of AN among the female population is around 1.4% (0.1–3.6%) (Galmiche et al., 2019).

To measure the incidence of AN, both community-based and register-based sampling strategies have been used. Depending on the source, incidence rates vary widely, ranging from 0.5 to 318.9 new cases per 100,000 women-years (Martínez-González et al., 2020). Since only a small proportion of individuals suffering from AN access treatment, observed incidence rates are definitively higher in community than in treatment-seeking samples (Treasure et al., 2015).

In the last decades, the overall incidence of AN appears to be stable, and increases in rates have been observed only among very young girls (<15 years) (van Eeden et al., 2021). Moreover, recent studies showed an increased incidence of AN following the Covid-19 pandemic, especially in teenage girls (Taquet et al., 2021). However, the exact effects of Covid-19 on AN are still to be clarified.

AN is more common in females than in males. The male to female ratio in incidence rates is of around 1:10, and the estimated lifetime prevalence of AN in males is only of the 0.2% (0–0.3%) (Galmiche et al., 2019). Nevertheless, these data should be interpreted as an underestimation, since due to stigma, male patients are less likely to access treatment and be diagnosed with AN (van Eeden et al., 2021).

In 90% of the cases, AN onset is between the ages of 13 and 20, with a peak between 15 and 16 years old. Recent evidence also shows that age of onset is progressively decreasing, with an increasing number of girls falling ill at a very young age (Favaro et al., 2019).

Etiopathogenesis

As often occurs in psychiatric disorders, the etiopathogenesis of AN is complex, involving a combination of biological, psychological, and sociocultural factors.

Family and twin studies have revealed the strong genetic component of AN. Relatives of patients are up to eleven times more likely to develop the illness than relatives of healthy individuals, and heritability is estimated to be around 50%-60% (de Jorge Martínez et al., 2022; H. Steinhausen et al., 2015). A recent genome-wide association study conducted on 16,992 patients identified eight significant loci and observed genetic correlations not only with other psychiatric disorders, but also with physical activity, and metabolic, lipid, and anthropometric traits (Watson et al., 2019).

This genetic vulnerability interacts with environmental risk factors. Among these, a role might be played by early risk factors, such as in utero exposure to viral infections, pregnancy complications, and early neonatal complications (Favaro et al., 2006, 2011). Other environmental factors include living in Western societies, in which there is great emphasis on thinness as an ideal, living in an urbanized area, or belonging to specific environments where preoccupation around body shape and weight is particularly high, such as the world of dance or fashion (Arcelus et al., 2014).

For many years, pathological family dynamics have been considered the primary etiological and maintenance factors of AN. Nowadays, the role of the family in the etiopathogenesis of AN has been significantly downsized (Le Grange et al., 2009). Nevertheless, specific family dynamics, such as high levels of parental demands, emotional reactivity, and difficulties in expressing emotions or communicating, are still considered risk factors for the development of eating disorders (Del Casale et al., 2022).

Research also showed that adverse life events may be involved in the aetiology of AN. A history of trauma is more frequent in individuals with an eating disorder than in healthy controls, and up to 50% of patients with AN experience some symptoms of PTSD (Briere & Scott, 2007; Sjögren et al., 2023). These events often occur during childhood, but they can also precede the onset of the disorder and act as specific precipitating factors. Looking at the 12 months before the onset of the disease, Pike and colleagues (2008) observed that patients with AN reported a significantly greater number of adverse life events than controls, including physical abuse and critical comments about shape, weight, or eating.

Psychiatric comorbidities and medical complications

AN often co-occurs with other psychiatric disorders, and the presence of comorbidities can complicate the diagnosis and the treatment of the condition (Hambleton et al., 2022).

In large population studies, the highest rates of comorbidity have been observed with anxiety disorders, in particular generalized anxiety disorder and social anxiety. Prevalence rates are around 40-60% and most of the patients report that the onset of the anxiety disorder preceded the onset of their eating disorder (Swinbourne & Touyz, 2007). High rates of comorbidity are also observed with unipolar depression, which severity seems to correlate with eating disorder symptomatology. Lower rates of comorbidity are instead observed with bipolar disorder (Hambleton et al., 2022). Obsessive compulsive disorder (OCD) co-occurs with AN in the 14% of the cases, against a prevalence of around 2% in the general population (Mandelli et al., 2020).

As regards personality disorders (PDs), a meta-analysis conducted on 87 studies reported that the mean percentage of personality disorders among patients with AN was 49% compared to 9% in healthy controls

(Martinussen et al., 2017). The most common co-occurrent disorders were obsessive-compulsive, avoidant, and borderline PDs.

As a consequence of malnutrition, patients with AN also present severe medical complications (see figure 1.1.1). These complications affect almost all major organ systems and account for more than half of the deaths in patients with AN (Mehler & Brown, 2015). Fortunately, many of them normalize after nutritional rehabilitation and weight recovery. However, AN that occurs in early adolescence or childhood can interfere with development and permanently disrupt optimum growth (Treasure et al., 2015).

Common medical complications include cardiac dysfunctions, such as bradycardia and hypotension, and gastrointestinal problems, including constipation and delayed gastric emptying (Mehler & Brown, 2015). Global endocrine dysregulation is common and includes hypothalamic–pituitary axis dysfunctions, responsible for amenorrhea, hypercortisolemia, and thyroid function abnormalities, and alterations in adipokine and appetite-regulating hormone levels (Schorr & Miller, 2017).

Endocrine dysregulation has deleterious consequences also on skeletal health and reduced bone mineral density (BMD) is a common comorbidity. A study conducted on 214 patients with AN revealed that more than half of them had osteopenia, 34% had osteoporosis, and only 14% had normal bone density (Miller, 2005). Electrolyte imbalances, such as hypokalaemia and hyponatremia must be monitored strictly and are more frequent in patients with purging behaviours or in patients who ingest large quantities of liquids.

Alterations have also been observed at the level of the brain. In the acute phase of the disorder, patients present widespread reductions in cortical thickness and surface area, reduced subcortical volumes, and lower cortical complexity, as estimated with fractal dimension analysis (Collantoni et al., 2020; Walton et al., 2022). These alterations are associated with BMI and tend to normalize with weight recovery, thus suggesting a causal role of malnutrition (Walton et al., 2022).

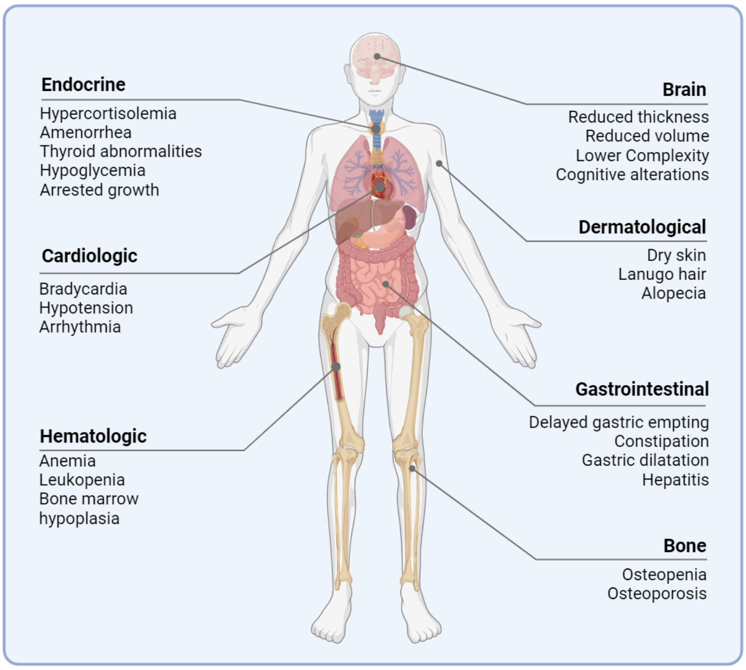


Figure 1.1.1 Common medical complications of Anorexia Nervosa

Treatment

According to international guidelines, the treatment of AN should be characterized by a multidisciplinary approach (American Psychiatric Association, 2023). The complex nature of the disorder, along with the presence of severe medical complications, requires the involvement of different professional figures, including psychiatrists, psychologists, dietitians/nutritionists, and medical doctors.

For most patients, outpatient care is appropriate as initial treatment setting. In the acute stages of the disease, visits should be conducted at least on a weekly basis, and the status of the patient must be monitored carefully. Compared to inpatient treatments, outpatient care has the advantage of allowing patients to remain with their families and continue to attend school or work. However, if patients do not respond to outpatient treatment, higher levels of care may be necessary, including full or partial hospitalization programs (e.g., day hospital) (American Psychiatric Association, 2023).

In both outpatient and inpatient settings, psychotherapy plays a central role in the treatment of AN.

For children and adolescents with AN, practice guidelines recommend the adoption of eating disorder family-based treatment (FBT). The focus of FBT is to absolve the parents from the responsibility of causing the disorder and have them take responsibility for nourishing their child (Lock & Le Grange, 2012). The intervention is divided into three phases, and, as treatment progresses, responsibility for independent eating is progressively given back to the adolescent.

For adults with AN, several psychotherapeutic approaches have been developed. Among them, those that have shown some efficacy in treating AN include enhanced cognitive behaviour therapy (CBT-E), Maudsley model of anorexia treatment for adults (MANTRA), focal psychodynamic psychotherapy (FPT), and specialist supportive clinical management (SSCM). However, so far, no specific approach has shown clear superiority compared to others (Treasure et al., 2015; Zeeck et al., 2018; Zipfel et al., 2015).

The essence of CBT-E is changing behaviours and beliefs about food and weight. The treatment is highly individualised, and it is divided into different stages. In the initial stage, the intervention focuses on understanding patients' eating disorder and setting a regular eating routine. Subsequently, the focus shifts to the processes that are maintaining the disorder, such as concerns about body shape and weight (Fairburn, 2008).

The MANTRA has been developed starting from a model proposing that AN is maintained by four broad factors: a rigid, detail-focused, and perfectionist thinking style; impairments in the socioemotional domain; positive beliefs about AN; and unhelpful responses of others to the disorder (Schmidt et al., 2014). These factors are targeted in treatment and the aim is to improve weight, eating disorder psychopathology, and psychosocial adjustment.

FPT, as compared to CBT and related approaches, places a greater focus on interpersonal relationships and insight rather than on cognitions and behaviour. The treatment comprises 40 sessions, during which the patient addresses pro-anoretic behaviours and ego-syntonic beliefs, works to improve self-esteem, identifies the association between interpersonal relationships and eating behaviour, and tries to transfer insights gained from the therapy to everyday life (Friederich et al., 2014).

Lastly, SSCM combines clinical management (e.g., giving information, advice, and encouragement) with a supportive therapeutic style designed to build a positive therapeutic relationship and foster change (McIntosh et al., 2006).

In the treatment of AN, pharmacotherapy plays a secondary role (Treasure et al., 2015). Commonly prescribed medications include antidepressants, in particular selective serotonin reuptake inhibitors (SSRIs), and atypical antipsychotics, such as olanzapine, quetiapine, and risperidone (Garner et al., 2016). Currently, there is no convincing evidence that pharmacological interventions have a significant impact on weight gain or AN psychopathology (de Vos et al., 2014; Dold et al., 2015). However, they may be useful for those patients with comorbid depressive, anxiety, or obsessive-compulsive symptoms (APA).

Despite psychotherapeutic interventions have shown some effectiveness in the treatment of AN, remission rates are still poor, and it is estimated that less than 50% of patients fully recover during treatment (Brockmeyer et al., 2018). Moreover, relapsing rates are high, especially in the first 3 months after treatment (Khalsa et al., 2017). This evidence has made it clear that improved treatment strategies for patients with AN are urgently needed (Schmidt & Campbell, 2013). According to many researchers, progresses can only be achieved through a better understanding of the mechanisms involved in the development and maintenance of the disorder (Schmidt & Campbell, 2013). For this reason, in recent years, many efforts are being made in order to better delineate the neurobiology of AN (Treasure et al., 2015).

Neurobiological models

Some of the most influential cognitive and neurobiological models of AN have placed a strong emphasis on self-control (Brooks et al., 2012; Ehrlich et al., 2015; Fairburn et al., 1999). According to these models, patients with AN are characterized by extremely high levels of cognitive control and inhibitory abilities. This excessive self-control can explain some of the core symptoms of the disorder, such as food restriction and hyperactivity. Moreover, it could also be related to specific cognitive and personality characteristics often observed in patients with AN, such as perfectionism, rigidity, and increased capacity to delay rewards (Pauligk et al., 2021; Steward et al., 2017).

Neurobiological evidence in favour of these models comes from studies showing that patients with AN present an increased activation of top-down cognitive control regions, especially in the prefrontal cortex, in response to both disorder-related and disorder unrelated stimuli (Bronleigh et al., 2022; Brooks et al., 2011; Ehrlich et al., 2015). Sanders and colleagues (2015), for example, observed that patients with AN (both in the acute and recovered state) displayed an increased activation of the right dlPFC when presented with food images. This activation was instead absent in healthy controls (Sanders et al., 2015). A similar result has also been obtained by Ehrlich and colleagues (2015), who observed that patients recovered from AN presented an increased dlPFC activity in response to anticipated monetary reward. According to the authors, this evidence, together with unaltered neural responses in ventral reward networks suggests an elevated degree of inhibitory control in response to rewarding stimuli in patients with AN (Ehrlich et al., 2015).

However, not all neuroimaging studies are consistent in showing an increased dlPFC activity in patients with AN. Moreover, functional alterations have also been observed in different cortical and subcortical regions (Bronleigh et al., 2022). Therefore, in recent years, alternative neurobiological models emerged.

Some researchers proposed reward-centred models of AN (Keating et al., 2012; O'Hara et al., 2015). Despite some differences, these models propose that AN is primarily characterized by alterations in reward system responsiveness. In particular, stimuli that typically engage the dopaminergic system, such as palatable foods, may partially lose their incentive value, while illness-compatible stimuli, such as stimuli associated with restriction, physical exercise, or thinness, become rewarding. In line with this, several studies observed an hypoactivation of ventral-striatal and insular systems in response to food stimuli in patients with AN (Bronleigh et al., 2022; Holsen et al., 2012), while greater activation of these same regions has been observed during the presentation of illness-compatible stimuli, such as pictures of underweight bodies (Fladung et al., 2010).

A slightly alternative approach has been provided by Steinglass and Walsh (2016; 2006), who proposed a habit-centred model of AN. Similarly to what suggested in reward-centred models, these authors believe that, at least in the initial stages of the disease, illness-compatible behaviours (e.g. dieting, exercising) are perceived as rewarding by patients with AN, and thus repeated over time. However, through repetition, these behaviours are learned, and pass from being goal-directed to habitual, thus becoming relatively insensitive to the receipt of the reward. According to this model, once the disorder is established, pathological behaviours become almost automatic, and are also unconsciously elicited by environmental cues. Scientific literature indicates that habitual behaviours are under the control of the dorsal striatum, in particular the posterior putamen (Morris et al., 2016). Consistently, Foerde and colleagues (2015) observed that during a food choice task patients with AN engaged the dorsal striatum more than healthy controls, while no differences were observed in reward regions.

Despite their differences, both reward-centred and habit-centred models reappraise the role of self-control and volition in the psychopathology of AN, suggesting the involvement of more automatic and unconscious mechanisms (J. E. Steinglass & Walsh, 2016). This perspective may explain why psychotherapy, which works on a conscious and deliberate level, fails so often, or why patients persist in pathological behaviours despite their intention to do otherwise. However, the neurobiological understanding of AN has only just begun, and available neuroimaging findings are often inconsistent (J. E. Steinglass et al., 2019).

From a behavioural perspective, a prediction of both these models is that, already from the very early stages of processing, salient stimuli (e.g., food stimuli) may elicit different responses in patients with AN compared to healthy controls.

Due to their evolutionary and motivational value, palatable foods are thought to implicitly attract our attention and elicit automatic approaching behaviours (van Alebeek et al., 2023; Werthmann et al., 2013). In patients with AN, however, this natural propensity toward palatable foods might be impaired, and patients might instead show greater responses toward more illness-compatible stimuli, such as low-calorie foods. As will be shown in the next paragraph, however, only few studies assessed automatic responses toward food in patients with AN, and they obtained quite inconsistent results.

1.2 Automatic processing of salient stimuli

Selective Attention

The human brain has limited resource capacities and thus it can only process a small amount of the information concurrently available in the environment (Mangun, 1995). Through selective attention, stimuli that are currently relevant or salient for the individual are prioritized by the system, often reaching conscious processing, and influencing behaviour (Desimone & Duncan, 1995; Posner & Petersen, 1990).

Evolutionary, the attentional system is biased toward stimuli with an appetitive or threatening value, as they may be relevant to the survival of the individual (Gupta et al., 2019; Pool et al., 2016). Although this generally represents an adaptive response, it has been hypothesized that biased attentional processing of salient stimuli may contribute to the development and maintenance of psychiatric disorders. In the addiction literature, for example, evidence shows increased attentional processing of substance-related stimuli, which may promote perseverative thinking about drugs, drug craving, and the initiation of compulsive or habitual drug use behaviours (O'Neill et al., 2020; Vujanovic et al., 2016). A similar hypervigilant response has been observed in highly anxious individuals, whose attention appears to be automatically captured by threatening stimuli, thus maintaining high levels of arousal and preoccupation (Gupta et al., 2019).

Historically, attentional biases have been investigated with behavioural tasks relying on the analysis of reaction times (RT). One of the most common measures was the emotional version of the Stroop Task (Ben-Tovim et al., 1989). In this task, participants are presented with both salient (e.g., threatening/appetitive) and neutral words, written in different colors. The task is simply to name the ink color of each word, while ignoring its meaning. Slower RT in response to salient words compared to neutral ones is usually interpreted as evidence of an attentional bias toward salient stimuli. However, this greater interference effect can be the result of both heightened attention as well as avoidance of salient stimuli (de Ruiter & Brosschot, 1994), which makes Stroop studies difficult to interpret.

To overcome this problem, researchers designed experiments capable of distinguishing heightened attention from avoidance. One of the most widely used is the dot-probe task (fig. 1.2.1a) (MacLeod et al., 1986). In this task, participants are simultaneously presented with two stimuli (one salient and one neutral), displayed for a predetermined length of time. Following pictures' disappearance, a probe appears in the location previously occupied by one of the stimuli, and participants are asked to respond to it as quickly as possible. The basic idea is that the response will be faster if the probe appears in the same location where the participant was already paying attention to. Therefore, if participants are faster in responding to the probe when it appears under the salient stimulus, they present a positive attentional bias, while faster responses to the probe when it appears in the same location as the neutral stimulus are indicative of a tendency to avoid salient stimuli (Cisler & Koster, 2010; Starzomska, 2017).

Another task that is commonly used in the assessment of attentional biases is the spatial cueing task, which is also able to distinguish facilitated engagement from difficulty in attentional disengagement (fig. 1.2.1b) (Posner, 1980; Veenstra & de Jong, 2012). In this task, a cue (salient or neutral) is presented in one of two rectangles, located on the left and right of a fixation point. Following cue disappearance, a target is displayed in one of the two rectangles. Participants are asked to indicate the position of the target by pressing a key. If the target appears in the same position as the cue, the trial is valid, while if it appears in the opposite position the trial is invalid. Positive attentional biases are indicated by faster responses on valid salient-cued trials relative to valid neutral-cued trials (greater attentional engagement), and by slower responses on invalid salient-cued trials relative to invalid neutral-cued trials (difficulty in attentional disengagement).

Subsequently, other tasks have been developed for the assessment of attentional biases, including the visual search task, in which participants must detect a salient stimulus that is embedded in a matrix of distracting stimuli (Hansen & Hansen, 1988; Rinck et al., 2003) the attentional response to distal vs. proximal emotional information task (Grafton & MacLeod, 2014), specifically designed to distinguish engagement from disengagement, and the rapid serial visual presentation task, for the assessment of the temporal dynamics of attentional deployment (Raymond et al., 1992).

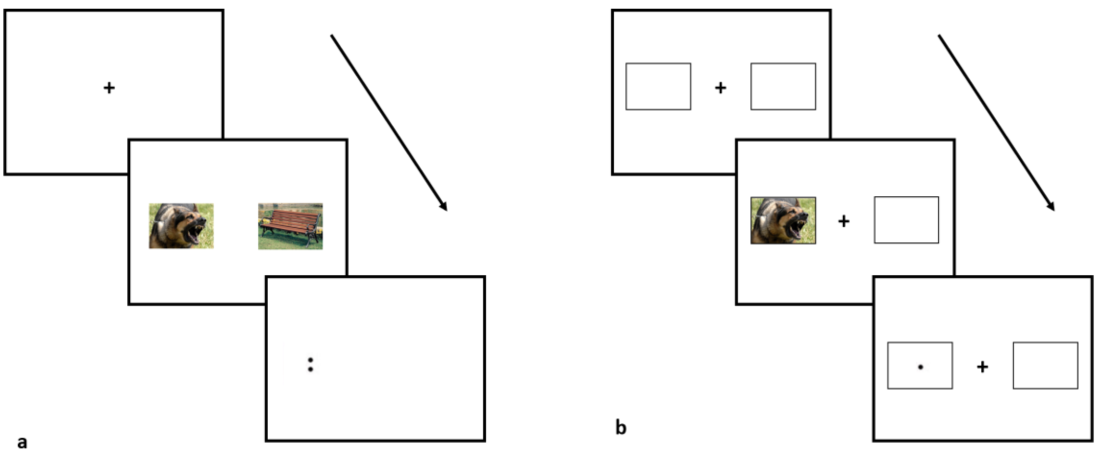


Figure 1.2.1. Graphical representation of a single trial of the a) dot-probe task: one salient (threatening) stimulus and one neutral stimulus are simultaneously presented on the left and right of a fixation point, followed by a probe; b) the spatial cueing task: a cue (salient or neutral) is presented on the left or right of a fixation point, followed by a target.

In the eating disorders literature, several studies adopted the approaches described above to investigate whether patients with AN and healthy controls differed in their attentional processing of food-related stimuli. Overall, the studies conducted with the modified Stroop paradigm found that patients with AN were slower than control participants in naming the color of food-related words, thus suggesting a bias in the way this information is processed (Faunce, 2002; Lee, 2004). When looking at the direction of this bias, however, the results are less consistent. Some authors observed an increased attentional bias toward high-calorie foods in patients with AN and interpreted it as either a fear response to highly threatening stimuli or a response elicited by their appetitive value (Neimeijer et al., 2017; Shafran et al., 2007; Smeets et al., 2008). Other studies, instead, reported that patients with AN showed a lack of engagement (Jonker et al., 2019), or even an attentional avoidance of high-calorie foods, associated, in those patients with a more severe eating pathology, with a tendency to direct their attention toward low-calorie food stimuli (Veenstra & de Jong, 2012), a pattern that is more consistent with patients' eating behaviour and might contribute to the maintenance of restrictive eating.

