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Attention, inhibition and food:

a neuroscientific investigation of eating disorders and obesity

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CONTENTS

Neuroscience and psychiatry

Can a neuroscientific approach benefit the clinical world?

Foreword

It is a truth universally acknowledged, that while talking about the mind, a scientist must talk about the brain (Andreasen, 1997; Austen, 1813). The idea that the brain is the physical substrate of cognitive functions, and that its study can lead to a better understanding of their mechanisms, has dominated the research of functions such as visual attention, sensation and perception, action, memory and emotion in the field of the cognitive neurosciences (Gazzaniga & Mangun, 2014). Human psychiatry has also been studied with the methods of the cognitive neurosciences (Andreasen, 1988). The clinical approach to psychiatry, however, is still very much separate from the neuroscientific one, and psychologists and psychiatrists around the world still base their diagnoses and treatments on principles that have nothing to do with the understanding of the cognitive mechanisms and the neural basis of psychiatric disorder (Osimo & Rumiati, 2017). At the dawn of psychiatry, clinicians (most famously Sigmund Freud) treated patients based on their theory of how the mind worked, in a completely unempirical way (Freud, 1899). The psychodynamic approach had such a long-lasting influence on the clinical world, that the first systematic attempt to classify mental disorders on behalf of the American Psychiatric Association, the Diagnostic and Statistical Manual (DSM-I, American Psychiatric Association, 1952), founded its categories on psychodynamic etiological explanations. Later editions of the DSM relied on more biologically-oriented diagnosis (Kawa & Giordano, 2012), in an attempt to increase its reliability. The current Diagnostic and Statistical Manual of Mental Disorders (DSM-5, American Psychiatric Association, 2013) is based on the principle that symptoms that co-occur most frequently should be attributed to the same disorder. While this data-driven approach can be marked as an important step towards a scientific approach to disorders classification, it still fails to be informative as to the mechanisms at play, the etiology, and possible treatment of the disorders. From this point of view, a cognitive neuroscientific approach can help switch the focus from the *diagnostic label* to the *pathophysiological mechanisms* at play. Studying the cognitive biases of a mental disorder, and their neural correlates, can be informative as to their etiology and treatment. In this perspective, the diagnostic label based on the co-occurrence of symptoms loses importance, and disorders with similar symptoms can be studied together to inquire which symptoms correlate with the same mechanisms at a cognitive level and with the same neural substrates at a neural level.

Eating disorders and obesity

Eating disorders (ED) and obesity can be described from different perspectives. The levels of description that are most commonly used are: the symptomatic level, used in the clinical world, the cognitive level, used in experimental psychology, and the neuronal level, described by the cognitive neurosciences. All of these levels of description are useful in their own way.

In the clinical world, ED are usually classified using the list of behaviors and thoughts that make patients deviate from the norm, such as a persistent restriction of energy intake, intense fear of gaining weight, or binge eating episodes. Obesity is not considered an ED, but can be described, on this level, as a significantly high body weight for the developmental phase; furthermore, obese individuals are very close to ED patients in terms of body dissatisfaction and excessive attempts at weight control (Day et al., 2009). From a cognitive perspective, eating disorders have been linked to attentional biases and altered inhibition (Shafran et al., 2007; Yano et al., 2016). Similar attentional biases and inhibition alteration have also been found in obese and overweight people (Hendrikse et al., 2015; Kulendran et al., 2017), which has led some scientist to argue that studies on ED should include also obese and overweight individuals (Starzomska, 2017). As to differences at a neuronal level, studies show that both ED and obesity can lead to altered brain structure (Van den Eynde et al., 2012; Zhang et al., 2017) and brain function (Val-Laillet et al., 2015).

None of these description levels is "more true" than any other, and each has a different function. Actually, considering all of these description levels at the same time can change our understanding of the mechanisms that underlie a certain group of disorders, which would allow us to classify, prevent and treat certain disorders in a more informed and efficient way.

Symptomatic description of eating disorders and obesity

Most clinicians base their diagnosis on the criteria of the latest edition of the DSM. The DSM provides a list of symptoms for each disorder. Some of the symptoms are core symptoms that all patients with a certain disorder must display, while other symptoms may occur in some patients and not in others. The DSM specifies, for each disorder, some conditions in order to formulate the diagnosis: which are the core symptoms, what is the minimum number of the listed symptoms a patient must display, and some specification as to the severity and the length of time that the symptoms should occur. If a patient meets all the criteria for a specific disorder, a diagnosis can be made. However, if any of the criteria is not met, no diagnosis can be made. This dichotomic approach

leaves no room in the assessment for the severity of a disorder, and can lead to diagnoses that are unreliable through time, as symptoms and severity of a disorder fluctuate. In addition, the way in which symptoms are clustered together in each diagnosis can vary in the different editions of the DSM, depending on the criteria that have been used to group symptoms into diagnoses. Indeed, studying how the classification of the disorders has changed in each new edition of the DSM can be very informative as to how the scientific and clinical community have changed perspective during the course of the years (Kawa & Giordano, 2012). Recently, the classification of ED has changed substantially from the fourth to the fifth edition of the DSM. The DSM-IV recognized only two specific eating disorders, i.e. anorexia nervosa and bulimia nervosa, and all patients that had a clinically significant disorder but did not satisfy the criteria for either anorexia or bulimia were assigned to the residual category "eating disorder not otherwise specified" (EDNOS). This meant that a large minority, if not the majority, of patients with an ED diagnose fell under the EDNOS category (Mancuso et al., 2015). To remedy these shortcomings, the number of categories in the DSM-5 has increased, most importantly including a new label for the Binge Eating Disorders. In addition, the fifth edition of the DSM has integrated ED and feeding disorders (such as pica, the persistent eating of non-nutritive substances, or rumination disorder, the repeated regurgitation of food) in a single category, in an attempt to diminish the number of individuals with a EDNOS diagnosis. As feeding disorders are not of interest for the present discussion, they will not be further mentioned.

In the following, we describe the symptomatology of each eating disorder, according to the criteria of the DSM-5.

Anorexia nervosa (AN)

Anorexia nervosa is characterized by significantly low body weight for the developmental stage. According to the DSM-5, there are three core diagnostic criteria:

- Persistent restriction of energy intake leading to significantly low body weight;
- Either an intense fear of gaining weight or of becoming fat, or persistent behavior that interferes with weight gain (even though significantly low weight);
- Disturbance in the way one's body weight or shape is experienced, undue influence of body shape and weight on self-evaluation, or persistent lack of recognition of the seriousness of the current low body weight.

AN has the highest mortality rate among ED (Arcelus et al., 2011). Patients that are first diagnosed with it are often in treatment for years, and go through phases of remission and relapses (Berends et al., 2016). In the DSM-5, AN has two subtypes:

14

- Restricting type: these patients restrict food intake, and can use fasting and/or diet pills to lose weight;
- Binge-eating/purging type: these patients can have binge eating episodes, or use purging behavior as a means for losing weight, or both. In spite of the occasional binging, patients are still significantly underweight.

According to the DSM-5, a binge eating episode is characterized by both of the following:

- Eating, in a discrete period of time (e.g. within any two-hour period), an amount of food that is definitely larger than most people would eat during a similar period of time and under similar circumstances;
- A sense of lack of control over eating during the episode (e.g. a feeling that one cannot stop eating or control what or how much one is eating).

Bulimia nervosa (BN)

Bulimia nervosa, according to the DSM-5, is characterized by recurrent episodes of loss of control over the amount of food eaten, especially during episodes of binge eating.

The diagnostic criteria for BN are:
- Recurrent episodes of binge eating;
- Recurrent inappropriate compensatory behavior in order to prevent weight gain, such as self-induced vomiting, misuse of laxatives, diuretics, or other medications, fasting, or excessive exercise;
- The binge eating and inappropriate compensatory behaviors both occur, on average, at least once a week for three months;
- Self-evaluation is unduly influenced by body shape and weight;
- The disturbance does not occur exclusively during episodes of anorexia nervosa.