These inconsistencies are probably due to heterogeneity in both sample selection and methodology (Neimeijer et al., 2017). While some studies only included patients with restrictive AN (Neimeijer et al., 2017; Veenstra & de Jong, 2012), other studies also recruited patients with binge-purging AN or BN (Jonker et al., 2019; Shafran et al., 2007). However, since restriction and binge eating represent two opposite behavioural responses toward food, a different pattern of attentional deployment can be hypothesized, thus highlighting the need to consider each diagnostic category independently (Veenstra & de Jong, 2012). As concerns methodology, the authors adopted various experimental paradigms, including the dot-probe task, the spatial cueing task, and visual search paradigms. These RT tasks, beyond assessing slightly different aspects of attentional deployment, have also been widely criticized. The dot-probe task, for example, presents both poor internal and test-retest reliability (Kappenman et al., 2014; Price et al., 2015). Reliability issues have also been observed in the emotional Stroop task and spatial cueing paradigms (Eide et al., 2002; Waechter & Stolz, 2015). Moreover, all these tasks are only able to capture a snapshot of attentional deployment, thus not providing information regarding the time course of attentional processing.

An alternative to RT tasks is to assess attentional biases through the analysis of participants' eye movements. Eye-tracking systems use near-infrared light to track the position of the pupils and thus infer where the participant is looking at any moment (see figure 1.2.2). Since gaze direction and focus of attention are assumed to be tightly coupled, eye-tracking is considered a more direct measure of attentional allocation compared to behavioural tasks, and it has also shown greater psychometric properties (Corbetta, 1998; Waechter et al., 2014).

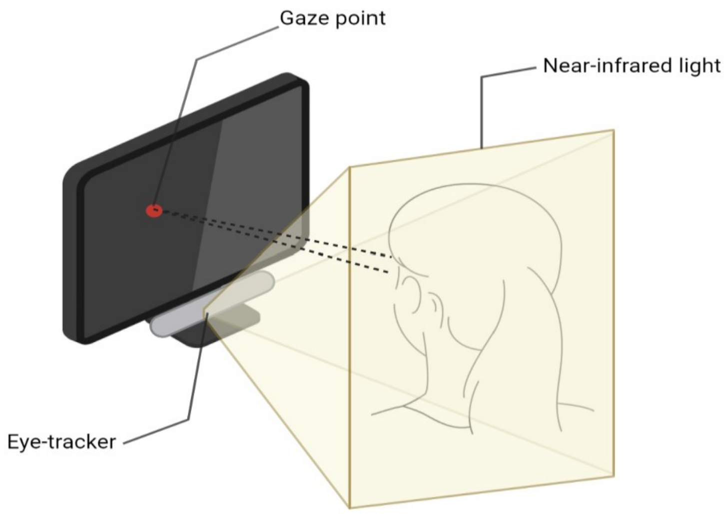


Figure 1.2.2 Graphical representation of the functioning of an eye-tracking system. The eye tracker sends out a near-infrared light, which is reflected in the eyes of the participant. Eye-tracking cameras take high resolution images of the user's eyes, and these images are used to identify the pupil center and the reflection of the illuminators on the cornea. The position of the pupil and the reflections of the illuminators are used to calculate the participant's gaze.

In the study of attentional biases, the most utilized paradigms are free-viewing tasks in which participants are presented with an array of stimuli, both salient and neutral, displayed on the screen for a few seconds (Armstrong & Olatunji, 2012). From the continuous eye-tracking data, several indices of attentional bias can then be extracted. Common indices of early attentional engagement include the *proportion of first fixations* that are directed toward salient stimuli compared to neutral ones and the l*atency* and *duration of first fixations* toward salient and neutral stimuli. Common indices of sustained attention include the *proportion of fixations* directed toward salient stimuli and the total *dwell time* spent looking at salient stimuli compared to neutral ones through the entire course of the trial (Skinner et al., 2018; Waechter et al., 2014).

Using these paradigms, an attentional bias toward high-calorie foods has generally been observed in healthy participants, as evidenced by both preferential orienting and sustained gaze direction toward food pictures (Nijs et al., 2010; Werthmann et al., 2013). This sustained attentional engagement with highly palatable foods is probably induced by the activation of the reward system, and it's thought to influence behaviour by promoting food consumption (Castellanos et al., 2009).

To date, only three studies adopted an eye-tracking methodology to assess whether this response is altered in patients with AN (Giel et al., 2011, 2020; Werthmann et al., 2019). Interestingly, they obtained quite consistent results. Both Giel and colleagues (2011) and Werthmann and colleagues (2019) reported that patients with AN displayed an initial gaze direction bias toward high-calorie foods, similar to the one observed in healthy controls. When looking at indices of sustained attention, however, they observed that only healthy controls spent overall more time looking at food stimuli than neutral objects. The absence of this bias in patients with AN suggests a tendency of these patients to avoid maintaining attention on food stimuli. According to the authors, this avoidance pattern could play a role in the maintenance of the disorder, as it might help patients in restrict their caloric intake by resisting high-calorie food consumption (Werthmann et al., 2019).

Although these studies are consistent in showing a general avoidance pattern in patients with AN, they do not provide any evidence regarding the time point at which patients start to differ from healthy controls by diverting their attention away from food stimuli. Indeed, they condensed eye-tracking data acquired over a period of 3000 ms in only one index of sustained attention. During this period, however, several mechanisms are thought to intervene in the control of attentional deployment, going from bottom-up automatic mechanisms to top-down cognitive control systems (Cisler & Koster, 2010; Gupta et al., 2019).

A better understanding of the time course of attentional deployment toward food stimuli in patients with AN is thus important to clarify the neurobiological mechanisms supporting this bias. Reduced attentional engagement already at initial stages of attentional processing would indeed reflect a difference in how food stimuli are automatically processed, thus supporting theories of altered reward responsiveness in AN (O'Hara et al., 2015). Differences in later stages of attentional orientation, instead, would probably involve higher order cognitive control systems and reflect more strategic inhibitory processes.

Motor distractibility

Action-centred models of selective attention state that attentional processes are intrinsically linked to movement organization (Cisek & Kalaska, 2010; Rizzolatti et al., 1987; Tipper et al., 1992; Welsh & Elliott, 2004). According to these models, when an object captures our attention a motor response toward that object is automatically planned and initiated (Tipper et al., 1992). Evidence to support these models come from studies showing that the presence of an irrelevant distractor can influence both the temporal and spatial aspects of goal-directed movements (Chang & Abrams, 2004; Chieffi et al., 2001; Tipper et al., 1992).

To explain this phenomenon, Welsh and Elliot (2004, 2005) developed the *response activation model*. The model posits that when two stimuli (a target and a distractor) are simultaneously presented, the motor system parallelly programs a response toward each of the stimuli. The two motor programs compete for activation and the target-directed movement wins the competition through the inhibition of the alternative response. However, if at the moment of response initiation the inhibitory process is not completed yet, the motor program will contain characteristics of both the target and non-target movement. The result will be a movement that deviates toward the location of the distractor. A prediction of this model is that the extent of the deviation will also depend on the saliency of the distractor. Indeed, since salient stimuli elicit a stronger response, which is more difficult to suppress, the model predicts a greater deviation toward salient compared to non-salient distractors (Welsh & Elliott, 2005).

Welsh and Elliot tested this model in a series of experiments involving both real and virtual (computerized) movements. In their experiments, participants were asked to perform a reaching movement toward a target (red light), while ignoring an irrelevant distractor (green light) presented in a different position (see figure 1.2.3a). Their results showed that when the target and the distractor were simultaneously presented, movements were drawn toward the distractor, while this effect was absent when the distractor was presented early enough to be completely inhibited (Welsh & Elliott, 2004). Moreover, they demonstrated that salient distractors elicited greater interference effect compared to non-salient stimuli (Welsh & Elliott, 2005).

In Welsh and Elliot experiments, the saliency of the distractor was associated with its capability of predicting the location of the target, however stimuli were all abstract perceptual visual cues. Ambron and Foroni (2015) moved forward, developing an experimental paradigm capable of assessing whether motor distractibility was influenced by the saliency of the distractor itself. In their experiment participants were asked to perform, on a digital tablet, a reaching movement toward a target (yellow dot), while an irrelevant distractor (a neutral or emotional face) was simultaneously presented on the screen (see figure 1.2.3b). In line with the response activation model, their results showed that movements' trajectories presented a greater deviation toward salient/emotional faces compared to neutral faces. Using a similar irrelevant distractor task, they assessed the interference effect of food-related stimuli, and they observed that participants trajectories veered consistently toward both food items and food-related objects (e.g., kitchen tools) (Foroni et al., 2016). Taken together, these results suggest that salient stimuli, even if irrelevant for the task, can automatically capture our attention and influence our behaviour by eliciting an involuntary approaching response.

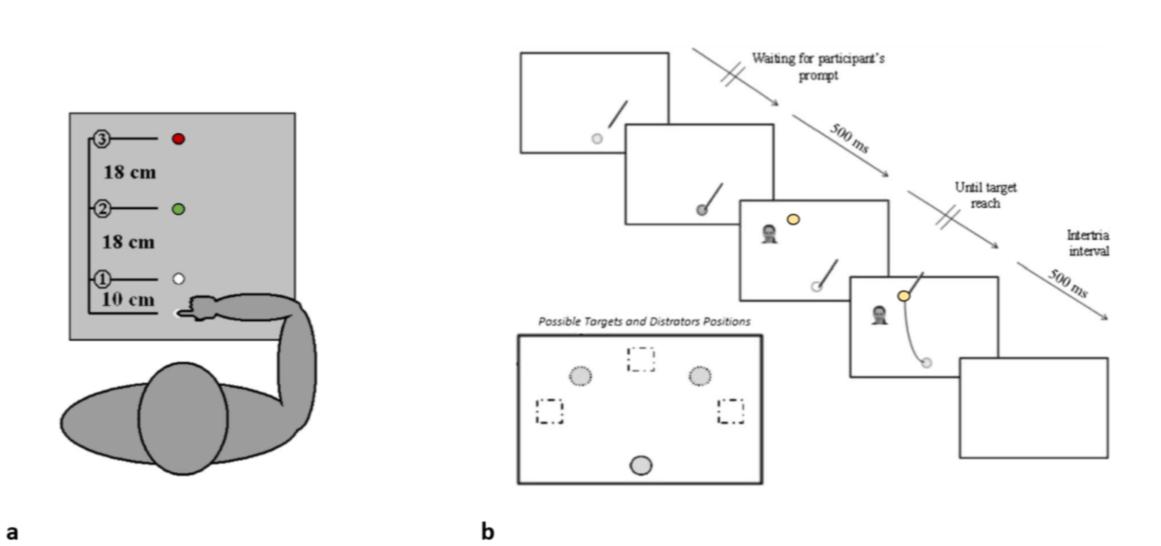


Figure 1.2.3. Graphical representation of a) the task developed by Welsh and Elliot (adapted from Welsh and Elliot, 2005); b) the irrelevant distractor task with emotional and neutral faces developed by Ambron and Foroni (adapted from Ambron and Foroni, 2015)

The association between attentional biases and explicit behaviour has already been proposed several times in the study of psychiatric disorders. In the addiction literature, for example, it is thought that paying attention to salient disorder stimuli may lead to drug seeking behaviours and relapses (Parvaz et al., 2021). However, to date, no study adopted an irrelevant distractor task to directly assess how the actions of patients with psychiatric disorders may be influenced by the presence of a salient distractor.

In the case of restrictive AN, patients may show an altered automatic response to food stimuli. Consistently with their eating behaviour, we can hypothesize that the interference effect observed by Foroni and colleagues (2016) in healthy controls may be reduced in these patients. Patients would thus show a smaller deviation of the movements toward high calorie irrelevant distractors, and this pattern could contribute to the maintenance of calorie restriction.

Approach-Avoidance tendencies

As already anticipated in the previous paragraph, when a stimulus is processed by the system, a set of potential actions toward that stimulus are automatically specified (Cisek & Kalaska, 2010). The nature of these actions is influenced by the spatial characteristics of the stimulus, but also by its emotional valence. Stimuli with a positive/appetitive valence (e.g. food, smiling faces) are indeed thought to automatically elicit an approaching response, while negative/threatening stimuli (e.g. angry faces) are preferentially avoided (Bradley & Lang, 2007).

Being able to quickly react to external stimuli in an appropriate and adaptive way can prove crucial for the survival of the individual. In the case of psychiatric disorders, however, these automatic approach-avoidance tendencies might be biased and contribute to the maintenance of the disorder (Loijen et al., 2020). Regarding addiction, for example, an approach bias toward substance related stimuli has been repeatedly observed (Kakoschke et al., 2019). This bias seems to be associated with both substance craving and consume and it is sensitive to priming effects, so that just thinking about the substance can increase the bias (Loijen et al., 2020). Anxious individuals tend to automatically avoid the stimuli they report to find threatening, thus sustaining the avoidance pattern also observed in real-life (Heuer et al., 2007; Reinecke et al., 2012). Lastly, depressed individuals appear to lack the adaptive responses displayed by healthy controls. Indeed, they present a diminished approach of positive stimuli and a reduced avoidance of negative stimuli (Bartoszek & Winer, 2015; Radke et al., 2014).

To assess automatic approach-avoidance tendencies in the laboratory, the most frequently adopted tasks are the Stimulus Response Compatibility Task (SRC, figure 1.2.4a) (De Houwer et al., 2001) and the Approach-Avoidance Task (AAT; figure 1.2.4b) (Rinck & Becker, 2007). In both tasks participants are required to perform approach and avoidance movements toward different categories of stimuli. RT are recorded and then analysed. An approach bias is inferred if a stimulus is approached faster than avoided, while an avoidance bias is inferred if avoidance movements are faster than approaching ones. For both tasks, relevant feature and irrelevant feature versions have been created. In the irrelevant condition, participants are instructed to approach or avoid pictures based on task irrelevant feature (e.g. the format, the colour of the frame). In the task-relevant condition, instead, the instructions make the content of the image relevant (e.g. "approach spiders and avoid butterflies"). Although biases can be observed with both versions, relevant feature instructions generally yield stronger effects (Lender et al., 2018; Phaf et al., 2014).

The difference between the SRC and the AAT is that in the SRC task, participants perform symbolic movements by pressing a key to move a manikin toward (approach) or away (avoid) from the picture (see figure 1.2.4a). In the AAT, instead, participants approach or avoid the pictures by respectively pulling a joystick toward themselves or pushing it away using actual motor movements. To improve the subjective impression of approaching and avoiding stimuli, in the AAT, movements are also accompanied by zooming effects, so that pushing the joystick away decreases the size of the picture, while pulling the joystick increases it (see figure 1.2.4b).

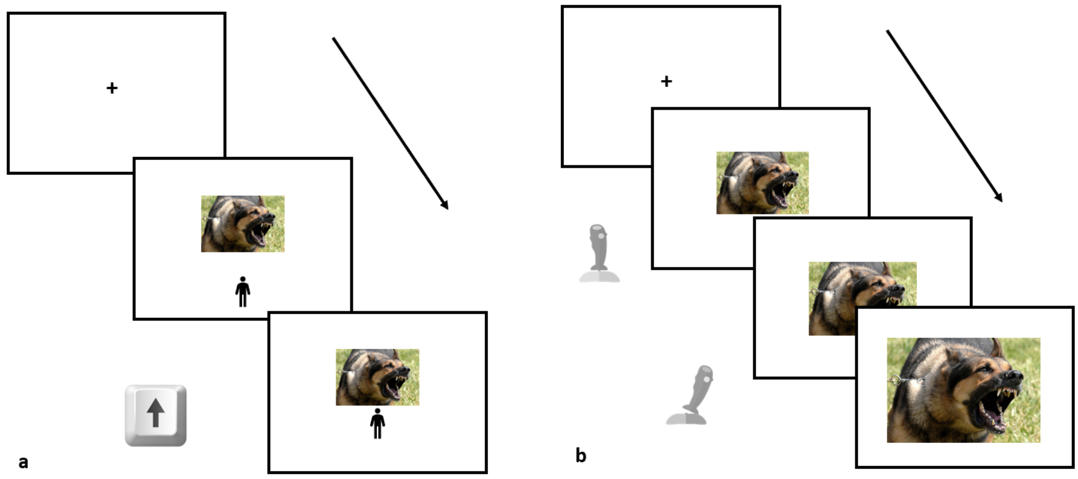
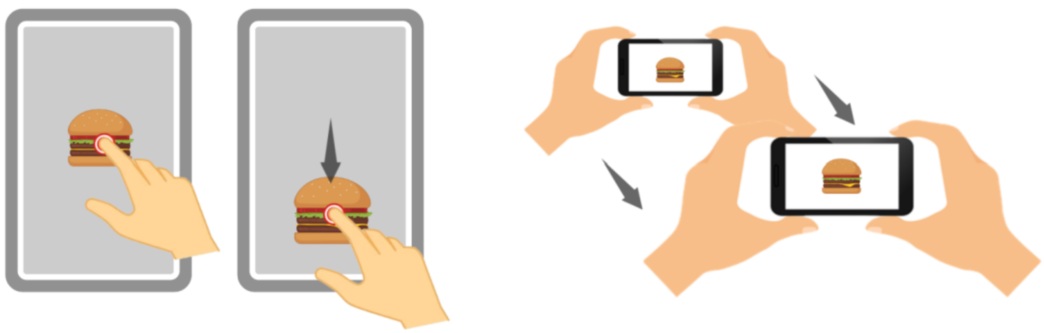


Figure 1.2.4. Graphical representation of an approach trial in the a) Stimulus Response Compatibility task: participants have to approach the picture by moving the manikin toward it by pressing the up key on the keyboard; b) the Approach-Avoidance task: participants have to approach the picture by pulling the joystick toward themselves.

Although these computerized tasks represent established tools for measuring approach–avoidance tendencies, they have faced repeated criticism for their limited ecological validity (Lange & Pauli, 2019; Meule et al., 2019). Real-life approach/avoidance behaviours, indeed, involve more complex and extended movements than pressing a key or pulling/pushing a joystick. Moreover, in real-life, approach and avoidance movements are associated with a decrease/increase of the distance between oneself and the stimulus, an effect that in the classic AAT can only be simulated through the zooming feedback (Lange & Pauli, 2019).

To overcome these limitations, researchers are now developing modified and more ecological versions of the AAT. Meule and colleagues (2019, 2020), for example, designed an AAT in which participants are instructed to move the stimuli towards or away from themselves by sliding their dominant hand on a touchscreen (figure 1.2.5a). Zech and colleagues (2020) developed a mobile AAT in which participants naturally approach stimuli by pulling their phone toward themselves and avoid stimuli by pushing the phone away from themselves (figure 1.2.5b). Lastly, using virtual reality, some researchers are programming AAT in which participants approach/avoid 3D stimuli using even more realistic reaching and grasping movements (Eiler et al., 2019; Schroeder et al., 2016). Moreover, a secondary advantage of these new versions of the AAT is that they can collect additional indices of approach/avoidance biases, such as the total duration of the movement and its force (Schroeder et al., 2016; Zech et al., 2020).



a b

Figure 1.2.5. Graphical representation of an approach trial in the a) touchscreen-based AAT developed by Meule and colleagues (2019); b) mobile AAT developed by Zech and colleagues (2020).

Using these new generation tasks, an approach bias toward appetitive food stimuli has been generally observed in the general population (Brouwer et al., 2021; Meule et al., 2019; Schroeder et al., 2016; van Alebeek et al., 2023; Wittekind et al., 2021). This bias appears to be stronger in individuals with high levels of food craving and to be associated with subjective ratings of palatability, liking, and valence (Meule et al., 2019; van Alebeek et al., 2023). Moreover, in some studies, approach tendencies were associated with participants' BMI. Schroeder and colleagues (2016), for example, observed that participants with higher BMI were faster in collecting food stimuli than neutral objects compared to participants with lower BMIs. Similar results were reported by Zech and colleagues (2023), who observed that the tendency to approach food stimuli decreases from before to after meal in normal weight individuals, but that this mechanism was disrupted in overweight and obese participants, who instead presented an increase in approach tendencies after meals.

When looking at literature on AN, however, only few studies can be found, and results are not always consistent. Veenstra and De Jong (2011) were the first assessing approach-avoidance tendencies toward food in patients with restrictive AN. They adopted an irrelevant-feature SRC task, and the analyses conducted on accuracy scores revealed that, in contrast to healthy controls, patients presented no approach tendencies toward food. However, no differences between patients and controls were observed when looking at RT. Reduced approach tendencies toward food has also been observed by Neimeijer and colleagues (2019), who adopted a relevant-feature SRC task, and Paslakis and colleagues (2016), who developed a computerized irrelevant-feature AAT, and observed that while healthy controls were faster in approaching rather than avoiding food stimuli, this effect was absent in patients with AN. A different result was instead observed by Kollei and colleagues (2022), who reported no differences between patients and controls in approach-avoidance tendencies toward foods.

In addition to being few, all the studies conducted so far in patients with AN adopted classic computer-based approach-avoidance paradigms. Given the observed limits of these tasks, however, it would be interesting to assess whether the reduced approach tendency toward foods, observed in some of the reported studies, can also be observed using more ecological experimental paradigms.

2 Aim and overview of the project

According to reward-centred and habit-centred models of AN, an altered automatic response to food stimuli may be involved in the maintenance of the disorder (O'Hara et al., 2015; J. E. Steinglass & Walsh, 2016). The natural tendency to pay attention to and approach palatable foods might indeed be reduced in patients with AN, thus facilitating the avoidance of caloric foods and hindering the treatment. On the other hand, since low-calorie foods are more coherent with patients' motivational drives, the automatic responses elicited by those stimuli might be enhanced in patients with AN, implicitly sustaining their low-calorie diet. These hypotheses have already been tested in previous studies, and supporting evidence has been obtained by some of them (Paslakis et al., 2016; Werthmann et al., 2019). However, results are not conclusive, and many questions remain to be answered.

To expand current knowledge, the present project aims at investigating the automatic responses elicited by both high and low-calorie foods in patients with AN, by looking at the process that goes from attention orientation to action preparation and execution. To do so, we designed three different experimental paradigms aimed at assessing, respectively, selective attention, motor distractibility, and implicit approach-avoidance tendencies. Moreover, to overcome some of the limitations observed in previous studies, we decided to recruit only patients with restrictive AN (AN-R), so as to isolate a specific eating behaviour, and to adopt reliable and innovative technologies.

In the first study (chapter 3), we used eye-tracking to assess attentional biases toward food stimuli in both patients and controls. Participants performed a dot-probe task while their gaze was continuously recorded with an eye-tracking system. From continuous eye-tracking data, we extracted two indices of attentional bias (AB): the percentage of trials in which the gaze was directed toward the food stimulus at three different time points (first fixation, 500 ms, and 1500 ms), and the percentage of time spent looking at food stimuli, compared to neutral ones, in different time intervals (500 and 1500 ms). By including different time intervals, we wanted to provide a better analysis of the time course of attentional deployment, with the aim of shedding some light on the possible neurobiological mechanisms involved.

In the second study (chapter 4), we aimed at assessing whether irrelevant food stimuli elicited a different interference effect in the motor actions of patients with AN-R compared to healthy controls. To do so, we designed an irrelevant distractor task in which participants had to perform a mouse-reaching movement toward a target while an irrelevant distractor was presented in the middle of the screen. Mouse trajectories were recorded with the MouseTracker software (Freeman & Ambady, 2010), and we analyzed how participants' movements deviated towards the different categories of distractors: high-calorie foods, low-calorie foods, and neutral objects.

Lastly, to assess approach-avoidance tendencies toward food (chapter 5) we developed a customized version of the mobile AAT designed by Zech and colleagues (2020). In this task, participants had to approach stimuli by pulling their phone toward themselves and avoid stimuli by pushing their phone away. In a preliminary study (paragraph 5.1), we assessed approach-avoidance tendencies toward food in a sample recruited from the general population. In addition to investigating differences in approach-avoidance tendencies toward different categories of stimuli (high-calorie food, low-calorie food, and objects), we also examined whether these were influenced by different factors, including BMI, contingent hunger level, time passed since last meal, and subjective scores of wanting, liking and fear for the observed foods. In a second study (paragraph 5.2), we adopted the same task in order to assess differences in approach-avoidance tendencies toward food between patients with AN-R and healthy controls.

3 Selective Attention

3.1 Strategic avoidance of food stimuli in patients with restrictive Anorexia Nervosa: an eye-tracking evaluation[1]

Abstract

A biased attentional processing of food stimuli may represent a disorder maintenance factor in patients with Anorexia Nervosa (AN). The present study aimed at investigating the temporal course of attentional deployment toward both high-calorie and low-calorie foods in patients with AN using eye-tracking. 52 patients with restrictive AN and 54 healthy controls performed a dot-probe task while their gaze was recorded with an eye-tracking system. The direction bias (percentage of trials in which the gaze was directed toward the food at first fixation, 500, and 1500 ms), and the duration bias (percentage of time spent looking at the food) were extracted. Regarding the direction bias, a group by time interaction emerged ($F=3.29$, $p=.038$): while in the control group the bias continued to increase over the course of the trial, patients with AN showed a reduction of the bias between the 500 and 1500 ms. No group differences were

[1] *Published:* Meregalli,V., Tenconi,E., Cardi,V., Bonifanti,A., Meneguzzo,P., Favaro,A., & Collantoni,E. (2023). Strategic avoidance of food stimuli in patients with restrictive anorexia nervosa: An eye-tracking evaluation. *European Eating Disorders Review*, 1–9. https://doi.org/10.1002/erv.3011, under license CC BY 4.0.

observed on the duration bias. Overall, the results show that on advanced stages of attentional deployment patients with AN start to differ from healthy controls by diverting their attention away from food stimuli, a strategic process that may contribute to food avoidance and calorie restriction.

Introduction

Anorexia Nervosa (AN) is a severe psychiatric disorder, characterized by a relapsing or protracted course, high rates of disability and mortality, and an elevated burden on individuals, the society, and families (Zipfel et al., 2015). Available treatments for AN are only partially effective and it is estimated that less than 50% of patients reach a full remission (Brockmeyer et al., 2018; H. C. Steinhausen, 2002; Zipfel et al., 2015). This evidence has made clear for many researchers the need to identify and then target specific neurobiological, cognitive, and behavioural mechanisms that may contribute to the development and maintenance of this disorder (Schmidt & Campbell, 2013).

Among these, a potential role may be played by biased attentional processing of disorder-related stimuli. To date, different studies adopted behavioural paradigms to investigate attentional biases (AB) toward food in patients with AN. However, findings are often inconsistent (Lloyd & Steinglass, 2018; Ralph-Nearman et al., 2019; Stott et al., 2021). Some studies have found an increased AB toward food in patients with AN, interpreted as either a fear response to threatening stimuli or a response elicited by their appetitive value (Ben-Tovim & Walker, 1991; Neimeijer et al., 2017; Shafran et al., 2007; Smeets et al., 2008), whereas others have demonstrated a lack of engagement (Jonker et al., 2019) or even an attentional avoidance of high-calorie food stimuli (Veenstra & de Jong, 2012), interpreted as an implicit mechanism that may contribute to calorie restriction, thus acting as a disorder maintenance factor.

These inconsistencies are probably due to heterogeneity in sample selection and/or experimental design. The decision to include transdiagnostic samples (whole ED spectrum/binge-purging AN/restrictive AN) (Shafran et al., 2007), or instead limit the recruitment to patients with restrictive AN (Veenstra & de Jong, 2012), may indeed have led to significantly different results, as food restriction and binge eating represent two opposite behavioural responses toward food. As concerns methodology, different experimental paradigms have been adopted, including modified versions of the Stroop task, the dot-probe task, and visual search paradigms (Ralph-Nearman et al., 2019). Beyond assessing slightly different aspects of attentional processing, these tasks have also been criticized for having poor internal and test-retest reliability, and for only capturing a snapshot of attentional deployment (Cisler et al., 2009; Kappenman et al., 2014).

Eye-tracking technology has important advantages compared to behavioural tasks based on reaction times, as it can provide more proximal estimates of attention allocation and exhibits stronger psychometric properties (Waechter et al., 2014). To date, only few studies recorded eye-tracking data to investigate AB in patients with AN (Kerr-Gaffney et al., 2019), and only three focused specifically on food stimuli (Giel et al., 2011, 2020; Werthmann et al., 2019). Interestingly, their results are quite consistent in showing that even if both patients and healthy controls display an initial AB toward high-calorie foods, only healthy controls continue to direct their attention towards food stimuli over time (Giel et al., 2011; Werthmann et al., 2019).

The finding that patients with AN avoid maintaining attention on food stimuli has been interpreted in line with the vigilance-avoidance model proposed to explain the maintenance of anxiety disorders (Mogg & Bradley, 1998; Werthmann et al., 2019). This model posits that, while in the earliest stages of attentional deployment threatening stimuli automatically capture attention, in later stages they are avoided as a strategy to reduce emotional arousal and anxiety (Mogg & Bradley, 1998). In patients with AN, the tendency to avoid threatening stimuli (e.g. high-calorie foods) could also play a role in the maintenance of the disorder, as it could reinforce food restriction (Werthmann et al., 2019). However, the studies conducted so far condensed eye-tracking data acquired over a period of 3000 ms in only one index of sustained attention. Although with this approach it was possible to observe a general avoidance pattern in patients with AN, it did not allow inferring at what point of attentional processing patients start to differ from healthy controls by diverting their attention away from food stimuli. A greater understanding of how attentional processing of food stimuli develops over time in patients with AN could provide valuable information regarding the neurobiological mechanisms supporting the disorder. Indeed, while the initial phases of attentional deployment are thought to rely on bottom-up automatic mechanisms, later stages are considered more strategic as they involve higher order cognitive control systems (Cisler & Koster, 2010; Gupta et al., 2019).

In the present study, we collected eye-tracking data during the execution of an attentional bias task (dot probe task) with both high-calorie and low-calorie food stimuli. From eye-tracking data, we extracted the percentage of time spent looking at food stimuli, compared to neutral ones, in different time intervals (500 and 1500 ms), and the position of the gaze at three different time frames (first fixation, 500 ms, and 1500 ms). The inclusion of different time intervals allowed us to provide a better analysis of the time course of AB in patients with AN, and on the neural mechanisms underlying it. By studying the first 500 ms, indeed, we can observe how participants initially orient their attention, which probably reflects the activity of the dorsal frontoparietal network and subcortical and limbic circuits. The study of longer time intervals (1500 ms), instead, provide evidence of AB in more advanced stages of attentional processing, which are likely to be mediated by conscious and evaluative processing of the stimulus (Gupta et al., 2019). As regards high-calorie foods, we expected to replicate previous findings, with an initial AB toward food in both groups (patients and controls), followed, only for patients, by the avoidance of such stimuli. However, we didn't make any prediction on whether the difference between patients and controls would already be present at early stages of attentional deployment (500 ms) or only at the end of the 1500 ms. Since low-calorie foods represent a less threatening stimulus for patients with AN, we expected to observe a different pattern than those hypothesized for high-calorie foods. In particular, we hypothesised the presence of a sustained AB directed toward low-calorie foods through the entire course of the trial, as already observed by Werthmann and colleagues (2019) on adolescent patients with AN.

Moreover, we wanted to assess whether some clinical or contextual factors (such as age, BMI, hunger level, time passed since last meal) influenced AB scores in both the healthy control group and in patients. Werthmann and colleagues (2019), for example, observed a different attentional pattern in adolescent patients compared to adult patients, and differences could also be observed as a function of the severity of the illness. For this reason, we conducted a series of correlations between AB scores and clinical/contextual variables.

Methods

Participants

The sample included 106 female individuals; 54 healthy controls (HC) and 52 patients recruited from the Eating Disorder Unit of the University Hospital of Padova. All patients met full criteria for AN restrictive subtype (AN-R), according to the DSM-5 (American Psychiatric Association, 2013). Exclusion criteria for both patients and HCs were: 1) male gender; 2) age under 14 years; 3) current or lifetime neurological diseases; 4) mental impairment or learning disabilities; 5) major psychiatric disorder in comorbidity (bipolar or schizophrenia spectrum disorder), and 6) self-reported history of drug/alcohol dependence. An additional exclusion criterion for healthy controls was the presence of a current or lifetime diagnosis of an eating disorder. Written informed consent was provided by all participants. In the case of underage participants, consent was provided by their parents or legal guardian. The study was approved by the ethical committee and was conducted in accordance with the latest version of the Declaration of Helsinki.

Procedure

An expert clinician confirmed the diagnosis of AN-R according to the Eating Disorders Section of the Structured Clinical Interview of the DSM-5 (American Psychiatric Association, 2013). The same interview was used to exclude the presence of a past or current eating disorder in HCs. Before performing the experimental task, all participants provided a series of demographic and clinical information (age, body mass index (BMI), current pharmacological treatments), while data related to illness duration and age of onset were collected by the experimenter by looking at patients' medical records. Participants reported the time passed since their last meal (in hours) and the level of perceived hunger in the moment (on a scale from 1 to 6). At the end of this preliminary assessment, all participants performed the dot-probe task while their eye movements were recorded with a wearable eye-tracking system.

Dot-Probe Task

The task was programmed and presented with Opensesame (Mathôt et al., 2012) and was performed on a computer screen of 24 inch, with a resolution of 1920 x 1080 pixels. The stimuli were selected from the food.pics database (Blechert et al., 2019) and included 15 pictures of high-calorie foods (HCF), 15 pictures of low-calorie foods (LCF), and 30 pictures of neutral objects (N). Each food picture was paired with a neutral picture and each pair was presented 4 times, for a total of 120 trials.

At the beginning of each trial, a fixation cross was presented in the middle of the screen for 500 ms, followed by a number from 1 to 9, presented for 1000 ms. Participants were instructed to read the number aloud in order to ensure that they all directed their gaze toward the centre of the screen. Subsequently, 2 pictures were presented: a high or low-calorie food and a neutral object, one to the right and one to the left of the screen. In half of the trials, the pictures were displayed for 500 ms while in the other half they were presented for 1500 ms. Immediately following pictures disappearance, a probe appeared in the position previously occupied by one of the two pictures. The probe consisted in two dots oriented either horizontally or vertically and participants were asked to indicate the direction of the dots by pressing "b" or "n" on the keyboard for respectively ".." or ":". See fig. 3.1.1 for a graphical representation of the dot-probe task. Response time (RT) and accuracy were automatically recorded by the software. Information regarding RT data processing and results are reported in Supplementary Materials.

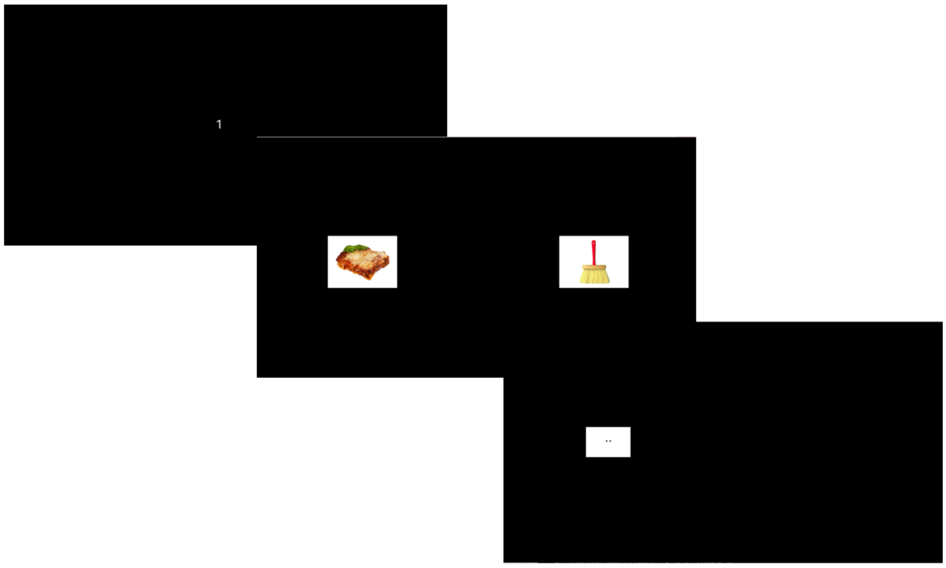


Figure 3.1.1 Graphical representation of a single trial of the dot-probe task. A number from 1 to 9 was displayed for 1000 ms at the center of the screen, and participants were required to read it aloud. Subsequently, two pictures (a high or low-calorie food and a neutral object) were displayed for either 500 or 1500 ms. Following pictures disappearance, a probe appeared in the position previously occupied by one of the two pictures.

Eye-tracking data: acquisition and processing

During completion of the dot-probe task, participants eye movements were recorded using the Pupil Core eye tracking system by Pupil Labs (Kassner et al., 2014). The system includes two eye cameras recording eye movements (200 Hz) and one world camera recording the user's field of view (120 Hz). All recordings were visually inspected, and 6 recordings (4 patients and 2 HC) were discarded due to poor quality.

For each trial, the following data were extracted: the direction of the first fixation, the position of the gaze at the end of the trial, and the total amount of time that participants fixated their gaze on each of the two pictures. "Fixation" was defined as a period lasting at least 100 ms in which no saccades or blinks occurred (van Ens et al., 2019). Participants who did not make eye movements in more than half of the trials, were defined as "starer" and excluded from the analyses (1 patient and 1 HC) (van Ens et al., 2019).

Attentional Bias Scores

Two indices of attentional bias, a gaze direction bias, and a duration bias, were extracted from the eye-tracking data for both HCF and LCF.

The gaze direction bias was calculated as the percentage of trials in which the gaze was directed toward the food stimulus, relative to all trials in which the gaze was directed toward either cue, at first fixation and at the end of the 500 and 1500 ms conditions[2]. Scores higher than 50 indicate that at that specific time point (first fixation, 500 ms or 1500 ms) participants were looking at the food stimulus in more than half of the trials.

The duration bias was calculated as the percentage of time participants spent looking at the food stimuli relative to the neutral stimuli in both the 500 and 1500 ms conditions[3] (Waechter et al., 2014). Scores higher than 50 indicate that participants spent more time looking at the food stimuli than at the neutral ones.

Statistical Analyses

All statistical analyses were conducted using the software SPSS, version 26 (IBM, 2019). Differences between groups in demographic and clinical characteristics were assessed by means of independent sample t-tests. To assess the presence of significant biases toward or away from food in both patients with AN-R and HCs, a series of one-sample t-tests were conducted (reference mean: 50). To investigate the influence of different variables on bias scores (gaze direction bias and duration bias), a series of linear mixed effect models (LMM) were conducted with 3 fixed factors (group, calorie, and time), and one random factor (participants' ID). Relationships between bias scores and clinical and demographic variables (age, BMI, age of onset, illness duration, hunger, and time passed since last meal) were tested by means of Pearson correlations, separately for controls and patients.

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[2] [n of trials with fixation directed toward food/ (n of trials with fixation directed toward food + n of trials with fixation directed toward neutral)] *100.

[3] [mean viewing time of food/ (mean viewing time of food + mean viewing time of neutral objects)] *100

Results

Demographic characteristics

Table 3.1.1 summarizes the demographic and clinical characteristics of patients and HC. Twenty-three patients were taking antidepressants, four benzodiazepines, and 12 atypical antipsychotics (olanzapine or risperidone). Thirty-three patients were receiving day care, while 19 were receiving outpatient treatment at the time of their participation in the study.

Table 3.1.1 Demographic and clinical data in patients and controls

	AN-R Mean (SD)	HC Mean (SD)	t (*p*)
Age (years)	19.92 (5.06)	21.26 (3.80)	1.61 (.110)
BMI (kg/cm^2)	16.08 (1.33)	21.48 (2.66)	13.16 (<.001)
Age of onset (years)	16.90 (2.98)	-	-
Illness duration (months)	38.22 (43.05)	-	-
Hunger (range 1-6)	1.84 (1.10)	2.96 (1.56)	4.17 (<.001)
Time since last meal (hours)	2.03 (1.94)	3.18 (3.14)	2.18 (.032)

AN-R, Anorexia Nervosa restrictive subtype; HC, healthy control; BMI, Body Mass Index

Attentional bias

The AB scores and the results of the one-sample t-tests are reported in table 3.1.2

As regards the gaze direction bias, the one-sample t-tests showed that both patients and HC directed their first fixation significantly more often toward the neutral stimulus than the LCF picture, thus suggesting an initial avoidance of LCF. At 1500 ms, a positive bias toward HCF was observed, but only in the control group. The LMM conducted on the gaze direction bias revealed a significant main effect of food (F=8.70, *p*=.003), a significant main effect of time (F=4.54, *p*=.011), and a significant group by time interaction (F=3.29, *p*=.038). In particular, the bias was generally higher for HCF than for LCF, and lower at first fixation, compared to both 500 ms (*p*=.023) and 1500 ms (*p*=.039). As for the interaction, figure 3.1.2 shows that both patients and HC presented an increase in the bias between the beginning of the trial and 500 ms, but then, while in the HC group the bias continued to increase, patients showed a reduction of the bias between 500 and 1500 ms.

As regards the duration bias, the results of the one-sample t-tests indicate that both patients and HC spent significantly more time looking at HCF than neutral stimuli in the 1500 ms condition. The LMM revealed a significant main effect of food (F=8.78, p=.003), so that the bias was higher for HCF than for LCF, and a significant main effect of time (F=7.84, p=.005), so that the bias was higher in the 1500 ms that in the 500 ms condition.

Table 3.1.2 Mean attentional bias scores and results of one-sample t-tests in patients and controls

	AN-R		HC	
	Mean (SD)	t (p)	Mean (SD)	t (p)
Gaze direction bias				
HCF first fix	51.78 (7.06)	1.73 (.091)	49.85 (7.66)	-0.14 (.891)
HCF 500 ms	52.46 (9.48)	1.76 (.085)	52.70 (11.56)	1.65 (.105)
HCF 1500 ms	50.51 (13.56)	0.25 (.808)	55.65 (13.85)	2.77 (.008)
LCF first fix	48.31 (5.40)	-2.15 (.037)	47.24 (6.86)	-2.87 (.006)
LCF 500 ms	51.51 (9.20)	1.10 (.277)	50.83 (11.24)	0.52 (.604)
LCF 1500 ms	49.44 (13.65)	-0.27 (.791)	51.56 (11.11)	0.95 (.346)
Duration bias				
HCF 500 ms	51.79 (9.44)	1.30 (.202)	50.96 (10.17)	0.68 (.502)
HCF 1500 ms	53.70 (10.10)	2.51 (.016)	54.13 (9.29)	3.18 (.003)
LCF 500 ms	50.28 (8.87)	0.22 (.828)	47.63 (9.91)	-1.71 (.094)
LCF 1500 ms	50.92 (10.62)	0.59 (.557)	51.55 (8.84)	1.25 (.216)

AN-R, Anorexia Nervosa restrictive subtype; HC, healthy control; HCF, high-calorie food; LCF, low-calorie food. Scores significantly higher than 50 indicate a positive bias toward foods.

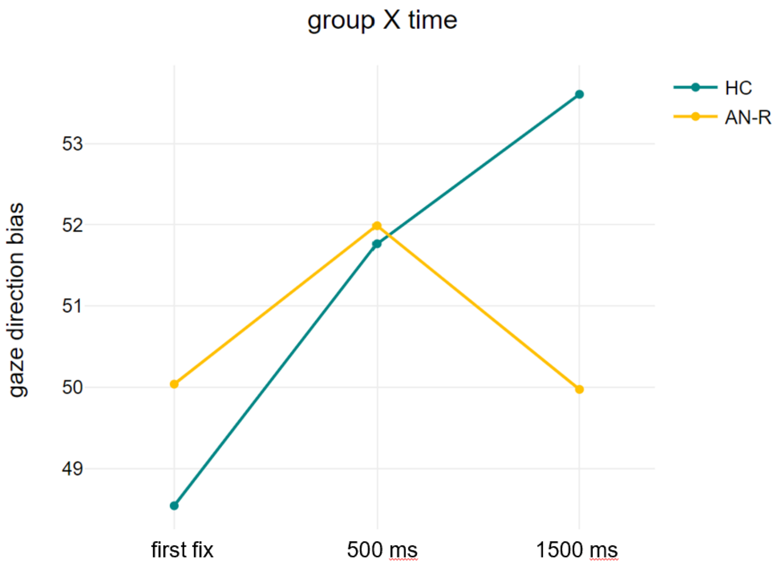

Figure 3.1.2 Graphical representation of the group X time interaction of the gaze direction bias score in the LMM.

Correlations between attentional bias scores and clinical/demographic variables

As shown in table 3.1.3, patients reported a significant negative correlation between the percentage of time spent looking at HCF in the 500 ms condition and time passed since the last meal (p=.046) and illness age of onset (p=.046). In the HC group, a significant positive correlation between the percentage of time spent looking at HCF in the 1500 ms condition and hunger level (p=.015), and a negative correlation between BMI and the percentage of trials in which participants were looking at LCF at the end of the 500 ms condition (p=.050) emerged.

Table 3.1.3 Correlations between attentional bias scores and clinical/ demographic variables in the two groups separately

	Age	*BMI*	*Hunger*	*Time since last meal*	*Illness duration*	*Age of onset*
HC group						
Gaze dir. HCF first fix	.174	-.046	.142	.228		
Gaze dir. HCF 500	.034	-.143	.204	.168		
Gaze dir. HCF 1500	.067	-.183	.248	.180		
Gaze dir. LCF first fix	.143	-.038	-.128	.124		
Gaze dir. LCF 500	-.028	-.282*	.019	.248		
Gaze dir. LCF 1500	-.119	.119	-.057	.087		
Duration HCF 500	.097	-.089	.008	.146		
Duration HCF 1500	.195	-.164	.352*	.149		
Duration LCF 500	.134	-.077	-.035	.140		
Duration LCF 1500	.166	-.050	.061	.142		
AN-R group						
Gaze dir. HCF first fix	-.277	.152	-.033	-.260	-.211	-.209
Gaze dir. HCF 500	-.249	.128	-.067	-.296	-.039	-.272
Gaze dir. HCF 1500	.002	.024	.101	-.227	-.031	.050
Gaze dir. LCF first fix	.114	.104	.092	-.090	.233	-.050
Gaze dir. LCF 500	.078	-.080	.172	.038	.141	-.048
Gaze dir. LCF 1500	-.111	-.129	-.004	-.138	-.072	.009
Duration HCF 500	-.275	.044	.006	-.300*	-.034	-.296*
Duration HCF 1500	.118	.092	.173	-.132	.084	.058
Duration LCF 500	.012	-.102	.134	-.104	.027	.049
Duration LCF 1500	.168	.014	.066	-.046	.200	.065

AN-R, Restrictive Anorexia Nervosa; HC, healthy controls; BMI, body mass index, HCF, high-calorie food; LCF, low-calorie food; RT, response time. Significant $p < .05$, uncorrected. Red boxes indicate negative correlations, while blue boxes indicate positive correlations. Stronger correlations are highlighted with more intense colours

Discussion

The overall aim of the present study was to assess AB toward both high-calorie and low-calorie foods in patients with restrictive AN, compared to healthy controls, using eye-tracking. The time course of the attentional deployment was also investigated, so as to shed light on the possible mechanisms involved in the maintenance of this bias.