Bulimia nervosa symptoms have many common features with anorexia's. Both patient groups spend a lot of thoughts and energy in their attempts to control weight, even though anorexic patients are more successful in keeping their weight low; both patient groups have a disturbed perception of their own body shape; both the anorexic binge-eating/purging types report binge eating episodes, and can use inappropriate compensatory behaviors to lose weight.

Binge Eating Disorder (BED)

Binge eating disorder is the new diagnostic label of DSM-5. In spite of being the youngest ED diagnosis, it has the highest prevalence, showing just how important the addition of this disorder to the DSM has been (Duncan et al., 2017; Mancuso et al., 2015).

The diagnostic criteria for BED in the DSM-5 are:

- Recurrent episodes of binge eating;
- The binge eating episodes are associated with three or more of the following:
  - eating much more rapidly than normal;
  - eating until feeling uncomfortably full;
  - eating large amounts of food when not feeling physically hungry;
  - eating alone because of feeling embarrassed by how much one is eating;
  - feeling disgusted with oneself, depressed or very guilty afterward.
- Marked distress regarding binge eating is present;
- Binge eating occurs, on average, at least once a week for three months;
- Binge eating not associated with the recurrent use of inappropriate compensatory behaviors as in Bulimia Nervosa and does not occur exclusively during the course of Bulimia Nervosa, or Anorexia Nervosa methods to compensate for overeating, such as self-induced vomiting.

Obesity

Obesity is not considered an ED in any edition of the DSM. The only criteria to define an individual as obese is the Body Mass Index (BMI), a measure of the proportion between height and weight calculated with the formula BMI $=\frac{\text{weight}}{\text{height}^2}$, and expressed in kg/m². According to the World Health Organization, a healthy BMI ranges between 18.5 and 25; above this range an individual is overweight, and below, underweight. Individuals with a BMI of 30 or above are obese. Although obesity is not considered a psychiatric disorder, it shares some features with ED, such as dissatisfaction with one own's body and excessive attempts at weight control (Day et al., 2009).

Common features among ED and obesity

Many symptoms are criteria of different eating disorders. Indeed, there is a continuum in the symptoms of different ED, with thresholds separating diagnoses that have similar features. For

example, binge eating episodes can occur in anorexia nervosa, bulimia nervosa and binge eating disorder, and can occur in some obese individuals that do not satisfy the criteria for an ED. The criteria to cluster symptoms together in a diagnosis, as well as the threshold of severity required for a diagnosis, are relatively arbitrary. Indeed, the DSM-5 includes another class of disorders, the Other Specified Feeding and Eating disorders (OSFED), which include subtypes of AN, BN and BED that do not meet all the requirements for the main diagnosis (in terms of weight loss, frequency or duration). We can therefore say that ED share a continuum of symptoms on different dimensions (graphically represented in Figure 1):

- Control over weight, with respect to the developmental stage, from extreme food restriction and dangerously low BMI, to lack of control over the amount of food eaten, and very high BMI;
- Frequency of binge eating episodes, from absent, to regular;
- Use of compensatory behaviors, from absent, to regular.

In addition, some features are common in all ED, and can be present in obesity, such as marked distress, which can be connected to body perception, eating habits, food, or all three, and difficulties in emotion regulation (Brockmeyer et al., 2014; Micanti et al., 2017).

Figure 1
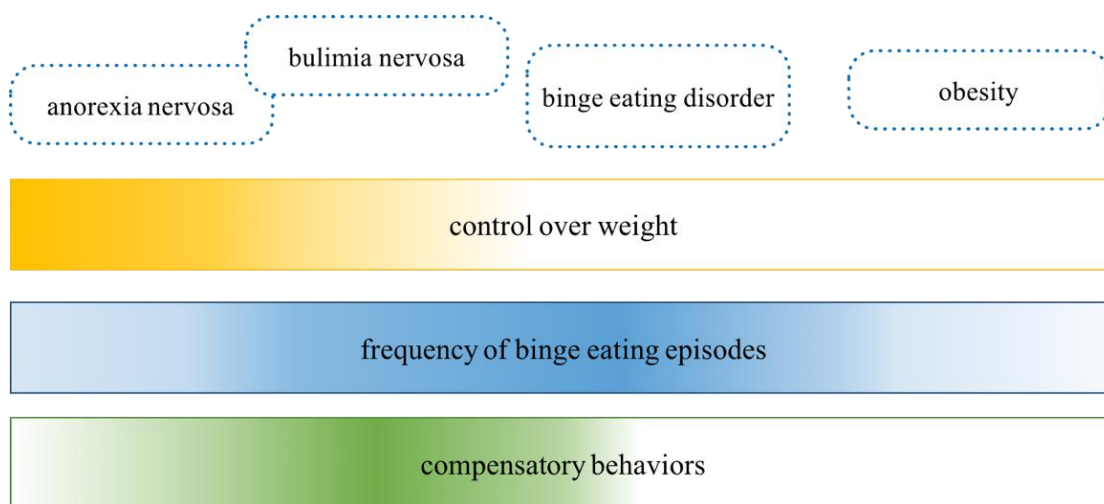
Symptoms continuum and diagnoses. Color intensity indicated the prevalence of symptoms in the disorders.

Cognitive alterations and biases in ED and obesity

ED and obesity are not exclusively connoted at a behavioral level. Indeed, an important part of these disorders comprises altered cognitions and extreme attitudes towards food, body shape perception, and misregulated inhibition. At a cognitive level, both ED patients and obese individuals have been shown to have cognitive deficits, such as degraded performance in attention and memory tasks (Jones et al., 1991; Phillipou et al., 2015; Prickett et al., 2015). These biases can be captured by monitoring patients' performance in attention tasks, and by observing altered response inhibition to disorder-specific cues.

Attentional biases

ED patients and obese individuals have been shown to have attentional biases towards disorder-salient stimuli, such as food and body shapes (Brooks, Prince, et al., 2011; Hendrikse et al., 2015; Kulendran et al., 2017). These biases are relevant in ED, as symptoms include an overvaluation of shape and weight and preoccupation with body image (American Psychiatric Association, 2013). These preoccupations, in the form of biased attention to disliked body parts and to foods, have been proposed to have a critical role in developing and maintaining ED and obesity (Aspen et al., 2013).

Attentional biases have been investigated using different paradigms, among which *priming tasks*, *eye-tracking tasks*, the *dot-probe task*, *the modified Stroop task*, and the *visual search task*. It is important to notice that these tasks measure the attentional bias at different stages of stimulus processing, in a continuum – following Dehaene's classification (2006) – from subliminal processing to explicit categorization of the stimuli. *Priming tasks* measure the influence of a subliminal stimulus on the processing of other stimuli, before it reaches awareness; *eye-tracking tasks* enable the monitoring of both early and later attentional processing, without waiting for a feedback from participants; the *dot-probe* and *modified Stroop tasks* measure the influence of a consciously perceived stimulus on an independent task; finally, a *visual search task* requires participants to explicitly categorize stimuli before responding. Early attention components are associated with involuntary, automatic mechanisms, while later attention components reflect top-down mechanisms of voluntary processing (Carrasco, 2011). It has been proposed that it is crucial to distinguish between different temporal attentional food bias components in ED and obesity, as they are indicative of different mechanisms (Werthmann et al., 2015).

Using a priming paradigm, Svaldi et al. (2015) found, for instance, that obese individuals, both with and without binge eating disorder, show increased priming effects for foods, compared to

controls. A bias at such an early stage of stimulus processing reflects a heightened salience of the stimulus at an automatic, involuntary phase. Indeed, using an affective priming task, Cserjesi et al. (2016) have shown that implicit and explicit preferences towards foods can be at variance: i.e. obese individuals showed an implicit preference for large food portions, but a rather negative explicit attitude for large portions. No implicit or explicit preference for food portion was found in the non-obese group. The incongruence between implicit and explicit preference in the obese group likely stems from a clash between automatic processing and cognitive knowledge. On the other hand, anorexic patients, contrary to controls, have been shown not to have a positive bias towards palatable foods in a priming paradigm (Roefs et al., 2005), reflecting a altered processing of foods from an automatic level.

Eye tracking paradigms show that obese individuals have a preferential orienting towards food images at the onset of each image (Castellanos et al., 2009), as well as greater visual attention towards high-calorie food images compared to low-calorie food images (Doolan et al., 2014). On the contrary, anorexic patients show overall less attention towards food pictures, with no difference in early vigilance, but later avoidance of food stimuli (Giel et al., 2011). The fact that anorexic patients differ from controls at a late stage of stimulus processing suggests that individuals with AN avoid food cues after having categorized them as food, i.e. reflecting a top-down process of cognitive avoidance.

In the dot-probe task (MacLeod et al., 1986), participants are asked to respond as fast as possible to a neutral cue (a dot) replacing one of two images previously shown to the right and left of a central fixation cross. Using this paradigm, it has been found that ED patients avoid high-calorie food images and are hyper-vigilant towards positively connoted low-calorie food images (Brooks, Prince, et al., 2011), whereas overweight/obese participants overall show a heightened attention towards food images (Nijs, Muris, et al., 2010).

In the modified Stroop task (Ben-Tovim et al., 1989), participants are asked to name the colors in which words are displayed, while disregarding the meaning of the word. Emotionally salient words have been shown to lead to longer naming times (Klein, 1964). Both ED patients and obese participants were found to be slower in naming the colors of words related to foods, although results have been inconsistent (Dobson & Dozois, 2004; Johansson et al., 2005; Kulendran et al., 2017). These results are probably due to the fact that food is emotionally salient for both obese individuals and ED patients.

These results together show that eating disorders and obesity influence attention towards foods at different stages of stimulus processing but in different ways. Obese and overweight participants show increased attentional approach towards high-energy food pictures on early

measures of attentional bias, but later avoidance of high-fat food pictures, which might reflect that while they automatically orient themselves towards food, they might try to avoid it consciously to regulate craving (Veenstra et al., 2010; Werthmann et al., 2011). On the other hand, anorexic patients don't seem to show an early attentional bias towards food, but only later avoidance (Sackville et al., 1998). These results seem to indicate that early visual attention might be connected to craving, and later stages of visual attention to top-down control mechanisms (Werthmann et al., 2015). Results are however inconsistent, and it is at present not possible to draw any definitive conclusion.

Inhibition

ED and obesity are tightly linked to different degrees of impulse control and inhibition. It has been suggested that a model of eating disorders as a spectrum of impulse control disorders would provide better classification and treatment (Brooks et al., 2012). In such a model, the anorexia nervosa restrictive subtype would lie at the over-controlling (inhibitory) extreme, followed by anorexia nervosa binge-purge subtype and bulimia. Binge eating disorder would be placed at the impulsive extremity. Indeed, studies have shown that self-reported inhibitory control is poorer in women with BN and greater in women with AN compared to healthy controls (Bartholdy et al., 2017; Claes et al., 2006). Behaviorally, impulsivity and inhibition can be studied with different paradigms. The ones most widely used include *temporal discounting paradigms*, linked to reward-based inhibition, *set shifting tasks*, measuring cognitive flexibility, and *Go/No-Go* and *stop signal tasks*, that measure reactive motor inhibition.

Temporal discounting paradigms consist in asking individuals to make a series of choices between an immediately available reward (usually money) versus a greater award after some time. The rate at which an individual reduces the value of future rewards can be mathematically modeled, allowing calculation of an individual's discount rate, and seems to remain fairly constant through life (Cardinal, 2006). Anorexic patients have been shown to have a greater tendency than healthy individuals to delay gratification linked to a monetary reward, in particular in individuals with AN restricting subtype (Steinglass et al., 2012), whereas the opposite has been shown for binge-eating and bulimic patients and obese individuals (Davis et al., 2010; Kekic et al., 2016; Mole et al., 2015). These results suggest that dysfunctional impulse inhibition in ED and obesity is not limited to food consumption.

Set shifting tasks measure the ability to move back and forth between multiple tasks, operations, or mental sets. Poor performance at these tasks is indicative of rigid approaches to problem solving, stimulus-bound behavior, and stereotyped behaviors. These paradigms have been

used in ED research to measure the ability to inhibit a preponderant response. Set shifting abilities impairment have been shown to characterize AN, BN and BED patients (Aloi et al., 2015; Blumberg et al., 2014; Shott et al., 2012; Tchanturia et al., 2012) as well as obese individuals (Perpiñá et al., 2017). Indeed, a consistent deficit in set-shifting ability seems to characterize ED in general (for a review, see Roberts et al., 2007).

Finally, *Go/No-Go* and *stop signal tasks* measure the ability to inhibit a preponderant motor response. In *Go/No-Go tasks* participants are asked to respond as fast as possible to a category of stimuli, but to refrain from responding to another stimulus category. The majority of the studies using the Go/No-Go task show impaired inhibitory control, especially for disorder-related stimuli such as foods, both in bulimic ED patients (Wu et al., 2013) and in overweight/obese participants (Price et al., 2015), but results are inconsistent (Kulendran et al., 2017; Loeber et al., 2012).

Structural and functional brain alterations in ED and obesity

The neural systems that control food intake are complex and distributed across the brain. In healthy individuals, energy homeostasis, reward and cognition are the principal determinants of food intake, and these systems work together to find a balance between homeostatic and hedonic signals. Homeostatic signals are needed to maintain body energy and to provide for its biological needs, while hedonic signals are involved in the motivation to eat and are based on pleasure and reward (Berthoud & Morrison, 2008). Brain areas involved in cognition, among which the prefrontal cortex (PFC), tend to decrease food intake. Under normal circumstances, reflective areas, such as the PFC, can regulate reflexive areas, to maintain a healthy body weight (Alonso-Alonso & Pascual-Leone, 2007). A schematic representation of these systems and their interaction is depicted in Figure 2.

Figure 2
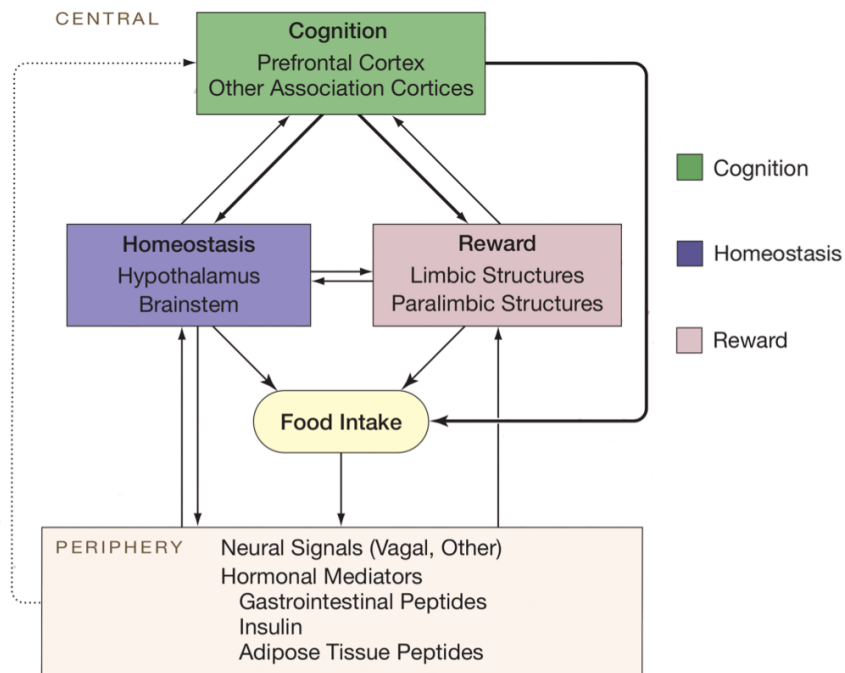
The three systems regulating food intake: homeostasis, reward and cognition(adapted from Alonso-Alonso & Pascual-Leone, 2007).