In the first phase of attentional deployment, both patients and healthy controls displayed an avoidance of low-calorie foods, as evidenced by their first fixations directed more often toward the neutral stimuli than towards the food pictures. Contrary to what hypothesised, neither patients nor healthy controls displayed a bias toward high-calorie foods in this initial stage of attentional processing. This result is inconsistent with previous studies, which observed a tendency of both groups to initially orient their gaze more often toward high-calorie foods than neutral stimuli (Giel et al., 2011; Werthmann et al., 2019). Nevertheless, the analysis of gaze direction biases at 500 and 1500 ms revealed an avoidance pattern similar to the one observed in existing literature in patients with AN. Indeed, while healthy controls start to engage in food stimuli, to the point of showing a significant positive bias toward high-calorie foods at the end of the 1500 ms, patients with AN-R show a reduction of the bias between the 500 and 1500 ms. Interestingly, and contrary to what hypothesized, this pattern was independent from caloric content, suggesting a tendency of patients to avoid directing attention toward food stimuli in general.

As regards duration bias, we did not observe any difference between patients and controls, and both groups spent significantly more time looking at high-calorie food stimuli than neutral ones over the course of the 1500 ms. This evidence, together with the observation that in the gaze direction bias patients and controls only differed at the end of the 1500 ms, indicates that patients start do divert from healthy controls only in advanced stages of attentional deployment, thus suggesting the involvement of higher-order cognitive control systems rather than automatic mechanisms (Cisler & Koster, 2010; Gupta et al., 2019). This result is consistent with theories hypothesizing an hyperactivation of top-down regulatory mechanisms in the neurobiology of AN (Brooks et al., 2012), while it does not support the involvement of automatic altered reward responses or habits formation in modulating attentional processing of food stimuli (O'Hara et al., 2015; J. E. Steinglass & Walsh, 2016). However, it is possible that these automatic mechanisms intervene at a different stage of the complex process which starts with stimulus perception and ends with action execution. Given the complexity of these processes, future studies should adopt experimental paradigms that can better evaluate this point.

Time spent looking at high-calorie foods in the 500 ms condition was negatively associated with time passed since the last meal and age of onset in patients. The fact that longer intervals of food deprivation are associated with a reduced AB toward food stimuli is opposite to the pattern observed in healthy controls, who instead reported a positive correlation between hunger levels and time spent looking at high-calorie foods in the 1500 ms. However, this pattern is consistent with the study conducted by Santel and colleagues (2006), who observed a reduced activation of occipital visual areas in response to food stimuli in patients with AN in a hungry compared to a satiated state. According to the authors, this decreased activation might reflect a reduced attentional processing of food stimuli in patients in a hungry state, a mechanism that might support restrictive behaviours (Santel et al., 2006).

This study has some limitations that needs to be considered. Firstly, although we took into consideration subjective levels of hunger and time passed since last meal, these variables were not experimentally controlled, and they also differed between patients and controls. Moreover, we did not take into consideration participants' status of energy balance, which also could contribute to explain variability in AB scores. Secondly, we did not include an evaluation of the observed pictures. By asking participants to evaluate the wanting, liking, and anxiety evoked by each of the food presented, we could have assessed whether participants' attentional deployment was influenced by any of these variables.

Despite these limitations, to date this is the first study investigating the temporal course of attentional deployment towards food stimuli in patients with AN-R using eye-tracking. Compared to previous studies, we decided to recruit a more homogeneous sample comprising only female patients with restrictive AN, so as to avoid potential confounding factors. Moreover, we decided to also include low-calorie foods in order to investigate whether the hypothesized vigilance-avoidance pattern would be specific for threatening high-calorie stimuli or if it extended to foods in general.

To conclude, our study is consistent with previous research demonstrating a tendency of patients with AN-R to avoid directing their attention toward food stimuli, a bias that is consistent with patients' behaviour and could contribute to the maintenance of calorie restriction. Findings also add to the existing literature by demonstrating that differences between patients and controls only occur at advanced stages of attentional deployment, thus suggesting the involvement of cognitive control prefrontal circuits rather than more automatic mechanisms. A better understanding of the neural mechanisms sustaining psychiatric disorders can inform clinical practice, by providing the foundations for the development of new brain-directed treatments. From this point of view, our study provides very valuable information that can be used to plan both psychological rehabilitation and cognitive remediation treatments, as well as neuromodulation or neurofeedback protocols.

Supplementary Materials

Response Time data processing and Attentional Bias score calculation

Error trials and trials with RT lower than 300 ms, higher than 2500 ms, and more than three standard deviations above the individual mean were excluded. Participants with less than 80% valid trials were excluded from the analyses. For each of the experimental conditions (HCF presented for 500 ms, HCF presented for 1500 ms, LCF presented for 500 ms, and LCF presented for 1500 ms) a bias score was calculated by subtracting the mean RT in congruent trials (in which the probe followed the food) from the mean RT in incongruent trials (in which the probe followed the neutral stimulus). Positive scores indicate a faster response to the probe when it appears in the position occupied by the food picture and are therefore interpreted as a positive attentional bias toward foods. Negative scores, on the contrary, are interpreted as an avoidance of food stimuli.

Statistical Analyses

Statistical analyses were conducted using the software SPSS, version 26 (IBM, 2019). To assess the presence of significant biases toward or away from food in both patients with AN-R and HC, a series of one-sample t-test were conducted. To investigate the influence of different variables on response time AB score we conducted a linear mixed effect model (LMM) with 3 fixed factors (group, calorie, and time), and one random factor (participants' ID). Pearson correlations were used to assess whether RT bias scores at 500 and 1500 ms were associated with the percentage of trials in which participants were looking at food stimuli at that time points.

Results

One patient with AN-R was excluded from the analyses due to too many invalid trials. In the remaining sample, the mean of rejected trials was 5.45% (SD=3.29), with no differences between patients and healthy controls (t=-1.36, p=.178).

In table S1 are reported the mean AB scores for both patients with AN-R and HC, and the results of the one-sample t-tests. These results show that both patients and HC presented a positive AB toward LCF at 1500 ms, but only HC presented a bias toward HCF at 500 ms. The results of the LMM only revealed a significant calorie X time interaction (F=9.96, p=.002). As shown in figure S1, while the bias for LCF increased from 500 to 1500 ms, the bias for HCF decreased between the two conditions.

Significant positive correlations between RT bias scores and eye-tracking gaze direction bias scores were observed for HCF at 1500 ms (r=.450, p=<.001), and for LCF at 500 ms (r=.268, p=.009) and 1500 ms (r =.308, p =.004).

Table S1. Mean attentional bias scores and results of one-sample t-tests

	AN-R		HC	
	Mean (SD)	t (p)	Mean (SD)	t (p)
RT bias				
HCF 500	13.65 (77.85)	1.25 (.216)	41.98 (87.15)	3.54 (.001)
HCF 1500	-10.67 (73.09)	-1.04 (.302)	2.83 (94.73)	0.22 (.827)
LCF 500	13.74 (68.46)	1.43 (.158)	6.62 (69.69	0.70 (.488)
LCF 1500	24.56 (70.40)	2.49 (.016)	26.48 (80.09)	2.43 (.019)

AN-R, Anorexia Nervosa restrictive subtype; HC, healthy control; HCF, high-calorie food; LCF, low-calorie food. Scores higher than 0 indicate a positive AB toward food stimuli

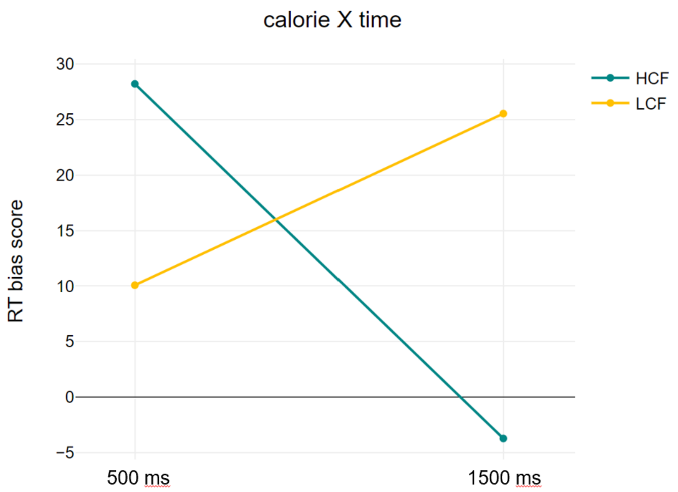

Figure S1 Graphical representation of the calorie X time interaction of the RT attentional bias score.

4 Motor Distractibility

4.1 Food induced distractibility in restrictive Anorexia Nervosa: different motor patterns for different foods as revealed by a mouse tracker evaluation.[4]

Abstract

An altered automatic processing of food stimuli may contribute to the maintenance of calorie restriction in patients with restrictive Anorexia Nervosa (AN-R). The present study aimed to assess whether task-irrelevant food distractors elicited a different interference effect in the motor actions of patients with AN-R compared to healthy controls (HC). 40 patients with acute AN-R and 40 HC performed an irrelevant distractor task in which they were required to perform a reaching movement from a starting point to a green dot, while an irrelevant distractor (a high-calorie food, low-calorie food, or neutral object) was presented in the middle of the screen. Mouse trajectories and response times (RT) were recorded. The analyses conducted on the kinematic variables revealed that while the trajectories of HC veered similarly toward the three categories of stimuli, AN-R patients showed an increased deviation toward low-calorie foods and a reduced deviation

[4] *Published:* Meregalli, V., Ambrosini, E., Tenconi, E., Schroeder, P. A., Cardi, V., Veronese, A., ... & Collantoni, E. (2023). Food induced distractibility in restrictive anorexia nervosa: Different motor patterns for different foods as revealed by a mouse tracker evaluation. *Appetite,* 106639. https://doi.org/10.1016/j.appet.2023.106639, under license CC BY 4.0.

toward high-calorie foods compared to neutral objects. No significant results emerged as regards RT. The pattern of responses observed in patients with AN-R (deviation increased toward low-calorie and reduced toward high-calorie) is consistent with their eating habits and may thus represent an implicit mechanism sustaining calorie restriction in patients with AN-R.

Introduction

Anorexia Nervosa (AN) is a severe mental disorder, characterized by body image disturbances, an intense fear of gaining weight or becoming fat, and a severe restriction of calorie intake, leading to significantly low body weight, and a range of medical complications (American Psychiatric Association, 2013). Although psychological interventions, such as cognitive behavioural therapy or family-based therapy, in the case of young patients, have shown some effectiveness in the treatment of this disorder, recovery rates are still poor, and it is estimated that less than 50% of patients obtain full remission (Brockmeyer et al., 2018; H. C. Steinhausen, 2002; Zipfel et al., 2015).

In recent years, a better understanding of the complex neurocognitive mechanisms involved in the pathophysiology of psychiatric disorders has made it possible the rise of informed therapeutic interventions, which have generally proved useful in improving patients' clinical outcome. Examples include cognitive remediation therapies, attentional bias modification and inhibitory control trainings, and non-invasive neurostimulation protocols (Mogg & Bradley, 2016; Perera et al., 2016; Wykes et al., 2011).

Studying the cognitive and behavioural mechanisms involved in the development and maintenance of AN could thus be important to improve patients' therapeutic options. So far, several studies have highlighted the presence of neurocognitive alterations in patients with AN, the most well established being high levels of inflexibility and poor central coherence abilities, which seem to translate into some of the psychopathological characteristics of the disorder, such as perfectionism and extreme attention to details (Meregalli et al., 2022; Tenconi et al., 2021).

Lately, research also focused on identifying possible neurobiological mechanisms involved in the maintenance of calorie restriction. According to some researchers, it has been hypothesized that patients with AN might exhibit an enhanced ability to resist food consumption and restrict calorie intake due to an altered automatic processing of food stimuli. In patients with AN, indeed, a change in reward system responsiveness might be associated with reduced automatic appetitive responses elicited by high-calorie food stimuli (O'Hara et al., 2015). Moreover, as the disease progresses, food restriction might pass from being an intentional and goal-directed behaviour to a habit, thus involving changes in implicit tendencies toward both high and low-calorie foods (J. E. Steinglass & Walsh, 2016). Overall, these models suggest that a shift in the automatic processing of food may sustain the maintenance of calorie restriction in patients with AN (Collantoni et al., 2016; Hill et al., 2016; O'Hara et al., 2015).

A possible way to assess differences in the automatic processing of food stimuli between patients and healthy controls is through the study of attentional biases (AB). Given their evolutionary and hedonic value, food stimuli are capable of attracting our attention, and it has been shown that the magnitude of the AB to food is associated with both hunger levels and subsequent food intake (Hardman et al., 2021). Action-based models of visual attention further strengthen the association between AB and behaviour. According to these models, when a stimulus captures our attention, a motor response toward that stimulus is automatically programmed and initiated. (Tipper et al., 1997; Welsh & Elliott, 2004). Consistent with this hypothesis, it has been demonstrated that, in the presence of an irrelevant distractor, participants' reaching movements tend to deviate toward the distracting stimulus (Welsh & Elliott, 2004), and that this deviation appears to be stronger in the presence of emotionally salient stimuli (Ambron & Foroni, 2015).

Several researchers in the field of eating disorders hypothesized a biased attentional processing of food in patients with AN. However, the studies conducted so far obtained quite inconsistent results (Lloyd & Steinglass, 2018; Stott et al., 2021). While some authors observed an increased attentional bias toward high-calorie foods in patients with AN (Neimeijer et al., 2017; Shafran et al., 2007; Smeets et al., 2008), other studies reported that patients with AN showed a lack of engagement/

attentional avoidance of high-calorie foods (Veenstra & de Jong, 2012; Werthmann et al., 2019) together with a tendency to preferentially direct their attention toward low-calorie food stimuli (Horndasch et al., 2020; Veenstra & de Jong, 2012). The lack of unambiguous results may depend on several reasons. A first reason lies in heterogeneities among recruited samples. While some studies included only patients with restrictive AN (AN-R) (Neimeijer et al., 2017; Veenstra & de Jong, 2012), other studies also included patients with binge-purging AN (AN-BP) or transdiagnostic samples (whole ED spectrum) (Giel et al., 2011; Jonker et al., 2019; Shafran et al., 2007). However, since food restriction and binge eating represent two opposite behavioural responses toward food, a different pattern of attentional deployment can be hypothesized, thus highlighting the need to consider each diagnostic category independently (Veenstra & de Jong, 2012). Secondly, many studies assessed AB using behavioural reaction times tasks, such as the modified Stroop test or the dot-probe paradigm (Dobson & Dozois, 2004; Shafran et al., 2007). These tasks have some important limitations: beyond having poor reliability, they also have a poor temporal resolution and can only capture a snapshot of attentional deployment (Price et al., 2019; Rodebaugh et al., 2016). Although eye-tracking has the potential to reveal the entire time course of attentional processing, the few studies that adopted an eye-tracking technology in patients with AN condensed continuous data acquired over a period of 2000 ms, or more, in only one measure of AB (Giel et al., 2011; Horndasch et al., 2020; Werthmann et al., 2019). However, during the course of attentional deployment, different neurobiological mechanisms are likely to intervene, going from automatic bottom-up mechanisms to more controlled and strategic ones (Gupta et al., 2019). Investigating the time course of the observed bias might thus be important to better delineating its nature.

Another shortcoming in the current literature on attentional processing of food in AN is the lack of studies investigating the impact of AB on participants' motor actions. This point takes on particular relevance, as it concerns the study of the complex relationship existing between implicit mechanisms (i.e., AB) and overt behaviours (i.e. actual food consumption) (San Martín et al., 2016).

Starting from action-based models of visual attention, Foroni and colleagues (2016) assessed the interference effect elicited by food-related stimuli on goal-directed reaching movements of healthy young adults. Participants performed an irrelevant distractor task on a digitalized tablet, and the analysis of movement trajectories revealed that they veered consistently toward both food items and food-related objects (e.g., kitchen tools). Although neutral non-food stimuli were not included in the task, these results suggest that food cues, given their strong motivational value, can automatically attract our attention and elicit involuntary approaching movements (Foroni et al., 2016).

In the present study, we aimed to assess whether food stimuli elicited a different interference effect in patients with AN compared to healthy controls. We asked participants to perform a series of mouse-reaching movements toward a target stimulus while an irrelevant distractor was presented in the middle of the screen. As irrelevant distractors we selected 3 different categories of stimuli: high-calorie foods (HCF; e.g. hamburger, fries, cake), low-calorie foods (LCF; e.g. salad, fruit, rice cakes), and neutral objects (e.g. pen, tape, keys). During the execution of the task, movement trajectories were recorded with the MouseTracker software (Freeman & Ambady, 2010). This approach, compared to more classical measures of AB, allows the collection of continuous data over time, and provides more direct evidence of the link between attentional processing and explicit motor behaviour. Since some of the heterogeneity observed in literature findings might be due to the difficulty of exploring a specific mechanism within a complex and multifaceted clinical context, it appears particularly important to employ recruitment strategies that can minimize potential confounding factors. Among these, diagnostic subtype is certainly one of the main possible elements, alongside others, such as sex. Male patients with AN, for example, may exhibit specific psychopathological profiles and behavioral patterns that should be investigated separately (Gueguen et al., 2012; Timko et al., 2019). In line with this, we decided to recruit only female participants and only patients with AN-R.

Consistent with the conclusions reached by previous studies (Foroni et al., 2016), we expected to observe, in the healthy control group, a greater attraction toward food stimuli, especially HCF, compared to neutral objects.

As regards patients with AN-R, our hypothesis is that a change in the automatic processing of food stimuli may sustain calorie restriction. Therefore, we expected to observe a pattern consistent with their real-life eating behaviour, characterized by the avoidance of HCF and the preferential consumption of healthy and LCF (Sysko et al., 2005).

In particular, we hypothesize that the natural tendency to pay attention to and approach HCF might be reduced in patients with AN-R, as already observed in previous studies (Paslakis et al., 2016; Veenstra & de Jong, 2012). In line with this, we expected to observe a reduction in movement deviation toward HCF in patients compared to healthy controls. Concerning LCF, instead, we hypothesized that they might elicit a greater response in patients compared to controls, given their greater motivational value. Therefore, we hypothesized a greater deviation toward LCF in patients compared to controls.

Methods

Participants

The sample included 40 patients with acute AN-R and 40 healthy controls (HC), all females.

Patients were recruited from the Eating Disorder Unit of the University Hospital of Padova, and they all met full criteria for AN-R, according to the DSM-5 (American Psychiatric Association, 2013). Exclusion criteria for both patients and HC were: 1) male gender; 2) age under 14 years; 3) current or lifetime neurological diseases; 4) mental impairment or learning disabilities; and 6) history of drug/alcohol dependence. An additional exclusion criterion for patients with AN-R was the presence of major psychiatric disorders in comorbidity (bipolar or schizophrenia spectrum disorders). Healthy controls were included only if they had no lifetime history of psychiatric disorders.

The sample size was determined based on an a priori power analysis performed on G*Power software (Faul et al., 2007), which revealed that 40 participants for each group were needed to detect a significant 2x2 within-between interaction with a small effect size (Cohen's f = 0.10, corresponding to d = 0.2 and $\eta 2p = 0.01$) with a statistical power $1-\beta = .80$ at a significant level $\alpha = .05$ and assuming a correlation among repeated measures of r=.8.

Written informed consent was provided by all participants. In the case of underage participants, consent was provided by their parents or legal guardian. The study was approved by the ethical committee of the Hospital of Vicenza (reference number 1831) and was conducted in accordance with the latest version of the Declaration of Helsinki.

Procedure

The diagnosis of AN-R was confirmed by an expert clinician using a diagnostic interview according to the Eating Disorders Section of the Structured Clinical Interview of the DSM-5 (American Psychiatric Association, 2013). The same interview was used to exclude the presence of a past or current eating disorder in HC. Before performing the experimental task, all participants provided a series of demographic and clinical information (age, body mass index (BMI), current pharmacological treatments), while data related to the age of onset was collected by the experimenter by looking at patients' medical records. To control for the possible confounding effect of hunger, participants also reported the time passed since their last meal (in hours). Hand lateralization was assessed through the Edinburgh Handedness Inventory (Oldfield, 1971), which yields scores ranging from –100, denoting consistent left-handedness, to +100, denoting consistent right-handedness. At the end of this assessment phase, all participants performed the Irrelevant Distractor Task.

Irrelevant Distractor Task

The Irrelevant Distractor Task was designed using the MouseTracker Software (Freeman & Ambady, 2010) and was performed on a computer screen of 24 inch, with a resolution of 1920 x 1080 pixels. Each trial started with the presentation of a starting point located at the bottom of the screen (see fig. 4.1.1). Participants were instructed to click on that starting button to begin the trial. Once they clicked on the starting point, a green dot appeared on the top right or left of the screen, and participants were required to perform a reaching movement toward the green dot using the mouse. Together with the green dot, an irrelevant distractor also appeared in the middle of the screen. Once participants reached and clicked on the green dot, the starting point reappeared following an inter-trial interval of 1500 ms. As irrelevant distractors, we selected 15 pictures of high-calorie foods (HCF), 15 pictures of low-calorie foods (LCF), and 15 neutral objects (OBJ). All the pictures were selected from the food.pics database (Blechert et al., 2019). The mean calorie content of HCF pictures was 570.18 Kcal, while the calorie content of LCF pictures was on average 72.05 Kcal. Each picture was displayed four times, two with the green dot appearing on the right and two with the green dot appearing on the left, for a total of 180 trials. The order of presentation of the trials was randomized. Before the beginning of the test session, participants were provided with 10 practice trials.

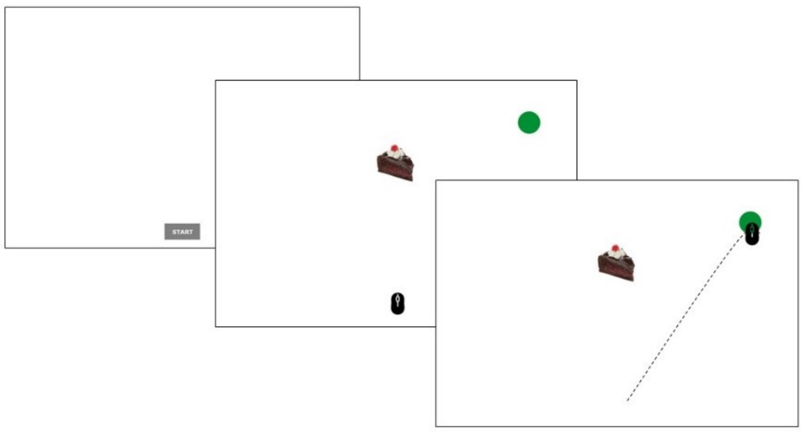

Figure 4.1.1. Graphical representation of a single trial of the irrelevant distractor task. After clicking on the starting button, participants were required to perform a reaching movement toward the green dot, while an irrelevant distractor was displayed in the middle of the screen.