At the basis of the reward system, some brain areas are specialized for the 'liking' or 'wanting' of foods. 'Liking' refers to the hedonic reaction to a reward that we experience as pleasure; 'wanting' is connected to a motivational component, the incentive salience of the stimulus, which induces approach. These two components have separate brain substrates (Berridge & Kringelbach, 2015). The 'liking'-hedonic circuit relies on hotspots in forebrain limbic structures, including the nucleus accumbens, ventral pallidum, and brainstem parabrachial nucleus, as well as on the insula and OFC. The activation of hedonic hot spots in the OFC or insula are key areas in the subjective pleasure of foods in humans. 'Wanting' circuits include wider opioid networks, largely modulated by dopamine, including the nucleus accumbens, the dorsal striatum, the amygdala, lateral hypothalamus, as well as mesolimbic dopamine systems (Berridge et al., 2010). See Figure 3.

Figure 3
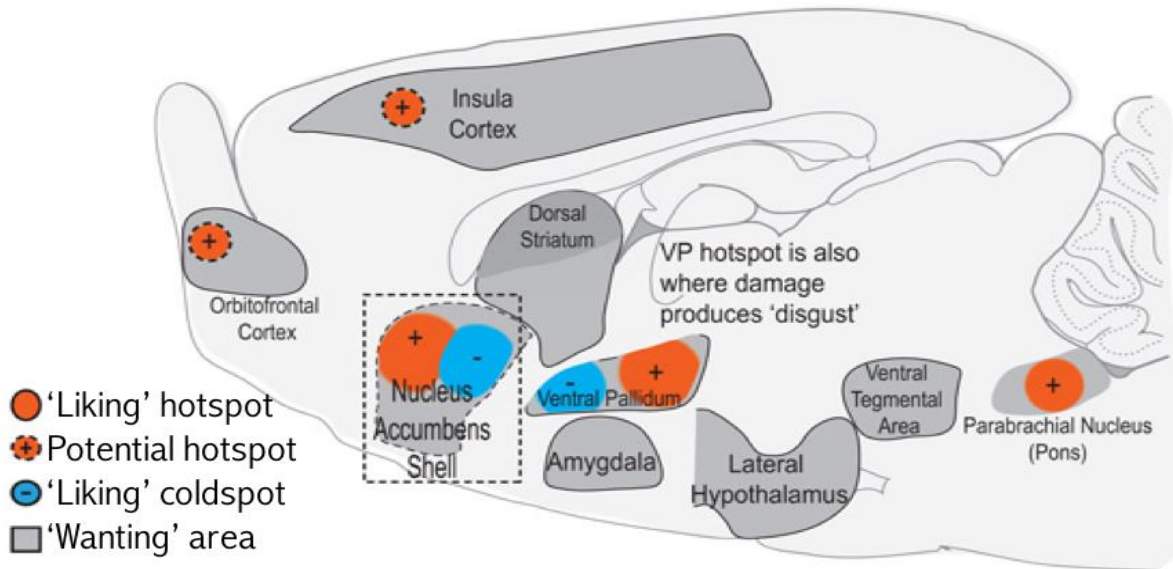
Cortical and subcortical areas supporting the 'Liking' and 'Wanting' circuits. Hotspots and coldspots indicate areas that respond to highly liked and highly disliked foods, respectively (Adapted from Berridge & Kringelbach, 2015).

Several findings report altered responses in the 'wanting' circuit at the sight of food between healthy individuals, ED patients, and obese subjects (García-García et al., 2013). A number of studies has found an increased activation in reward-specific regions in overweight and obese compared to normal-weight individuals when confronted with high-calorie food stimuli (Rothemund et al., 2007; Stoeckel et al., 2008), while AN patients showed decreased responses in the hypothalamus, amygdala, hippocampus, OFC, and insula in response to high-calorie foods (Holsen et al., 2012). Overeating and obesity are therefore related to an increased reward value of the sensory inputs produced by foods, which overrides satiety signals (Rolls, 2012).

At a more explicitly cognitive level, the integration of sensory information and metabolic cues about food is mediated by high-level areas, among which the prefrontal cortex (PFC), and in particular the orbitofrontal cortex (OFC), the anterior cingulate cortex and insular cortex (Timofeeva & Calvez, 2014). These areas store, update, and retrieve salient information related to food, and play a key role in inhibition of food intake, and in the down-modulation of the rewards system. Obese individuals show a diminished activity of the PFC, and it has been suggested that a dysfunction of the right PFC may represent a central event in the etiology of human obesity (Alonso-Alonso & Pascual-Leone, 2007). On the other hand, the prefrontal cortex has been shown to be hyperactive in response to food in AN and BN patients, reflecting the top-down cognitive control these patients display over food intake (Brooks, O'Daly, et al., 2011).

Studies of brain morphology, using Voxel Based Morphometry (VBM) or Diffusion Tension Imaging (DTI) in ED and obese patients, have shown that behavioral and cognitive deficits in these patients are reflected in structural brain changes too. Importantly, cognitive restraint of eating, which is a core symptom of AN, was positively correlated with the gray matter volume in the dorsolateral prefrontal cortex (Yao et al., 2016), while increased BMI has been linked to thinning of occipital and right PFC (Medic et al., 2016). These results reflect well the key role that the PFC has in regulating food intake.

Anorexic, bulimic and binge eating patients have also been shown to have increased gray matter volume of the medial orbitofrontal cortex (G. K. W. Frank et al., 2013; Schäfer et al., 2010). The OFC has connection to the hippocampus, amygdala, cingulate and insular cortex, areas that are involved in the processing of taste as well as reward, motivation and emotion (Rolls, 2012). Anorexic and bulimic patients have also been found to have higher left insula volume (G. K. W. Frank et al., 2013), an area that is involved in taste perception, as well as contributing interoceptive awareness and to self representation (Craig, 2009). BN has also been associated with increased gray matter in the ventral striatum (Schäfer et al., 2010), an area that is involved in reward pathways, and has been implicated in playing a critical role in addiction, as it mediates the reinforcing effects of drugs through dopaminergic stimulation (Everitt & Robbins, 2013). Lower gray volume in the orbitofrontal cortex, striatum, and insula, reflecting a disruption of reward pathways, have also been reported in obese individuals (Shott et al., 2015).

Furthermore, AN has been linked to global gray matter loss (Suchan et al., 2010), with focal loss in the cerebellum, hypothalamus, caudate nucleus, frontal, parietal and temporal areas (Boghi et al., 2011), but results are inconsistent (Van den Eynde et al., 2012). These abnormalities might be linked to the homeostatic, reward abnormalities and cognitive symptoms of behavioral inhibition and body representation. Castro-Fornieles et al. (2009), in a longitudinal study, found that successful treatment is associated with a recovery of the gray matter volume in AN patients.

Structural alterations have also been reported in white matter in ED and obesity. In particular, white matter loss has been reported anorexic patients, i.e. in the superior longitudinal fasciculus, which has been linked to body image distortion and impairment in reward processes (Boghi et al., 2011; Via et al., 2014). Obesity has also been linked to white matter loss, in particular in the corpus callosum, fornix, cingulum and corona (Kullmann et al., 2015). In particular, data indicates that white matter alteration might affect connectivity between corpus callosum and the right PFC, as well as structural interconnectedness with the anterior corpus callosum (Mueller et al., 2014), indicating a role of white matter loss in the functionality of high-level areas, such as the PFC.

A new technique for studying food processing: Continuous Flash Suppression

In the three studies reported in this thesis, subliminal processing of foods and non-foods have been studied with a novel paradigm, i.e. Continuous Flash Suppression (CFS; Tsuchiya & Koch, 2005). To the best of our knowledge, these studies comprise the first application of CFS to the study of food perception in ED and obesity.

Conscious, preconscious and subliminal

The idea that we are not aware of all the content of our mind has a long history in psychology. Freud referred to the unconscious as the place of our mind that collects all the information, feelings, thoughts, urges, and memories that keep existing outside of our conscious awareness (Freud, 1949). He was among the first to underline how unconscious ideas can influence our behavior and experience. It is now clear that there are many stages of stimulus processing, not all of which are connected to conscious experience, and stimuli we are not aware of can influence our thoughts and decisions. A famous example is that of blindsight, the ability of people who are cortically blind due to lesions in their striate cortex to respond to visual stimuli that they do not report consciously (see Stoerig & Cowey, 1997).

Dehaene et al. (2006) have proposed a taxonomy of visual awareness, distinguishing between three possible stages of visual processing: subliminal, preconscious and conscious. They consider information as conscious if the individual is able to report it. Evidence indicates that without attention, conscious perception cannot occur. That means that, when looking at a scene, only the part of the scene where attention is being focused is conscious. The information that is not conscious, but potentially carries enough activation for conscious access, and could become conscious if attention were directed to it, is called preconscious. Preconscious information is not accessed, but potentially accessible. This is the case, for example, of the not attended parts of a visual scene. Using the inattentional blindness paradigm, studies have shown that even a stimulus presented in the fovea for 700ms, when unattended, might fail to be seen (Vogel et al., 1998). Finally, Dehaene et al. (2006) define subliminal processing, etymologically 'below the threshold', as a condition for information inaccessibility, where bottom-up activation is insufficient to trigger large-scale reverberating states connected to consciousness, and the stimulation therefore does not give rise to awareness. Subliminal

processing can be subjected to top-down influences, such as temporal attention, spatial attention, and instructions given to participants.

A method of subliminal stimulation: Continuous Flash Suppression

A general overview

Continuous Flash Suppression (CFS) is a technique of binocular rivalry. It was first described by Tsuchiya and Koch less than 15 years ago (2005), and it has, since then, been widely used to investigate subliminal processing. Like all binocular rivalry techniques, it segregates the input of the two eyes, so that two different images are shown to the two eyes in the same field of view. One eye, typically the dominant, is shown a stream of colorful changeful patterns, such as Mondrian-like images, with a frequency between 1 and 32 Hz (Drewes et al., 2018). The other eye is shown a single static stimulus. As the geometric colorful changing patterns have more salient low-level visual features, they act as distractors, and the stimulus shown to the other eye is suppressed from consciousness for up to a few seconds. During this time, the percept coincides with the geometric patterns, and while the stimulus is not consciously seen, it is subliminally processed (Figure 4).

Figure 4
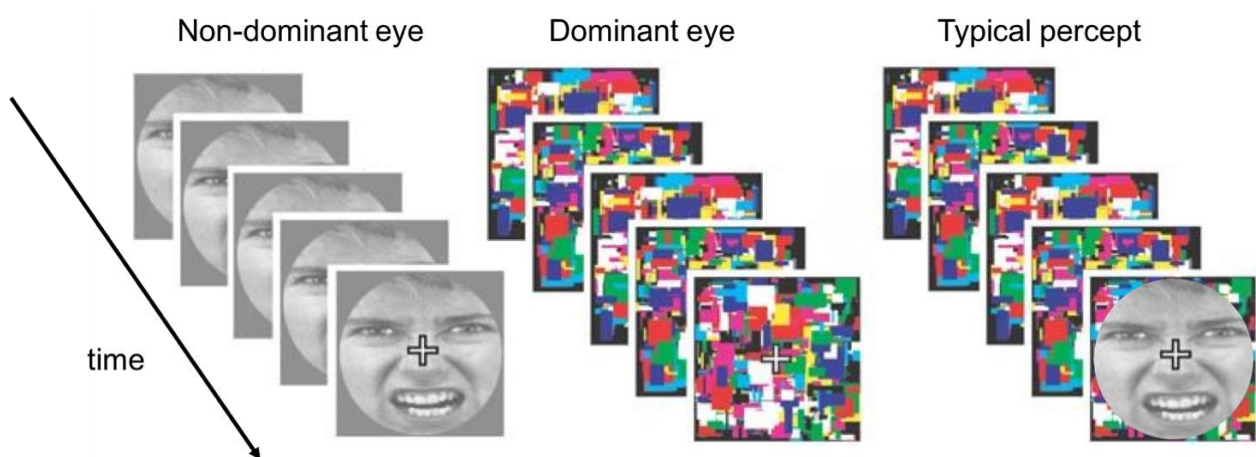
A stationary gray stimulus is presented in one eye (typically the non-dominant) while different, colored Mondrian patterns are flashed in the other eye every 100 ms. On the right, the typical percept: for the first few seconds of stimulation (here represented in the first four slides) only the distractors are visible. After a variable interval, the stimulus is suddenly visible, with a pop-out effect (here represented on the fifth slide). Image adapted from Tsuchiya & Koch, 2005.

26

Factors affecting suppression times

Evidence shows that emotional stimuli are processed even when they are unconsciously perceived (Tamietto & de Gelder, 2010), and that subliminal processing of emotional stimuli affects behavior, perception, and decision making (Puviani et al., 2016). Subliminal processing using CFS has been studied using different paradigms. When the dependent variable of a study is the duration of suppression time, CFS is often referred to as breaking CFS (bCFS) (Stein et al., 2011). Many studies have used bCFS in priming paradigms (e.g. Costello et al., 2009), and cross-modal priming paradigms (Alsius & Munhall, 2013) to study if consciously perceived information affects suppression times. Taken together, these studies show an advantage for detecting stimuli that match rather than mismatch consciously accessible information (Gayet et al., 2014; but see Korb et al., 2017).

Other studies compare categories of stimuli to see whether high-level differences, such as familiarity, influence suppression times. For instance, images of faces are detected faster when presented upright as compared to inverted (Gray et al., 2013; Korb et al., 2017), and familiar faces are detected faster than those of strangers (Gobbini et al., 2013).

Salience of the stimuli has also been shown to influence suppression times. In the subliminal processing of salient stimuli, it has been shown that subcortical regions play a role in the attentional guidance towards objects of relevance (Troiani & Schultz, 2013). Moreover, higher level areas, such as the parietal cortex, have been shown to be activated for emotionally salient stimuli, even in the absence of awareness (Troiani et al., 2014).

Continuous Flash Suppression and clinical findings

In addition to the fact that stimuli that are more inherently salient are processed differently by low- and high-level areas outside of awareness, it has been shown that personal features that alter the relevance of the stimuli influence suppression times. In a very interesting study, Schmack et al. (2016), recruited participants with varying degrees of spider phobia, and tested their suppression times for spider images as well as for flowers images. Schmack et al. (2016) also recorded neural responses evoked by suppressed spider and flower pictures, to relate suppression times to the undergoing neural processing, using fMRI. Interestingly, not only were suppression times on average shorter in spider than in flower trials, indicating a general higher salience for spiders compared to flowers at a subliminal level of processing, but the degree of arachnophobia of each participant was negatively correlated with suppression times in spider trials. At a neuronal level, individual

suppression times were predicted by fMRI activity in left orbitofrontal cortex and in the right fusiform gyrus. These results indicate that neural signals in these higher-level cortical areas during subliminal processing of complex visual information predict how fast this information gains access to conscious perception.