Mouse trajectories analyses

The MouseTracker software recorded in real-time x- and y-coordinates of the computer mouse with a nominal sampling rate of 60 Hz. These data were pre-processed in Matlab (version 2017b; The Mathworks, Inc. Natick, MA) using in-house scripts to extract the kinematics measures to be analyzed. In order to compare and average trajectories, they were first remapped into a standard coordinate space to correct for small deviations in their starting and ending points and the mouse trajectories for the left targets were horizontally flipped (Freeman & Ambady, 2010).

The mouse trajectories were then interpolated to 1-ms resolution using a shape-preserving piecewise cubic interpolation and smoothed using a linear Savitzky-Golay filter (span: 50 ms) to mitigate measurement noise. Based on the time course of the x- and y-coordinates, we extracted different measures both at the trial level (one summary measure for each trial) and at the time level (time-resolved measures reflecting the online evolution and updating of the mouse response for each trial). Since the trajectories had different lengths across trials, time-resolved measures were time-normalized to 101 time steps.

To provide a more complete picture of the participants mouse responses, we computed three trial-level measures reflecting complementary aspects of the dynamics of the competitive attraction from the distractor and the resolution of this interference: 1) a measure of the degree of spatial attraction of the mouse trajectory toward the irrelevant distractor (Maximum Attraction, MaxAttr)[5], calculated as the minimum of the Euclidean distance of the recorded trajectory from the center of the distractor stimulus, which is akin to the measures commonly used in mouse tracking studies employing food distractors (e.g., the distractor index used by Foroni et al.,(2016)); 2) a measure of the smoothness and spatial complexity of the mouse trajectory (Trajectory Length, TrajL), computed as the total length of the trajectory. This measure reflects decision uncertainty and potential changes of mind and is akin to other commonly used measures of trajectory complexity (e.g., trajectory entropy or x-flips, see Freeman and Ambady, (2010)) indicating the competition of the response alternatives; 3) a measure of the temporal dynamics of mouse trajectories (Starting Angle, StartA), computed as the angle between the starting point and the mouse coordinate at 50 ms after the response initiation (which in turn was computed as the first time point when the cursor was moving at a speed greater than 10 cm/s for at least 100 ms). This is a marker of movement planning reflecting the early attentional

[5] Note that the reported results were confirmed with different measures of spatial attraction/ interference.

attraction toward the distractor, an effect that, to the best of our knowledge, has not been investigated in previous studies using food stimuli (but see e.g., Wirth et al., (2020), for evidence of StartA sensitivity to visuospatial conflict). For the sake of completeness, we also extracted RT as an overall, end-state performance measure. The TrajL and RT dependent variables (DV) were inverse-transformed (using the 1/DV formula) to mitigate non-normality of their distributions.

For the time-level measures, we analysed the normalized time course of the deviation (DEV) from the ideal trajectory (i.e., a straight trajectory connecting the starting point and the centre of the target), calculated for each time bin as the orthogonal distance from the recorded trajectory and the ideal one.

Statistical analyses

We performed linear mixed-effects model (LMM) analyses in Matlab. This is a robust approach for the analysis of repeated measures designs, which allowed us to model the experimental effects (i.e., the participants' group and type of distractor) while taking into account trial-by-trial variability, controlling for the related confounding variables, and providing flexibility in assessing random and fixed effects both at within- and between-subjects levels (Baayen et al., 2008).

For each trial-level dependent variables (i.e., MaxAttr, TrajL, StartA, RTs; see above), the tested a-priori LMM included as fixed effects the participants' Group (AN vs HC) and type of Distractor (LCF, HCF, Obj), as well as their interactions. We also included as a regressor the ordinal number of each trial (Trial, scaled and centred), which accounted for potential effects of fatigue or progressive learning of the task, as well as the participant's age and BMI, to control for possible confounding effects of these variables. As random effects, we included the by-subject random intercepts and random slopes for the fixed effect of Distractor type, as well as the by-items random intercept. The Wilkinson-notation formula for the model is: DV ~ 1 + Trial + Age + BMI + Group*Distractor + (Distractor|Participant + 1|Item).

Follow-up control analyses were performed using minimal models that did not included the terms for the confounding variables (i.e., Trial, Age, BMI) to verify the robustness of our results. Moreover, follow-up control analyses were performed on the AN group adding a predictor for the age of onset, as well as its interaction with the Food factor, to control for its effect in modulating the results. Finally, a set of follow-up control analyses were also performed on the AN group to exclude possible confounding effect of medication by using four separate models that each included a dummy predictor coding for patients who were taking 1) benzodiazepine, 2) antipsychotic, 3) antidepressant, or 4) any psychotropic medication at the time of the study.

The models were refitted after excluding observations with absolute standard residuals greater than 3 (no more than 0.7% of observations were eliminated). The statistical significance of the coefficients for each regressor was calculated using the Satterthwaite's method to estimate degrees of freedom. Effect size estimates are reported as d values.

The same model and procedure were adopted for time-level dependent variables, with the only difference that we fitted a model for each of their 101 time points. The resulting 101 t-values were then corrected for multiple comparisons using a cluster-based permutation test based on the cluster mass to limit the Type-I error inflation.

Results

Demographic characteristics

Table 4.1.1 summarizes the demographic and clinical characteristics of participants (both AN-R and HC). All participants were young Caucasian females. Patients with AN-R presented a lower BMI compared to HC, and they were significantly younger. No differences between patients and HC were instead observed in mean time passed since the last meal and both groups showed mixed handedness. As regards the pharmacological treatment, none of the HC was taking psychotropic medications, while 5 patients were under antidepressant drugs, 3 were taking benzodiazepines, and 7 were taking antipsychotics drugs (olanzapine or risperidone). Of the sample of patients with AN, 22 patients were following a partial hospitalization program, while 18 were enrolled in an outpatient treatment program.

Table 4.1.1. Demographic and clinical data

	AN-R Mean (SD)	HC Mean (SD)	U (p)
Age (years)	20.15 (5.06)	23.33 (2.55)	402 ($<$.001)
BMI (kg/cm^2)	16.01 (1.44)	20.75 (2.02)	28 ($<$.001)
Handedness	57.19 (27.35)	69.60 (20.18)	476 (.054)
Age of onset (years)	16.95 (3.31)	-	-
Time since last meal (hours)	2.24 (2.17)	3.31 (3.24)	545 (.064)

AN-R, Anorexia Nervosa restrictive subtype; HC, healthy control; BMI, Body Mass Index

Irrelevant Distractor Task

As regards the LMM analyses on trial-level dependent variables, they revealed a significant interaction between Group and Distractor (see Table 4.1.2) on all the kinematic measures (MaxAttr, which is the minimum distance between the distractor and mouse trajectory; TrajL, which is the length of the trajectory in pixel; and StartA, computed as the angle between the starting point and the mouse coordinate at 50 ms after the response initiation). Specifically, the results indicate that the effect of HCF distractors on the trial-level kinematic measures was stronger in AN participants as compared to HC ones. Indeed, in HCF trials, AN participants' mouse trajectories were less attracted by the distractor, were shorter (i.e., less curved), and started with a greater clockwise angle as compared to both LCF and Obj trials. By contrast, HC participants' mouse trajectories were not modulated significantly by the type of distractor (see Figure 4.1.2 and 4.1.3). Conversely, the Group by Distractor interaction was not statistically significant in the analysis of RTs. The analyses also revealed a significant effect of the Trial confounder on all the dependent variables. Moreover, participants' age significantly modulated their RTs, with slower RTs for older participants. No other effect was significant (see Table 4.1.2).

The follow up control analyses performed using the models without confounders confirmed the reported pattern of results, the only difference being the significant Group effect on the RT ($p = .002$), with faster RTs for AN participants.

The follow-up analyses performed on the AN group revealed that neither the age of onset (AoO; MaxAttr: *ps* > .769, and .428; TrajL: *ps* > .771, and .103; StartA: *ps* > .676, and .061; RT: *ps* > .250, and .806 for the AoO:Food$_{LC}$ and AoO:Food$_{HC}$ effects, respectively) nor the use of benzodiazepine (BDZ; MaxAttr: *ps* > .308, and .608; TrajL: *ps* > .868, and .849; StartA: *ps* > .258, and .791; RT: *ps* > .902, and .653 for the BDZ:Food$_{LC}$ and BDZ:Food$_{HC}$ effects, respectively), antipsychotic (PSY; MaxAttr: *ps* > .934, and .885; TrajL: *ps* > .900, and .681; StartA: *ps* > .738, and .649; RT: *ps* > .467, and .468 for the BDZ:Food$_{LC}$ and BDZ:Food$_{HC}$ effects, respectively), antidepressant (DEP; MaxAttr: *ps* > .258, and .280; TrajL: *ps* > .678, and .156; StartA: *ps* > .343, and .172; RT: *ps* > .372, and .087 for the DEP:Food$_{LC}$ and DEP:Food$_{HC}$ effects, respectively), or any psychotropic medication (MED; MaxAttr: *ps* > .383, and .433; TrajL: *ps* > .951, and .434; StartA: *ps* > .364, and .158; RT: *ps* > .336, and .125 for the MED:Food$_{LC}$ and MED:Food$_{HC}$ effects, respectively) did significantly modulate the results reported above.

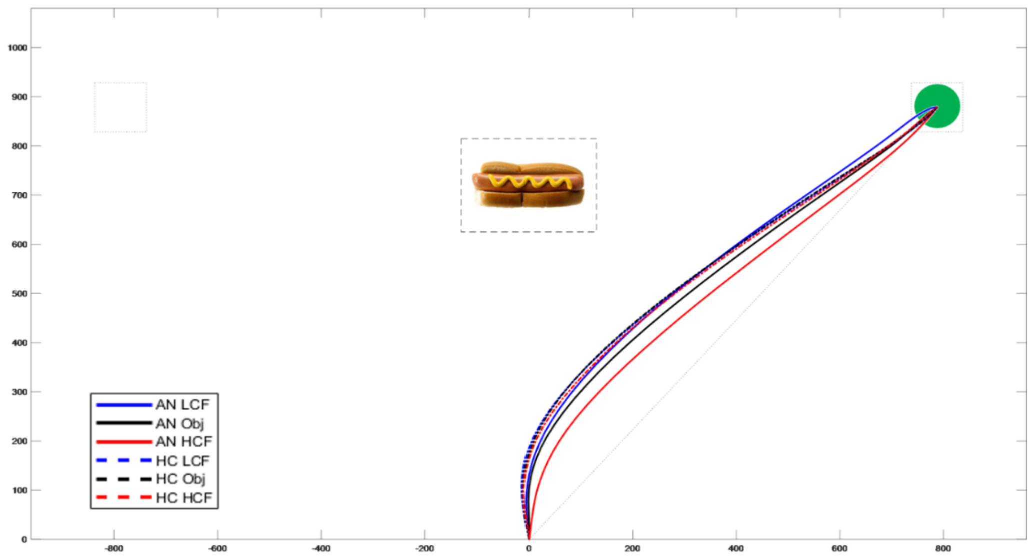

Figure 4.1.2. Graphical representation of a single trial of the irrelevant distractor task. After clicking on the starting button, participants were required to perform a reaching movement toward the green dot, while an irrelevant distractor was displayed in the middle of the screen.

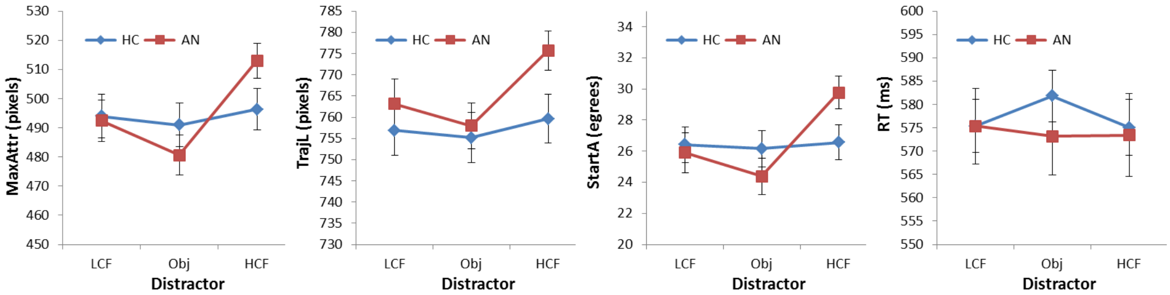

Figure 4.1.3. Mean maximum attraction (MaxAttr), trajectory length (TrajL), starting angle (StartA), and response time (RT) of the two groups in the presence of the different categories of distractors. Note that TrajL and RT were inverse-transformed.

As regards the LMM analyses on the time-level dependent variables DEV, it confirmed and refined the result reported above for the MaxAttr trial-level variable. Indeed, it revealed a significant Group by Distractor interaction for most of the middle part of the trajectories: as compared to Obj trials, the deviation of AN participants' mouse trajectory was significantly smaller in HCF trials (for the time bins between 18 and 68) and larger in LCF trials (for the time bins between 31 and 76), respectively (see Figure 4.1.4).

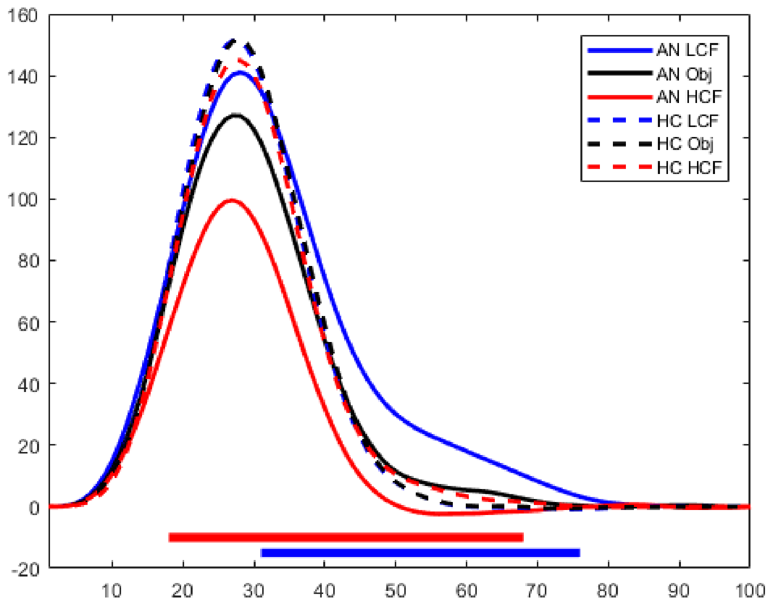

Figure 4.1.4 Mean time-dependent deviations from the ideal trajectory of the two groups in the presence of the three categories of distractors. The lines at the bottom of the graph represent the time bins for which the deviation of AN participants' mouse trajectory was significantly smaller in HCF trials (red) and larger in LCF trials (blue) than in the Obj trials. Abbreviations: AN, anorexia nervosa; HC, healthy controls; LCF, low-calorie foods; HCF, high-calorie foods; Obj, neutral objects.

Table 4.1.2 Results of LMM analyses on trial-level dependent variables

	MaxAttr					TrajL					StartA					RT				
Effects	*b*	*SE*	*t*	p	*d*	*b*	*SE*	*t*	*p*	*d*	*b*	*SE*	*t*	*p*	*d*	*b*	*SE*	*t*	*p*	*d*
Intercept	491.51	90.54	5.43	$<.001$	0.60	755.21	-70.60	-10.70	$<.001$	-1.18	26.15	15.13	1.73	0.088	0.19	581.84	147.96	-3.93	$<.001$	-0.44
Group_{AN}	-10.34	25.33	-0.41	0.684	-0.04	2.75	-19.97	-0.14	0.891	-0.01	-1.78	4.26	-0.42	0.678	-0.04	-8.67	40.28	0.22	0.830	0.02
Age	-2.65	1.88	-1.41	0.162	-0.16	0.52	-1.46	-0.36	0.722	-0.04	0.01	0.31	0.03	0.980	0.00	12.59	3.07	-4.10	$<.001$	-0.46
BMI	-3.87	4.30	-0.90	0.371	-0.10	-4.03	-3.35	1.20	0.232	0.13	-0.50	0.72	-0.69	0.489	-0.08	6.80	7.03	-0.97	0.336	-0.11
Trial	-6.31	1.12	-5.63	$<.001$	-0.05	2.62	-0.92	-2.86	0.004	-0.02	-1.11	0.24	-4.63	$<.001$	-0.04	7.76	1.20	-6.47	$<.001$	-0.05
Food_{LC}	2.97	4.46	0.67	0.507	0.08	1.64	-3.39	-0.48	0.631	-0.05	0.26	0.87	0.30	0.767	0.02	-6.48	4.26	1.52	0.133	0.17
Food_{HC}	5.37	4.24	1.27	0.207	0.11	4.43	-3.57	-1.24	0.218	-0.13	0.42	0.85	0.49	0.624	0.02	-6.80	4.25	1.60	0.113	0.18
Group_{AN} : Food_{LC}	-1.56	5.97	-0.26	0.794	-0.03	6.26	-4.66	-1.34	0.181	-0.09	-0.51	1.23	-0.42	0.678	-0.03	-0.01	6.03	0.00	0.998	0.00
Group_{AN} : Food_{HC}	16.66	5.63	2.96	0.003	0.11	16.11	-4.92	-3.27	0.001	-0.26	3.20	1.21	2.65	0.008	0.12	-1.61	6.01	0.27	0.790	0.03

AN, Anorexia Nervosa; LC, low-calorie; HC, high-calorie; BMI, Body Mass Index; MaxAttr, Maximum Attraction; TrajL, Trajectory Length; StartA, Starting Angle, RT, Response Time

Discussion

In this study, an Irrelevant Distractor Task was adopted to assess whether food stimuli elicited a different automatic response in patients with AN-R compared to healthy controls. During the task, participants were asked to perform a series of goal-directed movements toward a target while an irrelevant distractor, which could be either a high-calorie food, a low-calorie food, or a neutral object, was displayed in the middle of the screen. To investigate whether participants' reaching movements were differentially influenced by the three categories of distractors, mouse trajectories and response times were analyzed.

As expected from previous research, participants' movements deviated from the ideal trajectory in the presence of an irrelevant distractor (Ambron & Foroni, 2015; Foroni et al., 2016; Welsh & Elliott, 2004). However, while in healthy controls mouse trajectories veered similarly toward the three categories of stimuli, patients with AN-R displayed a different pattern of response for HCF, LCF, and neutral objects.

The analyses conducted on trial-level kinematic variables revealed that patients with AN-R displayed a lower deviation toward HCF compared to both LCF and neutral objects. Indeed, in the presence of HCF patients with AN started the movement with a greater clockwise angle, performed shorter (less curved) movements, and remained farther away from the distractor compared to when LCF or objects were presented. These results were confirmed by the analyses conducted on the time-dependent kinematic variable, which showed that for most of the central part of the movement patients' deviation from the ideal trajectory was lower in the presence of HCF than in neutral objects' trials.

Taken together, these findings suggest that high-calorie foods exerted a reduced interference effect on the motor actions of patients with AN-R. Based on our experimental design, we can hypothesize that this reduced motor/behavioral propensity might have an implicit basis, and, therefore, it could be mediated by the bottom-up processing of food stimuli. More specifically, this notion suggests that the motor representation evoked by specific food stimuli in individuals with AN may be – at least partially –

mediated by sensory inputs, particularly through the visual/attentional channel. This implicit process is probably linked to the activation of neural circuits associated with automatic behavioral responses and/or reward-related processes, as suggested in previous research and neurobiological models of AN (O'Hara et al., 2015). Although this is the first study assessing motor distractibility in patients with AN, similar results have been reported in some studies assessing approach-avoidance tendencies by means of reaction times, which showed that the automatic tendency to approach HCF observed in healthy controls was absent in patients with AN (Neimeijer et al., 2015, 2019; Paslakis et al., 2016).

As regards the time-dependent kinematic variable, results also showed that in patients with AN-R, movements' trajectories presented a greater deviation toward LCF compared to neutral objects. This increased motor attraction toward LCF has never been reported before. However, it is consistent with previous studies showing a relatively strong attentional engagement with LCF in AN (Veenstra & de Jong, 2012). This tendency to pay greater attention to and approach LCF is coherent with patients' motivational drives and could implicitly sustain the tendency of patients with AN to preferentially choose and consume foods with a low-caloric content (J. Steinglass et al., 2015).

As regards healthy controls, the analyses conducted on both the trial-level and time-dependent kinematic variables showed that movements' trajectories were similar for the different types of distractors. This evidence doesn't support our hypothesis. Indeed, since food represents a highly rewarding stimulus, we expected to observe, in the control group, a greater interference effect in response to foods, especially high calorie, compared to neutral objects. This finding is also inconsistent with the conclusions drawn by Foroni and colleagues (2016), who interpreted trajectories' deviation toward the distractors as an index of the high motivational value of food stimuli. However, since they only included food-related pictures, they could not investigate whether also neutral and not food-related objects would elicit a similar interference effect.

Lastly, the analysis conducted on response times yielded no significant results. Neither patients with AN nor healthy controls took significantly longer to perform the movement in response to specific distractors' categories.

Overall, the pattern of responses observed in patients with AN-R (deviation increased toward LCF and reduced toward HCF) is consistent with their eating habits, characterized by the avoidance of highly caloric foods and the preferential consumption of healthy low-calorie foods (Sysko et al., 2005), and may reflect the automatization of behaviours that in the initial stages of the disease are performed under higher cognitive control and effort (Lally et al., 2010; Uniacke et al., 2018). Since these mechanisms could contribute to the maintenance of restrictive behaviors in our experimental sample, future studies should further investigate how implicit attentional/behavioral mechanisms can contribute to the upkeep of AN-R psychopathology. If these results were confirmed, it would be appropriate to evaluate them from a translational point of view, i.e., by planning therapeutic interventions aimed at modifying implicit tendencies towards food in patients with AN. A promising approach could be to adopt modified versions of behavioural tasks such as the go/no-go task or the stop signal task, in which new stimulus/response association can be learned (Aulbach et al., 2019; Cardi et al., 2022).

This study has some limitations that needs to be considered. Firstly, although we included age as a covariate to the model, the two groups significantly differed as regards to this variable. Secondly, we did not include an evaluation of the observed pictures. By asking participants to evaluate the wanting, liking, and anxiety evoked by each of the food presented, we could have assessed whether participants' behaviour was influenced by any of these variables. Third, although we took into consideration the time passed since the last meal, this variable was not experimentally controlled. Since self-reported information regarding hunger and eating can be inaccurate in patients with AN, this information should be taken with caution. Lastly, some patients with AN were taking psychotropic medication at the time of the study, albeit control analyses suggested that this did not bias the reported results.

Despite these limitations, this is the first study assessing motor distractibility toward foods in patients with AN. The decision to recruit only female patients with AN restrictive subtype, instead of a transdiagnostic sample of patients with eating disorder, led to a more homogeneous sample in terms of eating habits and, possibly, automatic tendencies toward foods. Moreover, the inclusion of different types of stimuli (HCF, LCF, and neutral objects) enabled us to assess how they differentially interfered with goal-directed actions in both healthy controls and patients.

In conclusion, the present research explored the motor distractibility towards different categories of food stimuli in a sample of patients with AN-R, highlighting a reduced behavioural propensity towards high-calorie stimuli in the experimental sample compared to the healthy controls one. This reduced propensity is consistent with the eating pattern observed in AN-R and may be identified as an important component of those mechanisms participating in the ascending and descending processing systems of salient stimuli that is hypothesized to underlie the pathogenesis and the maintenance of the disorder. The presence of a greater motor propensity toward low-calorie stimuli compared to neutral ones in the AN-R sample seems in line with this hypothesis. Further studies are needed to confirm these patterns, to better explore their nature, and evaluate a possible role of these processes in a translational perspective.