Suppression times of relevant stimuli using CFS has also been investigated in clinical populations to explore the subliminal processing of disorder-related symptoms. For example, Capitão et al. (2014) used a CFS paradigm to inquire whether symptoms of anxiety are associated with automatic, preconscious biases of stimulus processing. Their results indicate that higher trait anxiety scores were directly associated with speed to detect fearful faces compared with happy faces, meaning that a bias toward threatening information associated with symptoms of anxiety operates, at least partly, at an early stage of information processing.

It is important to notice that relevant information is not necessarily processed faster; for example, Yang et al (2011) found that depressed individuals have longer suppression times for sad faces compared to healthy controls. These authors interpret these results hypothesizing that that depressed individuals may not subliminally orient their attention towards negative information in the environment, but once such information has come to be the focus of their attention, they may have greater difficulty disengaging from it.

To date, no study has investigated the subliminal processing of foods in individuals with eating disorders and obesity using bCFS.

Thesis aim and outline

The aim of this thesis is the investigation of the processes and the substrates underlying eating disorders and obesity. The studies in this thesis follow an approach that considers eating disorders and obesity not as separate diagnostic labels, but as a continuum of symptoms that should be understood and investigated on different levels. These are: the *behavioral/symptomatic* level, which is the basis for clinical diagnoses and treatment; the *cognitive level*, i.e. the mechanisms that underlie the symptoms, such as altered attention and inhibition; and the *neural substrate level*, i.e. the brain areas whose alteration is linked to the symptoms and mechanisms (Figure 5).

Figure 5
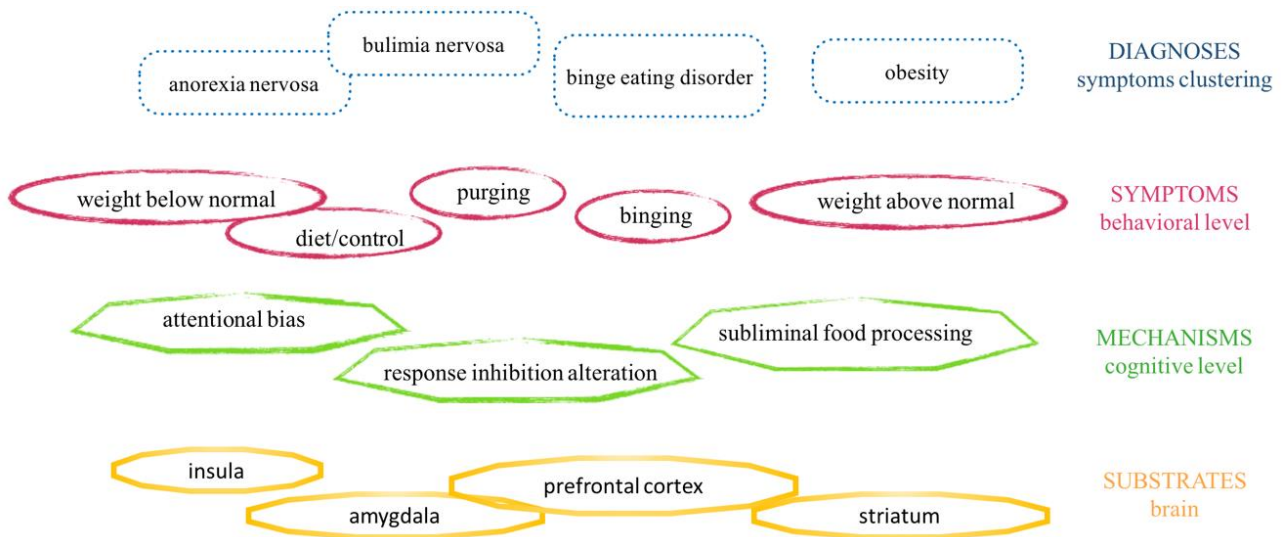
Different description levels of eating disorders.

This investigation has been brought forward in three studies. In the first study, we evaluate how eating habits and BMI are linked to subliminal processing and inhibition towards food (Osimo, Korb, Aiello, et al., under review). We test a range of participants that include ED patients, obese individuals and healthy controls. Subliminal perception of foods and nonfoods is explored using bCFS, a paradigm that has yet never been used in the investigation of food perception. In the second study, we consider the effect of transcranial direct current stimulation (tDCS) on the right prefrontal cortex (PFC) on subliminal perception of, and inhibition towards foods (Osimo, Korb, & Aiello, under review). In the third study, we explore the connection between subliminal perception and inhibition towards food and focal differences in brain anatomy, using Voxel Based Morphometry (VBM) (Osimo et al, *in preparation*).

Subliminal cognitive bias for food and impulsivity in obesity and eating disorders

Abstract

Eating disorders (ED, i.e. anorexia nervosa, bulimia and binge eating) and obesity
have been linked to attentional biases for and altered inhibition of responses to food
stimuli. However, these two groups of patients have rarely been investigated
together in the same studies. The goal of this study is to fill this gap in the literature
by investigating subliminal visual processing of food stimuli and response
inhibition in both ED patients and overweight/obese participants.

Seventy-four participants (25 ED patients, 24 overweight and obese, and 25 healthy
controls) were enrolled in this study. Subliminal processing of food and non-food
stimuli was measured with a breaking continuous flash suppression (bCFS) task,
while impulsivity was measured with a Go/No-Go task. Among participants with
ED symptoms, higher BMI predicted faster awareness in the bCFS task, especially
of food images compared to non-food images, and shorter RTs to food Go cues in
the Go/No-Go task.

Altered subliminal processing of and heightened attention for food stimuli was
found in patients who suffered from both dysfunctional eating habits and obesity.
These results demonstrate the need to also include obese participants in future
studies on processing biases in ED patients, to better understand attentional biases
for food.

Introduction

Eating disorders (ED), such as anorexia, bulimia nervosa, and binge eating disorder, are characterized by extreme attitudes towards food, distorted perception of body shape, and difficulties in weight regulation. In particular, ED patients show attentional biases for food- and body-image-related stimuli, which may act as a biomarker for ED and contribute to their development and maintenance (Starzomska, 2017; Aspen et al., 2013; Brooks, Prince, et al., 2011; Johansson et al., 2005; Faunce, 2002). Similar biases have also been found in obese and overweight people (Kulendran et al., 2017). To date, these cognitive biases have been investigated only explicitly, with participants being instructed to recognize and respond (or not respond) to food cues, and the response consequently being recorded only after the processing of the food cues has taken place. One aim of the current study was to fill this gap in the literature by investigating the subliminal processing of food pictures in ED patients, overweight and obese people, as well as healthy controls. Both participants' eating habits and their BMIs were used as continuous predictors of their task performance. In addition, we explored response inhibition in the context of food images.

To achieve these aims, the implicit processing of food and non-food images was measured with the breaking continuous flash suppression (bCFS) paradigm (Jiang et al., 2007; Tsuchiya & Koch, 2005). Previous research already suggested that the bCFS paradigm is a useful measure of attentional biases in other clinical populations (Jusyte et al., 2015; Schmack et al., 2016; Z. Yang et al., 2011). To our knowledge, this is the first time that this paradigm is employed to investigate food processing. Furthermore, participants completed a Go/No-Go task as a measure of response bias and inhibition to food stimuli.

We hypothesized that extreme eating habits and high BMI would induce a response bias for food images, reflected in shorter suppression times for food stimuli in the bCFS task, and faster reaction times and more false alarms for food stimuli in the Go/No-Go task.