5 Approach-Avoidance tendencies

5.1 Easy to get, difficult to avoid: behavioral tendencies toward high-calorie and low-calorie food during a mobile approach-avoidance task interact with body mass index and hunger in a community sample[6]

Abstract

In recent years, different studies highlighted the importance of assessing behavioral tendencies toward different food stimuli in healthy and pathological samples. However, heterogeneities in experimental approaches and small sample sizes make this literature rather inconsistent. In this study, we used a mobile approach-avoidance task to investigate the behavioral tendencies toward healthy and unhealthy foods compared to neutral objects in a large community sample. The role of some contextual and stable subjective variables was also explored. The sample included 204 participants. The stimuli comprised 15 pictures of unhealthy foods, 15 pictures of healthy foods, and 15 pictures of neutral objects. Participants were required to approach or avoid stimuli by respectively pull or push the smartphone toward or away from themselves. Accuracy and reaction time

[6] *Published:* Collantoni, E., Meregalli, V., Granziol, U., Gerunda, C., Zech, H., Schroeder, P. A., ... & Favaro, A. (2023). Easy to get, difficult to avoid: behavioral tendencies toward high-calorie and low-calorie food during a mobile approach-avoidance task interact with body mass index and hunger in a community sample. *Appetite*, 106619. https://doi.org/10.1016/j.appet.2023.106619, under license CC BY 4.0.

of each movement were calculated. The analyses were conducted using a generalized linear mixed-effect model (GLMMs), testing the two-way interaction between the type of movement and the stimulus category and the three-way interactions between type of movement, stimulus, and specific variables (BMI, time passed since the last meal, level of perceived hunger).

Our results evidenced faster approaching movement toward food stimuli but not toward neutrals. An effect of BMI was also documented: as the BMI increased, participants became slower in avoiding unhealthy compared to healthy foods, and in approaching healthy compared to unhealthy stimuli. Moreover, as hunger increased, participants became faster in approaching and slower in avoiding healthy compared to unhealthy stimuli. In conclusion, our results show an approach tendency toward food stimuli, independent from caloric content, in the general population. Furthermore, approach tendencies to healthy foods decreased with increasing BMI and increased with perceived hunger, indicating the possible influence of different mechanisms on eating-related behavioral tendencies.

Introduction

Eating behaviours are determined by multiple factors, which include hedonic drives, homeostatic needs, and deliberate choices. These systems do not work independently from each other, but they are integrated at different levels, ranging from genes to behaviours (Saper et al., 2002). To date, many research efforts have been made to understand how these mechanisms work in determining food intake and weight regulation (Makaronidis & Batterham, 2018; Woods & D'Alessio, 2008). Physiological models suggest the presence of feedback mechanisms regulating the balance between caloric intake and expenditure at a set point, which is probably encoded in the brain (Speakman et al., 2011). However, they struggle to explain many aspects related to social, environmental, and psychological determinants of eating behaviours, that appear particularly relevant in modern Western environments as well as in abnormal eating behaviours, such as sustained overeating or undereating often observed in eating disorders (Giskes et al., 2011; Keel & Forney, 2013).

Cognitive research on nutrition has particularly focused on trying to understand how the balance between cognitive control mechanisms and behavioural automaticity may alter respective to certain food categories and contribute to abnormal eating patterns (Fürtjes et al., 2020; Kakoschke et al., 2017). Various experimental paradigms have been proposed in order to explore the role of the different bottom-up/top-down processes in the regulation of eating behaviours, focusing in particular on those mechanisms sustaining the cognitive processing of foods from early attention to motor action (Hou et al., 2011). Exploring these mechanisms could help explain the respective role of cognitive control/behavioural automaticity in regulating food intake and identifying potential treatment targets if dysregulation occurs at that level.

In recent years, an experimental paradigm that has sparked some interest in assessing automatic tendencies toward food is the approach-avoidance task (AAT). This task was introduced by Solarz (1960) and later adapted for use on personal computers (Chen & Bargh, 1999; Rinck & Becker, 2007). The traditional AAT requires participants to pull or push a joystick in response to a picture, e.g., high-calorie food. Automatic approach tendencies are reported if pulling in response to food is faster than pushing. The central assumption of this paradigm is that approach and avoidance behaviours deploy with a certain level of congruity with the appetitive or aversive value of a stimulus (Kakoschke et al., 2019). In the eating domain, approach/avoidance tendencies have been assessed with respect to different characteristics related to both food qualities (for example, palatability, calorie content, level of processing) and subjective status or attitudes (for example, levels of food craving or hunger scores) (Castellanos et al., 2009; Moore et al., 2022). Moreover, some studies have focused on clinical samples to explore whether biased tendencies toward food may sustain specific disordered eating patterns (Kollei et al., 2022; Loijen et al., 2020). However, a methodological limitation in assessing behavioural tendencies toward food has been recently highlighted with regard to the experimental setup. To date, most studies have used a joystick-based paradigm, which has been criticized since it might excessively limit the extension of motor trajectories (Schroeder et al., 2016), the naturalistic value of movements (Meule et al., 2020), and, more in general, the ecological experimental validity (Lange & Pauli, 2019).

Based on these observations, recent research has used paradigms that allow the assessment of reaching and avoiding tendencies through more naturalistic movements using virtual reality or touchscreen-based AAT (Schroeder et al., 2016; van Alebeek et al., 2021). Another experimental implementation of the AAT has been proposed by Zech and colleagues (2020), which involves executing the task on a smartphone. In this mobile version of the AAT, the phone must be moved closer or away from oneself in order to simulate, in a flexible and naturalistic way, an approach or avoidance movement toward a specific item. The advantages offered by this method over more conventional ones are manifold and include the possibility of performing the task through extensive and naturalistic approach/avoidance arm movements and the opportunity to perform the task in non-laboratory settings. The latter is key to recruiting larger samples and ensuring greater ecological validity.

To date, approach/avoidance tendencies towards food stimuli have been measured mostly in response to appetitive and highly palatable stimuli, in order to explore how biases in these behaviours might be associated with craving or hunger measures (van Alebeek et al., 2021; Wittekind et al., 2021). However, recent studies have broadened this focus by also including healthy and/or low-calorie food items, in order to understand whether mechanisms other than hedonics may support automatic action execution. These studies reported the presence of a greater approach tendency toward low-calorie foods compared to high-calorie foods in both the general population and overweight/obese individuals, thus suggesting a possible role of motivational drives in influencing approach tendencies (Kahveci et al., 2021; Moore et al., 2022). Overall, the heterogeneity observed among AAT research in the eating domain is suggestive of the presence of different mechanisms underlying automatic behaviours toward food. These probably include both context-related variables (hunger and desire to eat), and more stable parameters, such as liking for specific food items or other individual characteristics. In this second case (behavioural automaticity rooted in stable individual characteristics), it may also be conceivable that behavioural tendencies have some regulatory role, thus sustaining stable subjective traits that may differently influence healthy/unhealthy eating habits and which can contribute to the maintenance of individual BMI (Maas et al., 2017).

The primary aim of this study was to analyze approach/avoidance tendencies toward different types of foods (low calorie/healthy and high calorie/unhealthy) compared to neutral objects, in a large sample of subjects from the general population, ranging from underweight to overweight (BMI ranges from 17 kg/m^2 to 29 kg/m^2). The secondary aim was to test whether approach/avoidance tendencies interact with both contextual factors (i.e., hunger, time elapsed since the last meal, and wanting for specific foods) and more stable variables (i.e., liking and fear scores for specific items and BMI). For the first aim, it was hypothesized that the tested sample would show a bias towards food stimuli compared to neutral items, with no specific preference for low-calorie or high-calorie foods. With regards to the second aim, no specific hypotheses were made due to the large heterogeneity of findings in the literature, and the exploratory nature of this study.

Methods

Participants

Participants were recruited from the general population through flyers, online adverts, and direct contact with the experimenters. Inclusion criteria were: 18 years or older, being fluent in Italian, having a BMI comprised between 17 and 30, and having a score lower than 2.8 on the global scale of the Eating Disorder Examination Questionnaire (EDE-Q) (Mond et al., 2008). In total, 244 participants completed the study. However, 7 were excluded for EDE-Q score higher than 2.8, and 33 were excluded because they did not reach the threshold for the minimum number of valid trials (see data exclusion section). The final sample consisted of 204 participants, with a mean age of 24.14 (SD = 9.12) and a BMI of 22.03 (SD = 2.76). 133 were females (age: 24.29 (SD = 8.76), BMI: 21.35 (SD = 2.57)), and 71 were males (age: 23.87 (SD = 9.83), BMI: 23.28 (SD = 2.68)).

All participants provided written informed consent prior to testing. The study was approved by the ethical committee of the Department of Psychology at the University of Padova (protocol number: 4149) and was conducted in accordance with the latest version of the Declaration of Helsinki.

Mobile AAT application

The mobile AAT app was programmed in Java using Android Studio (Zech et al., 2020). It could be downloaded from the University of Padova website (http://aatmobile.neuroscienze.unipd.it/) and installed on any Android smartphone. Once the application was started, participants provided written informed consent and confirm to be over 18 years old. Then, they were asked to report the following demographic and clinical information: age, education level, work condition, height, weight, and pharmacological treatment. To control for the effect of hunger, participants also reported the time passed since their last meal (in minutes) and the perceived level of hunger (on a scale from 1 to 5). Following this initial assessment, participants completed the approach-avoidance task, which is described in more detail in the following section. At the end of the task, they rated their level of liking ("how much do you like the taste of this food?"), wanting ("how much would you like to eat this food in this moment?"), and fear ("how much anxiety does the idea of eating this food cause you?") towards each of the food stimuli observed during the task using a likert scale going from 1 to 5. .

Lastly, participants completed the EDE-Q (Calugi et al., 2017; Fairburn & Beglin, 1994) which is a 28-item self-report measure of eating disorder psychopathology in which higher scores reflect greater severity, with a cut-off ≥ 2.8 on the global EDE-Q score for probable clinical cases (Mond et al., 2008).

Approach-Avoidance Task

In the AAT, participants were required to approach or avoid specific stimuli by either pulling their phone toward themselves or pushing it away, as shown in figure 5.1.1.

The stimuli comprised 15 pictures of high-calorie and high-processed foods (HCF), 15 pictures of low-calorie and low-processed foods (LCF), and 15 pictures of neutral objects (N). The pictures were all selected from the food.pics database (Blechert et al., 2019)[7], and an analysis of their characteristics revealed that HCF pictures had a significantly higher intensity (F (2,42) = 7.40, p = .002) and complexity (F (2,42) = 10.89, p < .001) than LCF and neutral pictures (Blechert et al., 2019).

Before starting the experiment, participants were provided with written instructions and two animated GIFs that displayed how to perform the approach and avoidance movements. The task was divided into two blocks. In one block, participants were instructed to pull food stimuli toward themselves and push objects away from themselves, while in the other block participants had to approach neutral objects and avoid food stimuli. The order of block presentation was randomized between participants. During each block, 20 pictures of each category (HCF, LCF, neutral objects) were presented, for a total of 120 trials. At the beginning of each block, and in the middle of each block, participants were instructed as to which stimuli to approach and which ones to avoid, and they were asked to respond as fast as possible. Each trial started with a fixation point, displayed for 1500 ms. Following the fixation point, a picture was displayed in the middle of the screen. If participants did not respond to the picture within two seconds, a clock was displayed on the screen to inform them that the trial had timed out. Before starting the real test, participants were provided with a series of additional practice trials, which were followed by a response feedback (an X for incorrect responses, and a V for correct responses). Participants could start the real test only after correctly responding to 16 practice trials.

For each trial, the phone's accelerometers and gyroscopes tracked the gravity- and rotation-corrected acceleration of the movement in the direction perpendicular to the face of the screen (100Hz sampling rate). Based on the acceleration response, the accuracy and reaction time (RT) of

[7] IDs of selected pictures: HCF (17, 20, 22, 25, 48, 68, 88, 106, 107, 131, 145, 167, 310, 339, 514); LCF (215, 249, 250, 251, 252, 258, 260, 261, 267, 278, 365, 430, 432, 460, 466); N (1009, 1012, 1026, 1059, 1130, 1132, 1144, 1151, 1155, 1210, 1213, 1218, 1251, 1256, 1273)

each movement were calculated. The procedure to preprocess data was the same used by Zech and colleagues (2020).

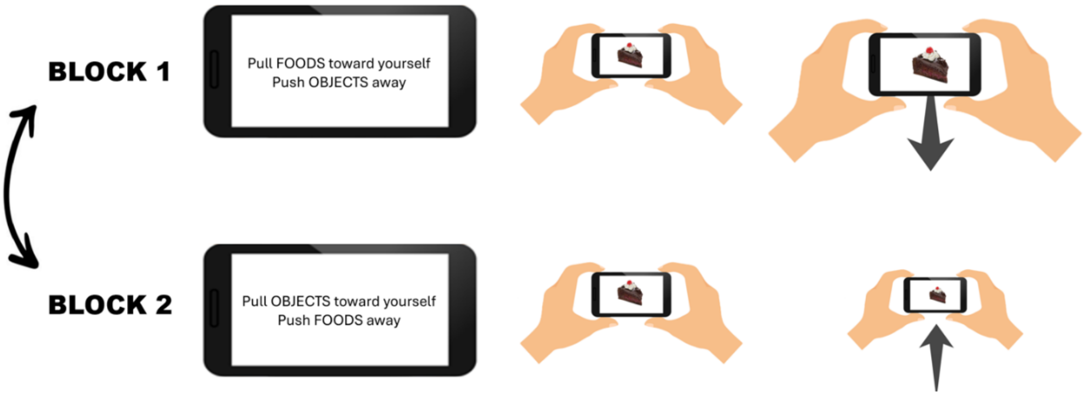

Figure 5.1.1 Experimental Setup. The task consists of two blocks, the order of which is randomized. In one block participants are instructed to pull food stimuli toward themselves and push objects away from themselves, while in the other block participants have to approach neutral objects and avoid food stimuli. During each block, 20 pictures of each category (HCF, LCF, neutral objects) are presented, for a total of 120 trials.

Statistical Analyses

Data exclusion

Following the procedure suggested by Zech and colleagues (2020), practice trials, error trials, trials with missing sensor data, and trials with RT below 200 ms or over two standard deviations from the mean RT were considered invalid. Participants with less than 80% valid experimental trials were excluded. In total, 33 participants were excluded and within the final sample, 9.75% of the experimental trials were excluded.

Data analysis

Statistical analyses were performed in R (R Core Team, 2022). Firstly, we were interested in assessing whether RTs of approach and avoidance movements were influenced by the type of stimulus. Since RTs were not normally distributed, we decided to test our hypothesis using a generalized linear mixed-effect model (GLMM), with a model tested under a Gamma distribution (identity link function). Participants' ID and trial number were used as clustering and random variable, respectively, and mixed effect models were used because of the advantage to account for repeated measures and missing data. We decided to set a priori comparisons and, in particular, reverse Helmert contrasts were used to test the average difference in RTs between (a) neutral objects and food in general, and (b) between high and low-calorie foods. For both contrasts, we were mainly interested in the two-way interaction between the type of movement (approach vs avoid) and the stimulus category (food vs objects; low vs. high-calorie foods).

The GLMMs were tested using the lme4 package (Bates et al., 2015) on R software (R Core Team, 2022). Effect sizes were estimated by calculating Cohen’s d through the t_to_d() function belonging to the effectsize package (Ben-Shachar et al., 2020). To avoid possible confounding factors, gender was added to the model as a covariate. Age was not used as a covariate because it had a very small standard deviation. Post hoc comparisons were tested using the emmeans package (Lenth, 2016).

As a second set of analyses, we wanted to test whether the previous model could be influenced by other variables, such as participants’ BMI, time passed since last meal, and level of perceived hunger. For each of those variables, independent GLMMs were calculated to establish the three-way interactions between type of movement, stimulus (food/objects and HCF/LCF), and each variable. Since those variables were measured on continuous scales, whenever significant interactions occurred, both simple slope analyses and/or post hoc comparisons across equivalent intervals on the third variable were performed. For instance, in the case of the BMI, values were clustered into intervals of 3 points (i.e.., 17, 20, 23, and over 26). To control for possible confounding factors, the linear associations between hunger, time passed since the last meal, and BMI were tested with Spearman's rank correlations.

Finally, it was tested whether the RTs of approach and avoidance movements could be influenced by liking, wanting, and fear ratings on a trial-by-trial base. GLMMs were calculated to test two-way interactions between type of movement and liking, wanting, or fear.

Results

Type of movement by stimulus interaction

Concerning the comparison between neutral objects and food in general, a statistically significant two-way interaction between type of movement and stimulus emerged ($\beta = -49.73$, $p < .001$, $d = 0.41$, Figure 5.1.2). In particular, participants were faster in approaching than avoiding food stimuli, while this effect was not observed for neutral objects, suggesting the presence of an approach bias only in response to food stimuli. No significant interaction (stimulus x type of movement) was observed for the comparison between HCF and LCF stimuli ($\beta = -27.63$, $p = 0.46$, $d < .001$).

Considering the main effects, we observed that participants were generally faster in responding to food than neutral stimuli ($\beta = 32.42$, $p < .001$, $d = 0.25$) and they were faster in responding to LCF compared to HCF stimuli ($\beta = 12.17$, $p < .001$, $d = 0.14$). In general, participants were also faster in approaching stimuli rather than avoiding them ($\beta = 24.62$, $p < .001$, $d = 0.22$).

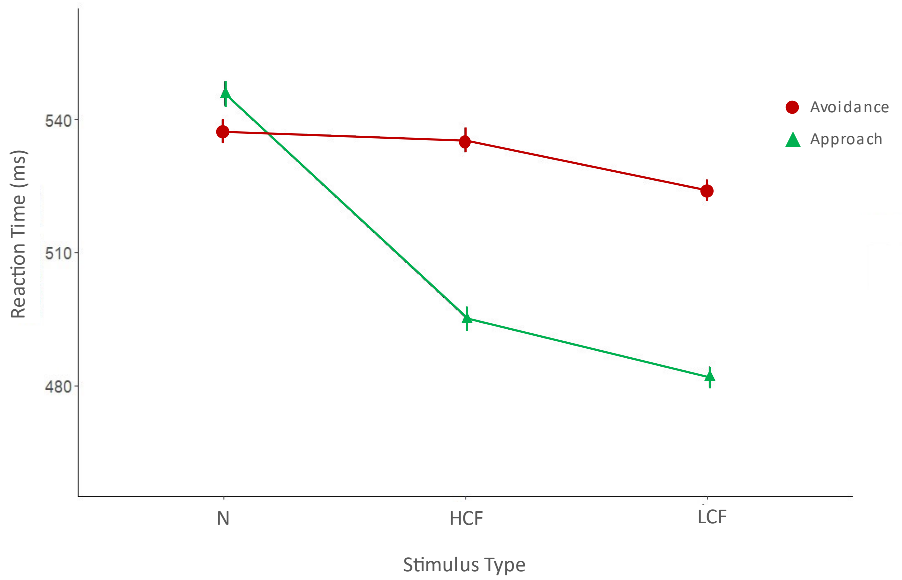

Figure 5.1.2. Mean (SE) reaction times for avoidance and approach movements for the three categories of stimuli. Abbreviations: N, neutral objects; HCF, high-calorie foods; LCF, low-calorie foods.

The association with the BMI

Concerning the comparison between neutral objects and food in general, there was a statistically significant 3-way interaction between BMI, stimulus, and type of movement ($\beta = 1.26$, $p < .001$, $d = 0.05$, Figure 5.1.3). In particular, although participants were generally faster in approaching food compared to neutral stimuli, this difference decreased as BMI increased, thus suggesting a reduced approach bias toward foods with increasing BMI (Table 5.1.1). As regards avoidance movements, the difference between food and neutral objects increased as the BMI decreased, and post hoc comparisons revealed that only participants in the lowest BMI range were faster in avoiding food stimuli than neutral objects (table 5.1.1). Comparing high- and low-calorie food stimuli, the results showed that the 3-way interaction (BMI x stimulus x type of movement) was significant ($\beta = 1.17$, $p < .001$, $d = 0.06$). As the BMI increased, participants became slower in avoiding HCF compared to LCF, and slower in approaching LCF compared to HCF, thus suggesting a reduced approach tendency toward LCF compared to HCF at increasing BMI (Figure 5.1.4).

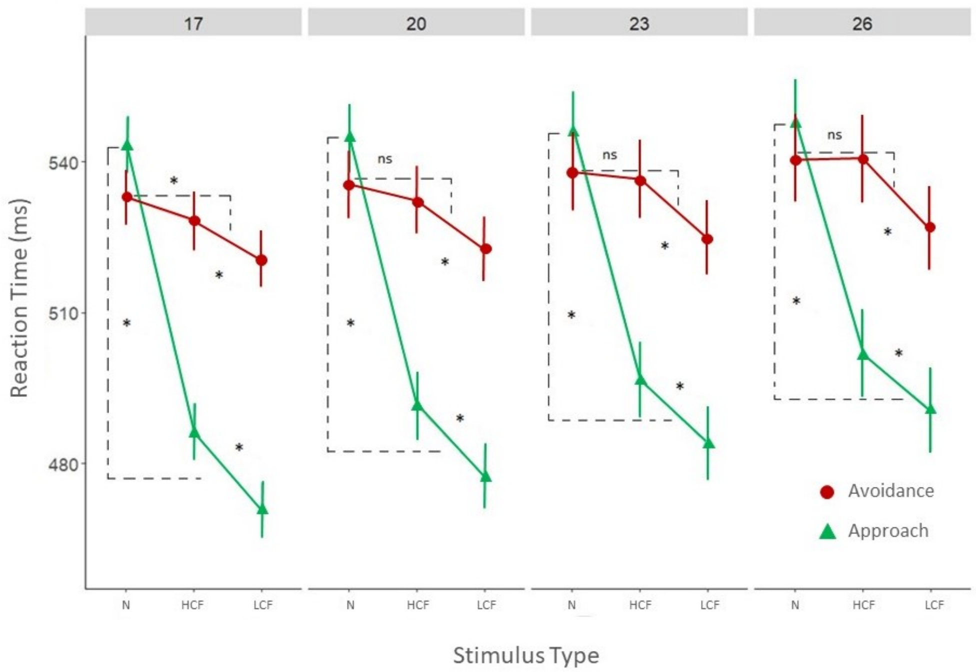

Figure 5.1.3. Mean (SE) reaction times for avoidance and approach movements for the three categories of stimuli at different BMI ranges. Abbreviations: N, neutral objects; HCF, high-calorie foods; LCF, low-calorie foods.

Table 5.1.1. Post-hoc contrasts for different levels of BMI

BMI	Food vs Neutral		HCF vs LCF	
	Avoidance Estimate (p)	Approach Estimate (p)	Avoidance Estimate (p)	Approach Estimate (p)
17-19 (51)	17.13 (.040)	129.46 (<.001)	7.76 (.016)	15.56 (<.001)
20-22 (87)	15.91 (.123)	120.70 (<.001)	9.80 (.008)	14.10 (<.001)
23-25 (51)	14.69 (.262)	111.95 (<.001)	11.83 (.005)	12.63 (.001)
>26 (19)	12.66 (.574)	97.35 (<.001)	15.23 (.003)	10.22 (.036)

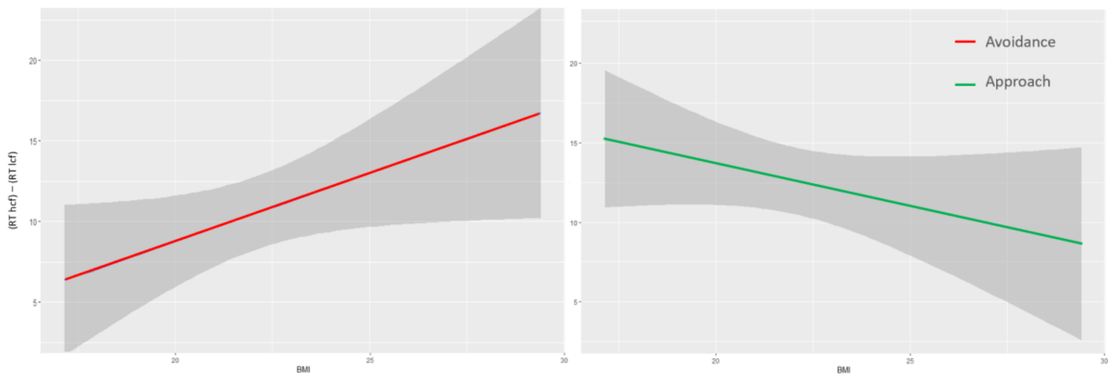

Figure 5.1.4. Differences in RT between HCF and LCF for the two types of movements as a function of the BMI. As the BMI increases participants become slower in avoiding and faster in approaching HCF compared to LCF. Abbreviations: N, neutral objects; hcf, high-calorie foods; lcf, low-calorie foods.

The association with hunger

As regards the comparison between food stimuli and neutral objects there was no significant 3-way interaction with hunger and type of movement ($\beta = -2.35$, $p = .20$, $d = 0.12$, fig 5.1.5).

However, there was a significant three-way interaction for hunger, stimulus, and type of movement when considering HCF and LCF ($\beta = -3.28$, $p = .01$, $d = 0.26$). In particular, as hunger increased, participants became faster in approaching and slower in avoiding LCF compared to HCF, thus suggesting an increased approach bias toward LCF compared to HCF at increasing levels of hunger. Accordingly, post hoc analyses showed that while participants were generally faster in avoiding LCF than HCF, participants who reported the higher level of hunger did not show this difference (Table 5.1.2).

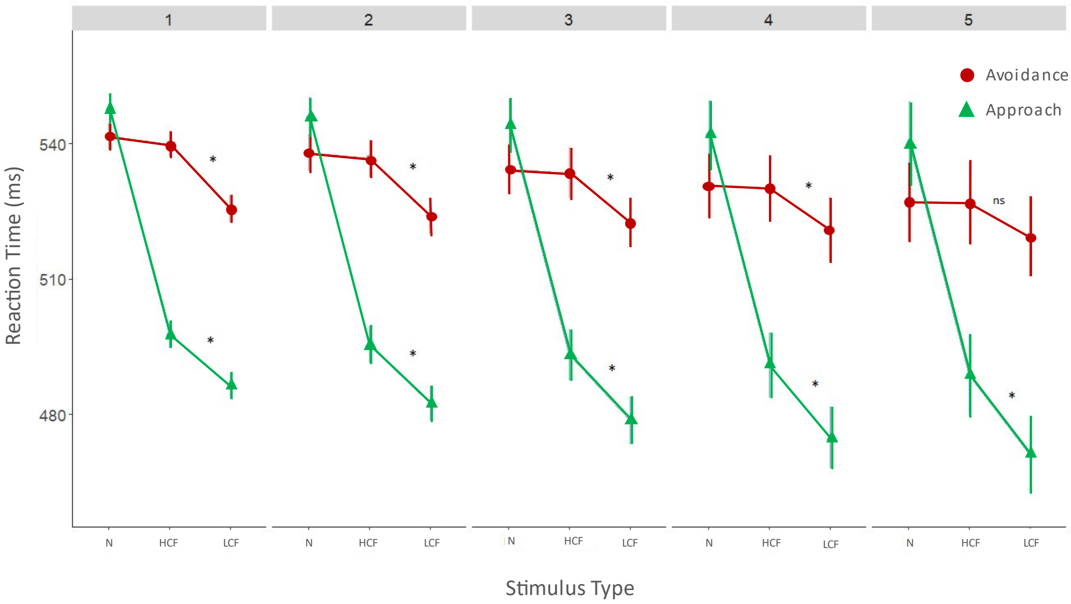

Figure 5.1.5 Mean (SE) reaction times for avoidance and approach movements for the three categories of stimuli at different hunger levels. 1 = lowest hunger, 5 = highest hunger. Abbreviations: N, neutral objects; HCF, high-calorie foods; LCF, low-calorie foods.

Table 5.1.2. Post-hoc contrasts for different levels of hunger

Hunger (N)	HCF vs LCF	
	Avoidance Estimate (*p*)	Approach Estimate (*p*)
1 (63)	14.33 (<.001)	11.42 (<.001)
2 (59)	12.63 (<.001)	13.00 (<.001)
3 (45)	10.93 (.002)	14.58 (<.001)
4 (32)	9.23 (.030)	16.16 (<.001)
5 (4)	7.53 (.212)	17.74 (<.001)

The association with time passed since last meal

The mean time passed since the last meal was of 160.92 minutes (range: 0-802 min). For this model, neither the comparison between food stimuli and neutral objects (β = -0.01, p =.695, d<0.001) or the comparison between HCF and LCF (β = -0.03, p =.242, d = 0.02) revealed a significant three-way interaction.

The association with wanting, liking, and fear scores

None of the three scores showed a statistically significant interaction with the type of action (Wanting: β = -0.74, p = .64, d = 0.04; Liking: β = -0.05, p = .97, d< 0.001; Fear: β = -0.11, p = .94, d< 0.001).

Correlations between different measures

Neither hunger nor time passed since the last meal showed a significant linear correlation with the BMI (hunger: ρ=0.02, p=.790; time: ρ=0.02, p=.740). Hunger and time passed since the last meal correlated weakly (ρ=0.20, p < .001).

Discussion

In this study, approach/avoidance tendencies toward food stimuli varying in calorie content (i.e., high-calorie/high-processed and low-calorie/low-processed food) and neutral objects were measured by means of a dedicated mobile-based AAT in a large sample recruited from the general population. Interactions between automatic tendencies toward food and individual variables, such as BMI, hunger level, time elapsed since the last meal, and food liking, wanting, and anxiety were also explored.

As for the first aim of this work, our data demonstrated an automatic preference for food over neutral objects. Indeed, participants were generally faster in approaching food stimuli compared to neutral ones, while no differences were observed concerning avoidance movements. The automatic preference for approaching foods compared to neutral objects is in line with our hypothesis and corroborates the proposal that the appetitive value of a stimulus can play a role in the behavioural disposition toward it (Kemps et al., 2013; Piqueras-Fiszman et al., 2014). The lack of a difference concerning avoidance movements, instead, is probably explained by the absence of negative/aversive stimuli in our experimental setup.

As concerns the difference between high-calorie/high-processed foods and low-calorie/low-processed foods, we didn't observe any significant result. The lack of a difference in reaction times based on calorie content suggests that this behavioural response may be underpinned by a nonspecific propensity towards food in general, rather than towards food items with specific caloric content. Overall, this result is consistent with previous AAT studies that investigated differences in automatic tendencies between foods with different caloric content in the general population (Kahveci et al., 2021; Paslakis et al., 2016). These studies are indeed fairly consistent in not showing a general approach tendency for high-calorie foods compared to low-calorie foods. More consistent differences between high-calorie and low-calorie foods seem, instead, to emerge in more homogeneous samples of individuals with abnormal eating behaviours or attitudes (e.g. patients with eating disorders, obese individuals, or individuals craving for specific foods) (Kemps et al., 2013; Kollei et al., 2022; Moore et al., 2022).

This observation suggests that behavioural dispositions towards specific categories of foods may be sustained and better explained by individual characteristics, and thus support the importance of investigating them more specifically. In this study, we decided to assess the predictive value of parameters that represent both stable subjective traits, such as BMI and anxiety/liking scores, and context-related features, such as hunger level, time elapsed since the last meal, and craving level for specific items.

Regarding the BMI and the comparison between food in general and neutral objects, a statistically significant effect of the BMI was found. This result indicates that as the BMI changes, different behavioural responses toward food compared to neutral objects are observed. In the current study, unexpectedly, although participants were always faster in approaching food stimuli than neutral items, this difference decreased as BMI increased, suggesting a reduced approach bias toward foods in individuals with higher BMI. Note, however, that this comparison included both high and low-calorie foods. With regards to avoidance tendencies, while participants in the lowest BMI range were faster in rejecting food items compared to neutral stimuli, no differences were observed in the other BMI ranges. Faster avoidance of food stimuli at lower BMI ranges suggests the presence of regulatory mechanisms facilitating the maintenance of a limited caloric intake. Indeed, if this implicit reaction was also reflected in explicit behaviours in everyday life, it could represent a key element of the processes regulating food intake homeostasis (Cifuentes & Acosta, 2022).

When comparing the effect of BMI on the approach/avoidance tendencies toward high- and low-calorie food cues, results showed that as BMI increased, participants became slower in avoiding high-calorie foods compared to low-calorie foods. This evidence is in line with findings from a study using a joystick-based task assessing approach tendencies towards sweet snacks, salty snacks, and neutral pictures, which found that individuals with higher BMI showed an impaired ability to avoid sweet snacks specifically (Maas et al., 2017). Moreover, as the BMI increased, participants became slower in approaching low-calorie foods compared to high-calorie foods. This suggests that the approach tendency towards healthy foods decreases with increasing BMI. Overall, these approach-avoidance tendencies toward food could partially explain why individuals with higher BMI might be more likely to experience difficulties in avoiding high-calorie foods, while participants with lower BMI might be more inclined to consume low-calorie and healthy foods. To establish whether this trend may be associated with actual food intake, further studies that objectively measure food intake and possible associations between these and mobile AAT scores are needed.

With regards to the predictive value of other context-independent factors, results show no significant association of either food-related liking or anxiety with approach and avoidance tendencies toward specific foods. In this regard, it is useful to consider that these data were collected in a sample of subjects recruited from the general population and in a weight range that excludes clinical presentations. It is therefore possible to hypothesize that in non-clinical conditions, these factors do not predict the automatic propensity toward food. At the same time, it is possible that these factors exert a more marked effect in specific clinical populations (e.g., obesity, anorexia nervosa). Moreover, it is important to interpret these findings with caution, as they are based on preliminary data. Specifically, the measures used to assess liking and anxiety tendencies were limited to single items. Future studies should examine the reliability and sensitivity of these items or adopt more comprehensive measures.

Regarding context-dependent measures, the approach tendency toward high-calorie and low-calorie foods seemed to be predicted by perceived hunger, which replicates previous studies (Castellanos et al., 2009). In the present study, higher levels of hunger were associated with a faster approach and a slower avoidance of low-calorie compared to high-calorie foods, suggesting an increase in the approach bias toward healthy foods as hunger increases. The interpretation of this result is not straightforward, and it should also be noticed that hunger was not experimentally manipulated, but only self-reported by participants. Therefore, future studies are needed to better clarify the effect of hunger on approach/avoidance tendencies.

Although time passed since the last meal was positively associated with perceived hunger, it did not predict approach/avoidance tendencies toward foods, and neither did the reported level of craving for specific stimuli.

Strengths and limitations

Compared to previous studies, this study has the strength of having assessed approach/avoidance tendencies toward foods in the general population by recruiting a large number of participants and by adopting a novel and ecological paradigm, i.e., a mobile-AAT. Moreover, the inclusion of both HCF, LCF, and neutral objects, together with the examination of various stable and context-dependent variables, provides a comprehensive description of automatic approach/avoidance tendencies toward foods and of the factors that might influence them.

Despite these strengths, this study has also some limitations. Firstly, as also described in the method sections, the pictures depicting HCF were, on average, more intense and complex than LCF and neutral pictures. These differences in visual characteristics may have affected content processing and recognition, thus influencing reaction times at a general level. Since the main focus of the work was the interaction between stimulus and type of movement, this does not impact conclusions. However, future studies could try to avoid this confounding factor by matching pictures for visual characteristics. The second limitation is that most participants had a BMI comprised between 17 and 25, and therefore splitting the sample into different BMI ranges did not produce equal sample sizes. Similarly, in the post-hoc analysis regarding hunger levels, it should be noted that only 4 participants reported the highest level of hunger, thus possibly explaining the absence of a significant difference in the avoidance of HCF compared to LCF in this subgroup. A third limitation is that by contrasting pleasant food items with neutral objects, it is not possible to assess whether the observed differences in approach-avoidance tendencies are caused by valence (positive vs neutral) or by edibility. Lastly, many of the variables included in the analyses were self-reported (e.g. BMI, time passed since last meal).

Conclusion

To conclude, our results show an overall approach tendency toward food stimuli, independent from caloric content, in the general population. Differences between HCF and LCF only emerged when specific individual characteristics were added to the model. In particular, approach tendencies to low-caloric foods decreased with increasing BMI and increased with perceived hunger, thus suggesting the presence of various mechanisms influencing eating behaviours. The possibility of disentangling the biological, psychological, and behavioural mechanisms underpinning the interaction between BMI and behavioural tendencies appears to be particularly important to understand how food intake is determined and regulated.

5.2 Motor insensitivity to food as a potential mechanism contributing to calorie restriction in Anorexia Nervosa: a Mobile Approach-Avoidance task

Abstract

A change in implicit behavioural tendencies toward foods may contribute to the maintenance of calorie restriction in Anorexia Nervosa (AN). To test this hypothesis, we assessed approach-avoidance tendencies toward different categories of stimuli using a novel mobile version of the classic approach-avoidance task (AAT). The sample included 66 patients with restrictive AN and 84 healthy controls (HC), all females. All participants performed the AAT in which they were required to approach or avoid stimuli (high-calorie foods, low-calorie foods, and neutral objects) by respectively pulling their phone towards themselves of pushing it away. Both the response time and the maximum acceleration force of each movement were collected. The results revealed that both patients and controls presented an approach bias toward food stimuli, as they were faster and stronger in approaching rather than avoiding these stimuli, while this effect was not observed for neutral objects. However, this bias was significantly reduced in patients with AN. This reduction in the natural tendency to approach food stimuli is consistent with patients' eating behaviour and may contribute to the maintenance of calorie restriction, thus representing a possible target for novel therapeutic approaches.

Introduction

Anorexia Nervosa (AN) is a severe psychiatric disorder, characterized by an extreme restriction of calorie intake accompanied by significantly low body weight, fear of weight gain or becoming fat, and preoccupation with body shape or weight (American Psychiatric Association, 2013). Despite psychotherapeutic approaches, such as cognitive behavioural therapy or family-based treatment, are widely recognized as the treatments of choice for individuals with AN, their efficacy is still limited (Treasure et al., 2015).

It is indeed estimated that fewer than half of patients fully recover, and AN remains the psychiatric disorder with the highest mortality rate (Brockmeyer et al., 2018; Treasure et al., 2015; Zipfel et al., 2015).

Given the need of new therapeutic approaches for the treatment of AN, many efforts are being made to better delineate the complex neurocognitive mechanisms and circuits underlying core aspects of AN psychopathology (Brockmeyer et al., 2018; Zipfel et al., 2015). Among these, particular attention has been devoted to the study of calorie restriction, which is one of the most central and puzzling symptoms of AN (Ehrlich et al., 2015). Over the years, several neurobiological models have been proposed. According to some of these models, the ability of patients to resist food consumption and restrict their calorie intake is linked to extremely high levels of self-control, characterized by an excessive activity of top-down cognitive control systems over the appetitive response elicited by food stimuli (Ehrlich et al., 2015). However, alternative explanations exist. Steinglass and colleagues (2006, 2016), for example, proposed a habit-centered model of AN. According to this model, as the disease progresses, calorie restriction passes from being a voluntary and goal-directed behaviour to a habit, thus involving changes in automatic stimulus-response associations (Uniacke et al., 2018). A similar hypothesis has also been suggested by O'Hara and colleagues (2015), who proposed that due to changes in reward system responsiveness, the automatic appetitive responses usually elicited by food stimuli might be altered in patients with AN.

A possible way to test these hypotheses and thus assess whether patients with AN differ from healthy controls in their automatic responses to food stimuli, is by looking at implicit approach-avoidance tendencies. Automatic approach-avoidance tendencies are usually investigated using behavioural tasks (e.g. Approach-Avoidance task, AAT; Stimulus Response Compatibility task, RSC; Affective Simon task, AST) in which participants are required to perform approach and avoidance movements toward different categories of stimuli (De Houwer et al., 2001; Rinck & Becker, 2007). Reaction times (RT) are then analyzed, and an approach bias is inferred if participants are faster in approaching rather than avoiding a specific stimulus, while an avoidance bias is inferred if avoidance movements are faster than approaching ones.

To date, only few studies adopted these tasks to study implicit behavioural tendencies toward foods in patients with AN. Despite in some cases they failed to observe any significant difference between patients and controls (Kollei et al., 2022), most of them reported a reduction in the tendency to automatically approach foods in patients with AN (Neimeijer et al., 2019; Paslakis et al., 2016; Veenstra & de Jong, 2011). This result is consistent with neurobiological models suggesting the involvement of automatic processes in the maintenance of calorie restriction. However, given the limited number of existing studies, together with a certain variability from a methodological point of view, replication of these results is needed. Moreover, all the studies conducted so far adopted classic computer-based approach-avoidance paradigms. Although these computerized tasks represent established tools for measuring approach–avoidance tendencies, they have been repeatedly criticized for their limited ecological validity (Lange & Pauli, 2019; Meule et al., 2019). Real-life approach/avoidance behaviours, indeed, involve more complex and extended movements than pressing a key or pulling/pushing a joystick. Moreover, in real-life, approach and avoidance movements are associated with changes in the distance between oneself and the stimulus, an effect that cannot be adequately replicated in computerized tasks (Lange & Pauli, 2019).

To overcome these limitations, researchers are now developing more ecological paradigms for the assessment of approach-avoidance tendencies, involving, for example, the use of virtual reality or touchscreen-based versions of the AAT (Meule et al., 2019, 2020; Schroeder et al., 2016). An example of these new generation paradigms is a mobile version of the AAT developed by Zech and colleagues (2020). In this task, participants are instructed to approach, by pulling their phone toward themselves, or avoid, by pushing their phone away, different categories of stimuli. The advantages of this application, compared to classical versions of the task, include the execution of more naturalistic approach-avoidance movements, the possibility of performing the task in non-laboratory settings, and the fact that it can collect, in addition to RT, also the strength of the movement.

Using this mobile version of the task, an approach bias toward appetitive food stimuli has been repeatedly observed in the general population (Brouwer et al., 2021; Zech et al., 2023). Interestingly, this bias appears to be associated with participants BMI and nutritional status. In the study presented in paragraph 5.1, for example, we observed that as the BMI decreased, participants became faster in avoiding unhealthy compared to healthy foods, and in approaching healthy compared to unhealthy stimuli. An association with the BMI has also been observed by Zech and colleagues (2023), who reported that while the tendency to approach food stimuli decreases from before to after meal in normal weight individuals, this mechanism was disrupted in overweight and obese participants, who instead presented an increase in approach tendencies after meals.

In the present study, we adopted the mobile AAT to assess approach-avoidance tendencies toward both high-calorie and low-calorie foods in patients with restrictive AN. Our hypothesis is that changes in automatic behavioural tendencies toward food stimuli may sustain calorie restriction and dieting. Therefore, we hypothesized that the tendency to automatically approach foods, especially high calorie, would be reduced in patients compared to healthy controls. Since low-calorie foods are preferentially consumed by patients with AN, instead, we expected to observe greater approach tendencies toward these stimuli as compared to high-calorie foods.

Methods

Participants

The sample included 66 patients with restrictive AN and 84 healthy controls (HC), all females. Five patients with AN and six HC participants were excluded from the analyses due to bad data quality or poor performance (accuracy $< 60\%$).

Patients were recruited from the Eating Disorder Units of Padova, Vicenza, and Torino. They all met full criteria for AN restrictive subtype, according to the DSM-5 (American Psychiatric Association, 2013), and their diagnosis was confirmed by an expert clinician. The participants of the HC group constituted a subgroup of participants from the study conducted on the general population (see paragraph 5.1) who met specific inclusion and exclusion criteria. Inclusion criteria for both patients and controls were: 1) female gender; 2) 14 years or older; 3) being fluent in Italian. Additional inclusion criteria for the HC participants were: 1) having a BMI comprised between 18.5 and 24.9; and 2) having a score lower than 2.8 on the global scale of the Eating Disorder Examination Questionnaire (EDE-Q) (Mond et al., 2008).

The sample size was determined based on an a priori power analysis performed on G*Power software (Faul et al., 2007), which revealed that 66 participants for each group were needed to detect a significant 2x3 within-between interaction with a small effect size (Cohen's f = 0.10, corresponding to d = 0.2 and $\eta 2p = 0.01$) with a statistical power $1-\beta = .80$ at a significant level $\alpha = .05$ and assuming a correlation among repeated measures of r = .8.

Written informed consent was provided by all participants. In the case of underage participants, consent was provided by their parents or legal guardian. The study was approved by the ethical committees of the University of Padova (reference number: 4149) and of the San Bortolo Hospital of Vicenza (reference number: 1831) and was conducted in accordance with the latest version of the Declaration of Helsinki.

Mobile AAT application

The mobile AAT app was the same as presented in the previous study (see paragraph 5.1). The only methodological difference is that for patients with AN height and weight were collected by the experimenters by looking at patients' medical records.

Data Analyses

Data preprocessing

For each trial, the phone's accelerometers and gyroscopes tracked the gravity- and rotation-corrected acceleration of the movement in the direction perpendicular to the face of the screen and recorded it at a nominal sampling rate of 100 Hz. These data were pre-processed in Matlab (version 2017b; The Mathworks, Inc. Natick, MA) using in-house scripts to extract the kinematics measures to be analyzed, based on the procedure used by Zech and colleagues (2020).

The acceleration data were first interpolated to 1-ms resolution using a shape-preserving piecewise cubic interpolation and smoothed using a linear Savitzky-Golay filter (span: 50 ms) to mitigate measurement noise.

We then extracted two dependent variables at the trial level (i.e., one summary measure for each trial): 1) the response time RT, indicating the start of the push/pull movement; 2) the peak acceleration value AF, computed as the value of the absolute acceleration force (m/s^2) at its peak. The RT data were inverse-transformed (using the -1000/RT formula) and the AF was log-transformed (using the ln (AF) formula) to mitigate non-normality of their distributions.

Data Exclusion

Practice trials, error trials, trials with missing sensor data, trials with RT below 200 ms, and trials in which the push/pull response lasted either less than 50 ms or more than 500 ms were considered invalid. In total, 21.88% of the experimental trials were excluded from the analyses.