Methods

Participants

Seventy-four participants (nine males) aged 19-58 years ($M = 35.1$, $SD = 12.9$) with normal or corrected-to-normal eyesight took part in the study. The sample included three groups of

participants. Overweight participants (cutoff based on the Word Health Organization guidelines, World Health Organization, 2000) were recruited from a dietician's clinic on the base of their BMI (BMI > 25; n = 24). Participants with a DSM-5 diagnosis of ED, namely anorexia nervosa, bulimia, or binge eating (American Psychiatric Association, 2013) were recruited recruited at the Center for Weight and Eating Disorders of Portogruaro (n = 25). Healthy control participants were recruited through advertising on the campus of SISSA (n = 25). In the final sample, 12.5% of participants were underweight, 41.7% normal-weight and 45.8% overweight or obese. 22.2% of participants had pathological EAT-26 scores. All demographic and clinical characteristics of participants are displayed in Table 1. This study was approved by SISSA's Ethics Committee and by the Ethics Committee for Clinical Experimentation of the Province of Venice (deliberation number 878).

Table 1

Group	N	Age	BMI	EAT-26
Healthy controls	25	28.8 (10.3)	23.3 (6.0)	9.84 (9.5)
ED patients	25	30.5 (11.4)	23.7 (9.25)	23.4 (19.6)
Overweight/obese	24	46.5 (9.2)	31.7 (4.5)	6.0 (6.0)

. Demographic and clinical data of the participants of the three recruitment groups.

Procedure and experimental tasks

Participants were tested individually in a quiet room. After signing informed consent, they completed the questionnaire and reported their height and weight. Then, participants completed, in this order, the bCFS task, a NoCFS control task, and the Go/No-Go task.

Questionnaire

The participants' eating habits were investigated through a questionnaire, the Eating Attitudes Test -26 (EAT-26) (Garner et al., 1982), in its Italian validated version (Dotti & Lazzari, 1998). The EAT-26 is often used in clinical screenings to evaluate the risk of anorexia and bulimia nervosa. It is comprised of three subscales. The first subscale measures 'dieting', and reflects a pathological avoidance of fattening foods and shape preoccupations. This subscale is associated with several parameters of the multidimensional body-image construct, and participants who score highly on this scale tend to overestimate their body size, are dissatisfied with their body shape, and have a strong

desire to be thinner. It has items such as "*I like my stomach to be empty*", "*I am terrified about being overweight*", and "*I am preoccupied with the thought of having fat on my body*". Anorexic patients usually have very high scores on this subscale. The second subscale measures 'bulimia and food preoccupation'. While it also has some items relative to body-image disturbances, such as "*I give too much time and thought to food*", or "*I feel that food controls my life*", it also measures the propensity towards binge-eating behaviors, with items like "*I have the impulse to vomit after meals*" and "*I have gone on eating binges where 1 feel that I may not be able to stop*". It is positively related to bulimia and a heavier body weight. The third subscale is labelled 'oral control' and was largely comprised of items reflecting self-control about food (i.e. "*I cut my food into small pieces*", or "*I avoid eating when I am hungry*"), as well items about social pressure to gain weight ("*I feel that others would prefer if 1 ate more*"). The final score is considered indicative of the likelihood of having an eating disorder.

Stimuli

Stimuli in the bCFS and NoCFS tasks consisted of 40 images of food and 40 images of non-food items (i.e. animals, plants and non-living natural and man-made objects), selected from the FRIDa database (Foroni et al., 2013). The caloric content of the depicted food items varied from low-calorie to high-calorie foods. To achieve binocular stimulation during the bCFS task (see below), the stimulus images were modified, keeping only the red channel and deleting the green and blue one. This ensured that the images were not visible when observed through a cyan filter, but they were visible when observed through a red filter (for a similar procedure see the third experiment in Korb et al., 2017). The luminance of all images thus obtained was equalized in Matlab (http://www.mathworks.com/) using the SHINE toolbox (Willenbockel et al., 2010). Final stimuli were sized 530×530 pixels and saved in .png format. Distractor images in the bCFS task were a set of 100 pictures with colorful oval shapes of different sizes creating random patterns. They were filtered to contain only the blue channel, and thus only be visible by the eye covered by the cyan filter.

Breaking Continuous flash suppression and control tasks

bCFS is a technique of binocular rivalry, in which a stimulus, slowly increasing in contrast, is shown to one eye, while continuously changing high-contrast Mondrian-like patterns are shown to the other eye in the same field of view. The incongruence between the stimuli leads to suppression of

the low-contrast stimulus. Suppression times are calculated based on participants' key presses indicating the position (left, right of a central fixation cross) of the stimuli. To induce binocular rivalry, participants wore anaglyph glasses with a red filter on their non-dominant eye and a cyan filter on their dominant eye. Prior to the bCFS task, participants' ocular dominance was assessed with the Miles test (Miles, 1930). Each distractor was shown in red and each stimulus was shown in blue (Figure 6). This procedure ensured that the stimuli were only perceived by the non-dominant eye, and that distractors only entered the dominant eye. Stimuli were presented in one quadrant, while distractors covered the entirety of a centrally presented square. The position of the stimuli was random, and each participant saw each stimulus once in all four quadrants in a different order. Distractors were shown at 100% contrast and changed at a rate of 10 Hz, while the contrast of the stimuli increased linearly from 0% to 60% over the course of one second, and then stayed at 60% until response. After 10 seconds, if no response was given, the trial ended. Participants fixated a central fixation cross, and responded as fast and as accurately as possible to indicate the position of the stimulus (left, right) with respect to the central fixation cross, by pressing with the index fingers 'f' or 'j' on a QWERTY keyboard. The bCFS task included 320 trials; every 30 trials the task paused and participants were allowed to rest. An example trial is shown in Figure 6.

As customary in studies using the bCFS paradigm, participants were also asked to perform the equivalent task without suppression (hence NoCFS). The NoCFS task is designed to make sure that the results of the bCFS task can be attributed to visual processing during suppression times, and not to other factors. This task had the same instructions and stimuli as the bCFS task, but stimuli and distractors were both shown in full RGB and were therefore visible to both eyes simultaneously, thus preventing suppression of stimulus awareness. The no-suppression task included 180 trials. An example trial is shown in Figure 6.

Figure 6
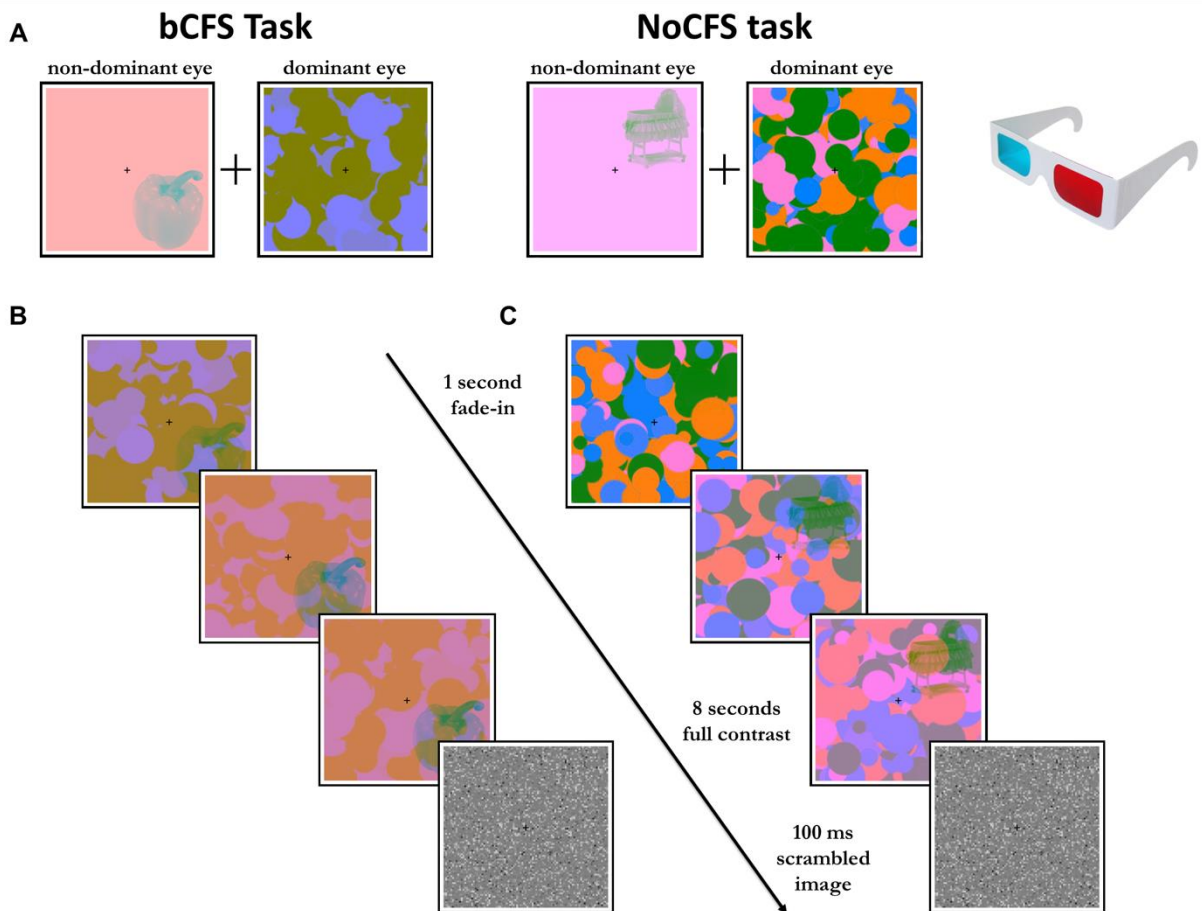
A) Original images composing an example trial of the bCFS task and of the NoCFS control task, before being superimposed. In the actual tasks the two images were superimposed. Binocular rivalry was achieved with red and cyan goggles worn by participants. B) An example trial of the bCFS task. C) An example trial of the NoCFS task.