Statistical analyses

We performed linear mixed-effects model (LMM) analyses in Matlab. This is a robust approach for the analysis of repeated measures designs, which allowed us to model the experimental effects (i.e., the participants' group, GROUP, the type of movement, MovType, and the stimulus category, Stim) while taking into account trial-by-trial variability, controlling for the related confounding variables, and providing flexibility in assessing random and fixed effects both at within- and between-subjects levels (Baayen et al., 2008). For each trial-level dependent variables (i.e., RT, and AF; see above), the tested LMM included as fixed effects the participants' GROUP (AN vs. HC), MovType (Push vs. Pull), and Stim (LCF, HCF, and N), as well as their interactions. As random effects, we included the by-subject and by-items random intercepts. The Wilkinson-notation formula for the model is: DV ~ 1 + GROUP*MovType*Stim + (1|Participant) + (1|Item). The significant interactions involving the

GROUP factor were further explored by performing separate analyses for the two groups of participants.

Follow-up analyses were performed to investigate whether experimental effects were modulated by BMI and by other by-participant variables, such as time passed since the last meal, level of perceived hunger, and wanting liking and fear for specific stimuli, by using the same models described above where four-way interactions with the variable of interest were included in the fixed part.

Finally, to exclude that the effects involving the GROUP factor were simply explained by the observed difference in age between AN and HC (see below), the participants' experimental effects were estimated by the by-participants random slopes of models including the MovType by Stim interaction in the random part, and then they were correlated with the participants' age.

The statistical significance of the coefficients for each regressor was calculated using the Satterthwaite's method to estimate degrees of freedom.

Results

Participants

Table 5.2.1 summarizes the demographic characteristics of both AN and HC participants. As expected, AN participants presented a lower BMI compared to HC. As regards age, patients with AN were significantly younger than HC.

Table 5.2.1. Demographic and clinical data

	AN Mean (SD)	HC Mean (SD)	T (p)
Age (years)	17.57 (3.23)	20.69 (4.11)	4.87 (< 0.001)
BMI (kg/cm^2)	15.55 (1.38)	20.84 (1.93)	18.1 (< 0.001)

AN, Anorexia Nervosa; HC, healthy control; BMI, Body Mass Index

Approach-Avoidance Task

Response Times

The LMM analysis conducted on RTs revealed the significant interactions GROUP by MovType, GROUP by Stim, and GROUP by MovType by Stim (see Table 5.2.2). In particular, the 3-way interaction indicates that participants are faster in approaching rather than avoiding food stimuli, both HCF and LCF, as compared to neutral objects (see Figure 5.2.1a), thus suggesting the presence of an approach bias toward food stimuli. However, as can be seen in figure 5.2.1b, this food-specific approach bias was larger in healthy controls than in patients with AN. The analysis also revealed that this effect was not statistically different between HCF and LCF.

Table 5.2.2. Results of the LMM analysis on RTs

Effect	$F_{(1,13019)}$	p
GROUP	2.284	.131
MovType	4.728	.030
Stim	1.937	.144
GROUP:MovType	11.155	.001
GROUP:Stim	11.853	< .001
MovType:Stim	1.311	.270
GROUP:MovType:Stim	13.022	<.001

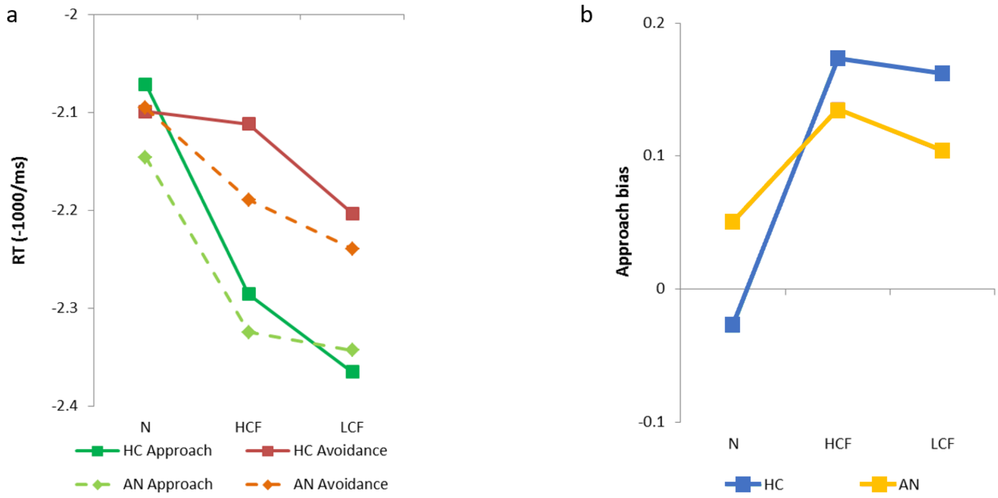

Figure 5.2.1 a) Mean reaction times for avoidance (red) and approach (green) movements for the three categories of stimuli for both patients (dotted lines) and controls (continuous lines). b) approach bias toward the three categories of stimuli, calculated as (RTavoidance – RTapproach) for both patients (yellow), and controls (blue). Higher values indicate a greater approach bias. Abbreviations: HC, healthy controls, AN, Anorexia Nervosa, N, neutral objects; HCF, high-calorie foods; LCF, low-calorie foods.

The follow-up LMM analysis on RTs revealed that the above-reported 3-way interaction was further modulated by BMI for HCF ($t = 2.67$, $p = 0.010$) but not LCF stimuli ($t = 1.55$, $p = 0.121$). This result was confirmed by the analyses performed on the two groups separately. In particular, the results revealed that there was a significant relationship between BMI and the approach bias for HCF (relative to neutral) that was stronger in AN compared to HC participants, with the former and the latter showing, respectively, a significant positive BMI modulation ($b=.245$) and a non-significant inverse BMI modulation ($b=.072$) of the 3-way interaction for HCF stimuli, while this pattern was reversed, but non-significant, for LCF stimuli. In other words, patients with AN with higher BMI values showed a stronger relative approach bias for HCF stimuli (relative to neutral objects) compared to AN participants with lower BMI values. No other participant-level variable modulated the experimental effects.

Absolute Acceleration Force

The LMM analysis conducted on the AF revealed the significant interactions GROUP by MovType, GROUP by Stim, and GROUP by

MovType by Stim (see Table 5.2.3). In particular, the 3-way interaction indicated that participants applied more force in performing approach than avoidance movements for both HCF and LCF, as compared to neutral objects (see Figure 5.2.2a). Moreover, as can be seen in figure 5.2.2b, this food-specific approach bias was larger in healthy controls than in patients with AN. However, the results also revealed that this effect was not statistically different between HCF and LCF.

The follow-up LMM analysis on AF revealed that these results were not significantly modulated by any participant-level variable.

Table 5.2.3. Results of the LMM analysis on AF

Effect	$F_{(1,13019)}$	p
GROUP	23.154	< .001
MovType	0.063	.801
Stim	113.790	< .001
GROUP:MovType	3.929	.047
GROUP:Stim	106.110	< .001
MovType:Stim	21.108	< .001
GROUP:MovType:Stim	76.786	< .001

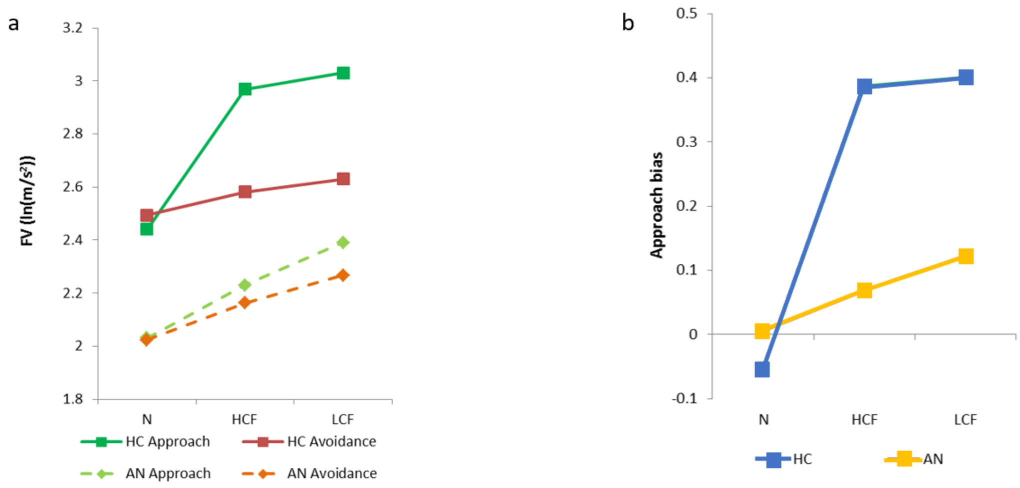

Figure 5.2.2. a) Mean acceleration values for avoidance (red) and approach (green) movements for the three categories of stimuli for both patients (dotted lines) and controls (continuous lines). b) approach bias toward the three categories of stimuli, calculated as

(AVapproach – AVavoidance) for both patients (yellow), and controls (blue). Higher values indicate a greater approach bias. Abbreviations: HC, healthy controls, AN, Anorexia Nervosa, N, neutral objects; HCF, high-calorie foods; LCF, low-calorie foods.

Discussion

This study aimed at assessing automatic approach-avoidance tendencies elicited by both high-calorie and low-calorie foods in a group of patients with restrictive AN. To do so, we developed a novel mobile version of the classic AAT in which participants were asked to approach and avoid stimuli by respectively pulling their phone toward themselves or pushing it away (Zech et al., 2020). Adopting this new paradigm allowed, compared to previous studies, the investigation of approach-avoidance tendencies in a more ecological setting and the collection of data related also to the force of the movement, in addition to the more traditional RTs.

Consistent with previous studies, the analyses conducted on RT revealed a significant approach bias toward food stimuli in the healthy control group (Brouwer et al., 2021; Zech et al., 2023). Indeed, participants were generally faster in approaching foods rather than avoiding them, while this effect was not observed for neutral objects. This result was also supported by the analyses conducted on movements' force. Even in this case, indeed, no difference between approach and avoidance movements was observed in response to neutral objects. However, when participants had to respond to food stimuli, they were significantly stronger in approaching rather than avoiding them.

This general approach bias toward food stimuli was observed also in patients with AN. However, it was reduced with respect to healthy controls. Looking at both RT and strength, indeed, patients presented a lower difference between approach and avoidance movements in response to food stimuli as compared to healthy controls. This reduction in automatic approach tendencies toward food is consistent with our hypothesis and it also replicates some of the results obtained in previous studies (Neimeijer et al., 2019; Paslakis et al., 2016; Veenstra & de Jong, 2011).

Contrary to our expectations, however, we did not observe any difference between high-calorie and low-calorie foods. Consistently with the psychopathology of patients with AN, we hypothesized that the reduction in the approach bias would be specific to high-calorie foods, while we expected no differences or even a greater approach bias toward low-calorie foods in patients than in healthy controls. Despite some studies using different methodologies reported a greater approach bias toward low-calorie foods than high-calorie foods in patients with AN (see chapter 4, Neimeijer et al., 2015), our results are in line with those obtained by the only two other studies that specifically adopted an AAT in AN, and which also failed to observe differences related to the caloric content of the stimuli (Kollei et al., 2022; Paslakis et al., 2016).

Interestingly, we also observed a positive relationship between patients' BMI and RTs approach tendencies for HCF. This result indicates that patients with more severe levels of malnutrition present a further reduction in the natural tendency to approach caloric and palatable foods. While we expected to replicate, in the healthy controls group, the results obtained in our previous study, in which we observed an association between approach tendencies and both BMI and hunger (see paragraph 5.1), we failed to observe any effect of clinical or contextual factors on healthy controls approach-avoidance tendencies. A possible explanation for this inconsistency may lie in the greater homogeneity of the current control group, which only included adolescent and young adult women.

Taken together, our results show that in patients with restrictive AN, the automatic and natural tendency to approach food stimuli is significantly reduced, and this reduction is even stronger in patients with greater illness severity. This decrease in automatic responses elicited by food stimuli might implicitly sustain calorie restriction and thus contribute to the maintenance of the disorder (Paslakis et al., 2016).

Although the precise neural mechanisms underlying this phenomenon are yet to be delineated, the evidence that something is different at an implicit and unconscious level supports those neurobiological models suggesting the involvement of mechanisms other than self-control in the pathophysiology of AN (O'Hara et al., 2015; J. E. Steinglass & Walsh, 2016). Moreover, it should also encourage the development of interventions specifically targeting these implicit and automatic mechanisms. Examples of these interventions may include approach-avoidance modification trainings, in which the AAT is designed so that the patients consistently approach stimuli that they tend to avoid, or vice versa (Loijen et al., 2020), or protocols of non-invasive brain stimulation techniques.

Overall, this study has the strength of having assessed approach-avoidance tendencies toward food in a large sample of patients with AN, using a novel and ecological paradigm. For the first time, the analysis of movements' force was added to the traditional analyses conducted on RT, providing a more complete description of approach-avoidance tendencies in both patients and controls. Moreover, the decision to only include patients with the restrictive subtype of AN probably led to the formation of a more homogeneous sample, in terms of both psychopathology and, more importantly, implicit tendencies toward food stimuli.

However, some limitations need also to be considered. Firstly, although we controlled for the effect of age, the two groups significantly differed as regards to this variable. Secondly, the pictures depicting HCF were, on average, more intense and complex than LCF and neutral pictures. These differences in visual characteristics might affect content processing and recognition, and thus influence reaction times at a general level. However, since the main focus of the work was the interaction between stimulus, type of movement, and group, this does not impact conclusions. Lastly, the cross-sectional nature of the study does not allow for assessing whether the observed reduction in approach-bias represents a stable characteristic of patients with AN or, instead, normalizes with recovery. Future longitudinal studies might help in clarifying this aspect.

In conclusion, the present research adds to a body of literature indicating a reduction in the automatic tendency to approach food stimuli in patients with AN. This evidence is consistent with their eating behavior and may contribute to the maintenance of the disorder. Although future studies are needed to confirm this pattern and better delineate the neural underlying mechanisms, this result provides a significant contribution to our understanding of the disorder and may open new perspectives for the development of targeted therapeutic strategies.

6 General Discussion

The present project aimed at assessing whether patients with restrictive AN differed from healthy controls in the way they automatically respond to food stimuli. To do so, we designed three different experimental paradigms, investigating the automatic responses elicited by food stimuli in the process that goes from attention orientation to action preparation and execution. Consistent with AN psychopathology, we hypothesized that patients would demonstrate a reduction in the natural tendency to orient to and approach high-calorie foods. On the other hand, since low-calorie foods represent a more illness-compatible stimulus, we expected no differences or even a greater response toward low-calorie foods in patients than in healthy controls.

By looking at attentional processing, the analyses conducted on eye-tracking data revealed a tendency of patients with AN to avoid maintaining their attention on food stimuli. This result is consistent with previous studies, as both Giel and colleagues (2011) and Werthmann and colleagues (2019) observed that only healthy controls continued to direct their attention toward foods over time. However, the fact that we observed differences between patients and controls only in advanced stages of attentional deployment, suggests the involvement of cognitive control prefrontal circuits. This result is thus more consistent with models emphasising the role of self-control in the maintenance of calorie restriction (Ehrlich et al., 2015), rather than with models suggesting a change in automatic tendencies toward foods (O'Hara et al., 2015; J. E. Steinglass & Walsh, 2016).

When looking at more behavioural indices, however, we actually observed a difference in the way patients and controls automatically react to food stimuli.

As regards motor distractibility, we analysed how mouse trajectories were influenced by the presence of different distractor stimuli (high-calorie foods, low-calorie foods, and neutral objects). While healthy controls presented a similar deviation toward the three categories of stimuli, patients with AN presented a lower deviation toward high-calorie foods and a greater deviation toward low-calorie foods, compared to neutral objects. Motor distractibility represents a process that combines attentional capture and action preparation. Therefore, this result suggests that even if patients and controls do not differ in their initial attentional orientation toward foods, as observed in the first study, the motor program that is automatically initiated is different.

This hypothesis is further supported by the results obtained in the studies on approach-avoidance tendencies. As a first step, we developed and tested a mobile application for the assessment of approach-avoidance tendencies toward both high and low-calorie foods in the general population. The results of this study indicated the presence of a general approach bias towards food stimuli. Moreover, we observed that this bias was influenced by other factor such as participants' BMI and hunger level. Then, we applied the same task on a sample of patients with restrictive AN. Our results showed that the automatic tendency to approach food stimuli, that we observed in the healthy control group, was reduced in patients with AN, and this reduction was even stronger in patients with more severe levels of malnutrition.

As concerns high-calorie foods, the results obtained on both the motor distractibility and approach-avoidance studies are consistent with our hypothesis. Indeed, patients displayed a reduction in the natural tendency to approach palatable foods. This change in automatic tendencies toward high-calorie foods has already been observed in previous studies and is coherent with patients' eating behaviour (Neimeijer et al., 2019; Paslakis et al., 2016). Moreover, since it represents an unconscious and automatic mechanism it could implicitly facilitate patients in resisting high-calorie food consumption thus contributing to the maintenance of the disorder.

As concerns low-calorie foods, instead, our results are less conclusive. While in the irrelevant distractor task we observed that patients presented an increased tendency to approach low-calorie foods, which was consistent with our hypothesis, in the approach-avoidance task we observed that their tendency to approach food stimuli was reduced for both high and low-calorie foods. This inconsistency regarding low-calorie foods is present also in previous literature, as some studies observed an increased approach bias toward low-calorie foods in patients with AN (Neimeijer et al., 2015), while other studies failed to observe any difference (Kollei et al., 2022; Paslakis et al., 2016). Future studies should try to better investigate this aspect, as it's also possible that approach tendencies toward high and low-calorie foods are mediated by different mechanisms, reflecting, respectively, responses of the reward systems or higher- order motivational drives (Kahveci et al., 2021; Moore et al., 2022).

In spite of this, the results obtained in my PhD project are consistent in showing that in patients with AN something changes at an implicit and unconscious level. This evidence is in favour of those models suggesting the involvement of mechanisms other than self-control in the pathophysiology of AN. Examples include changes in reward system responsiveness (O'Hara et al., 2015) or the formation of maladaptive stimulus-response associations involving the habit system (J. E. Steinglass & Walsh, 2016; J. Steinglass & Walsh, 2006). However, the exact neurobiological correlates underlying the observed behavioural changes have yet to be fully elucidated. Moreover, different mechanisms may intervene in different phases of the disease. If in the initial stages of the disorder a significant role of deliberate and controlled choices can be hypothesized, as the disease progresses, automatic mechanisms may become more prominent and pervasive.

Future studies should try to better delineate these aspects. An initial step to understand how these automatic responses to food stimuli evolve over the course of the disease could be to analyse differences among patients with different duration of the illness (e.g. less or more than 1 year). An even better approach would be to conduct a longitudinal study, in which the progression of these behaviours is assessed by tracking patients' responses at different stages of the illness. These approaches could be integrated with neuroimaging studies, employing techniques such as functional magnetic resonance imaging (fMRI) or electroencephalography (EEG) to investigate brain activity patterns associated with attentional processing, motor distractibility, and approach-avoidance tendencies towards different food stimuli. These studies could also focus on specific region of interests such as the dopaminergic reward system, or regions involved in habit formation, such as the posterior putamen in connection with premotor and sensorimotor cortices (Seger, 2018).

A better understanding of the progression and neurobiological basis of the observed behaviour could also contribute to the development of new and more informed therapeutic strategies. Among these, an option could be represented by non-invasive brain stimulation interventions that target specific brain areas believed to contribute to the reduction in approach tendencies toward food observed in AN. Moreover, these neurobiological interventions might also be coupled to approach-avoidance bias modification trainings (ABM), in which the AAT is designed so that the patients consistently approach stimuli that they tend to avoid, or vice versa (Loijen et al., 2020). It has been indeed proposed that non-invasive brain stimulation interventions, in particular transcranial direct current stimulation (tDCS), might enhance the effects of behavioural trainings by increasing neuroplasticity (Fritsch et al., 2010; Grycuk et al., 2020).

Overall, this project has the strength of having assessed for the first time the automatic responses elicited by food stimuli in patients with AN looking at different stages of processing, from attentional capture to action execution. The results we obtained are substantially consistent with our initial hypotheses and, compared to previous studies, delineate a rather coherent picture. A factor that may have contributed to achieving such linear results may be represented by our recruitment strategy. Indeed, we decided to include in our studies only patients with the restrictive subtype of AN, instead of transdiagnostic samples of patients with eating disorder. This decision probably led to a more homogeneous sample in terms of eating habits and, possibly, automatic tendencies toward foods. Another strength of this project is the adoption of innovative methodologies that allowed us to collect and analyze various types of data, including behavioral data, eye-tracking data, and movement trajectory data. Compared to more classic approaches based on reaction times only, this strategy has allowed us to obtain a clearer and more comprehensive picture.

Despite these strengths, this project has also some limitations that need to be considered. Firstly, all the presented studies are cross-sectional in nature. This characteristic prevents drawing conclusions on whether the observed behaviours represent a trait or state characteristic of patients with AN. Moreover, no inference can be drawn on the impact that these changes in automatic tendencies have on the outcome of the disease. Another limit is represented by the fact that, in this project, the neural correlates of the observed behaviours were not directly investigated. As noted earlier, this represents a crucial step for the development of brain informed interventions. Therefore, this gap will need to be addressed in future studies. Moreover, our samples were mainly composed by young women, but due to limited sample size, we did not specifically address differences between adolescents and adults. Since the adolescent brain is structurally different from the adult brain, this may represent an area of interest for future studies.

To conclude, we observed a propensity of patients with AN to avoid maintaining their attention on food stimuli. This bias appears to be accompanied by a decrease in the natural tendency to approach food stimuli, especially those with high caloric content. Despite many aspects remain to be understood, these results emphasize the importance of focusing on changes in automatic tendencies toward food as a possible maintenance factor of AN.

Impact and generalization of the results

As reported in the introduction, to date, the treatment of choice for AN is represented by a multidisciplinary approach in which psychotherapy plays a central role. Despite differences among alternative approaches, psychotherapy mainly works at an explicit and deliberate level. Therefore, the identification that also implicit mechanisms could be involved in the maintenance of the disorder implies the need to reconsider treatment approaches. Psychotherapy could thus be coupled to interventions specifically targeting these implicit mechanisms, such as behavioural trainings or non-invasive brain stimulation paradigms. Moreover, the recognition of these automatic mechanisms may lead both patients and therapists to adopt a different perspective toward the setbacks and difficulties often encountered during the treatment, and not seeing them simply as consequences of a lack of motivation or volition. These mechanisms are indeed beyond the patient's awareness and voluntary control, but they can interfere with the patient's ability to follow therapeutic guidelines, thus undermining the success of the intervention.

In this project I decided to focus only on young woman with restrictive AN, with the aim of identifying implicit mechanisms associated with a specific behavioural pattern. However, the attentional and behavioural responses observed in the healthy control group, and the results reported in study 3 (see paragraph 5.1), suggest that these implicit mechanisms are present across the entire population, and change according to BMI. Alterations in automatic responses to food stimuli might thus be involved even in eating disorders other than AN, such as bulimia nervosa or binge eating disorder, even if in a different, or even opposite, way. A better characterization of these mechanisms across the entire spectrum of eating disorders, and within each specific disorder, could lead to a more individualized treatment, offering each individual the most appropriate therapeutic option.

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