In the bCFS and NoCFS tasks stimuli were shown on a 17-inch LCD monitor with a resolution of 1280 × 1024 pixels and a refresh rate of 60 Hz. Stimuli were shown with 9.6° × 9.6° of visual angle (330 × 330 pixels), in one of the quadrants of a 660 x 600 pixels square. The tasks were programmed in and presented with Python using the Psychopy library (Peirce, 2007), running on a notebook computer with Windows XP.

Go/No-Go task

Participants were instructed to respond as quickly as possible to Go stimuli but to refrain from responding when a No-Go stimulus was presented. In two blocks, Go cues consisted of food images

and the No-Go cues of non-food images (kitchen utensils), while in the other two blocks the assignment was reversed. In each block, 12 out of 40 trials (30%) were No-Go trials. The Go/No-Go task and the stimuli were the same as those used by Aiello and colleagues (Aiello et al., 2017). An example trial of both types of blocks is depicted in Figure 7.

Figure 7
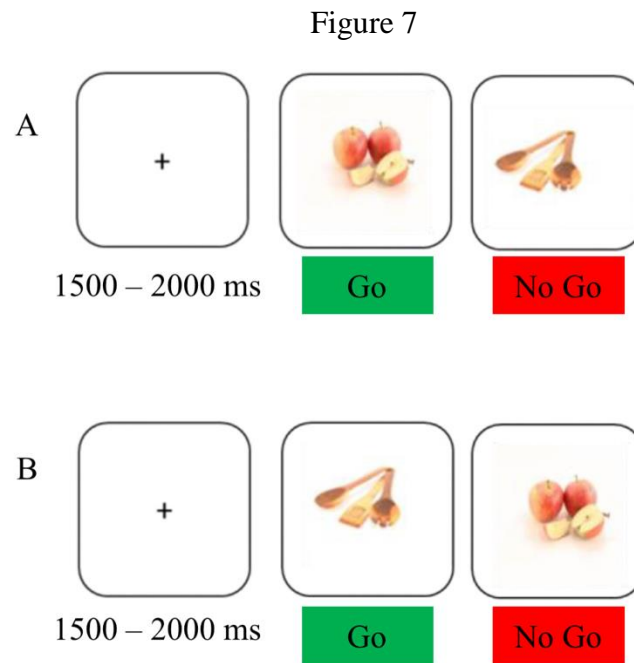
Example trial in the Go/No-Go task in a block using food images as Go cues (A) and in a block using non-food pictures as Go cues (B). This picture is adapted from Aiello et al. 2017.

Analyses

In order to include in the statistical model the features shared by participants with EDs and those with overweight/obesity, we used their scores on the eating habits questionnaire, as well as their BMI, as continuous predictors of performance in all tasks. Linear mixed-effects models (LMMs), which compared to ANOVAs reduce Type I errors and allow for better generalization of findings (Judd et al., 2012), were computed with R (version 3.4.3, R Core Team, 2017) using the lmer function (lme4 package; Bates et al., 2015). Six participants were excluded from the analyses due to several reasons (not responding to more than a third of the bCFS task trials ($n = 2$), having closed one eye during part of the bCFS task ($n = 2$), and not completing the questionnaires ($n = 2$)). Trials with no responses (3.70%), wrong responses (1.43%), with RTs below 500 ms (0.02%), and with RTs that were more than 2.5 SDs from the mean of each subject (0.03%) were excluded from analyses of the

bCFS and NoCFS tasks. Demographic and clinical data of the final sample is reported in Supplementary table 1. Statistical significance for all analyses was set at alpha < 0.05.

In order to compare the RTs during the bCFS and the NoCFS tasks and to normalize the data, RTs were log transformed within each of these tasks. As far as the bCFS and NoCFS tasks are concerned, a random intercept for Participants, nested in Recruitment Group, Stimuli and Stimulus Location were included in every model to account for individual differences and the variability related to the different images of each category being shown in the four quadrants. The initial model included all the variables directly derived from the experimental design, i.e. Task (bCFS, NoCFS), Stimulus Category (Food, NonFood), BMI and EAT-26 scores. To make sure that all predictors significantly increased the model fit, each predictor was removed from the initial model one at a time, and were kept in the model only if they significantly improved its fit as measured by the Akaike Information Criterion (AIC). A significantly reduced AIC was used as criterion for model selection, because it favors parsimonious models (Bolker et al., 2009). Reduced AIC was verified comparing the new model with the basic model using the anova function of the *lmerTest* package in R (Kuznetsova et al., 2017). All predictors significantly increased the model fit [*ps* < 0.001], and were therefore kept in the model.

The same stepwise procedure was used in the analysis of the RTs of the Go trials in the Go/No-Go task. Go trials with no response (1.59%) were excluded from the analyses. RTs were log transformed as for the bCFS and NoCFS analyses. The initial model only included Stimulus Category (Food, NonFood), BMI and EAT-26 scores as a predictors, and Participants, nested in Recruitment Group, and Stimuli as random intercepts (Stimulus Location was not added as all images were presented at the center of the screen). All predictors significantly increased the model fit [*ps* < 0.001] and were therefore kept in the model.

To focus on the effects of BMI and EAT-26 scores on inhibition, accuracy on Go an No-Go trials was used as a depended variable in an LMM. The initial model included Trial Type (Go, No-Go), Stimulus Category (Food, NonFood), BMI and EAT-26 scores as a predictors, and Participant, nested in Recruitment Group, as a random effect. Following the same stepwise procedure used in the analyses of RTs, Stimulus Category resulted not significantly improving the model fit [*p* = 0.37], and was removed from the model. All other predictors significantly improved the model fit [*ps* < 0.005].

Results

bCFS and NoCFS tasks

In order to assess if suppression had been successful, the raw reaction times of the two tasks were compared. As expected, RTs were significantly shorter during the bCFS task [$M = 2.47$ s, $SD = 1.38$] than during the NoCFS task [$M = 1.18$ s, $SD = 0.26$, $t(22799) = 128.3$, $p < 0.001$]. The raw RTs are shown in Figure 8.

Figure 8
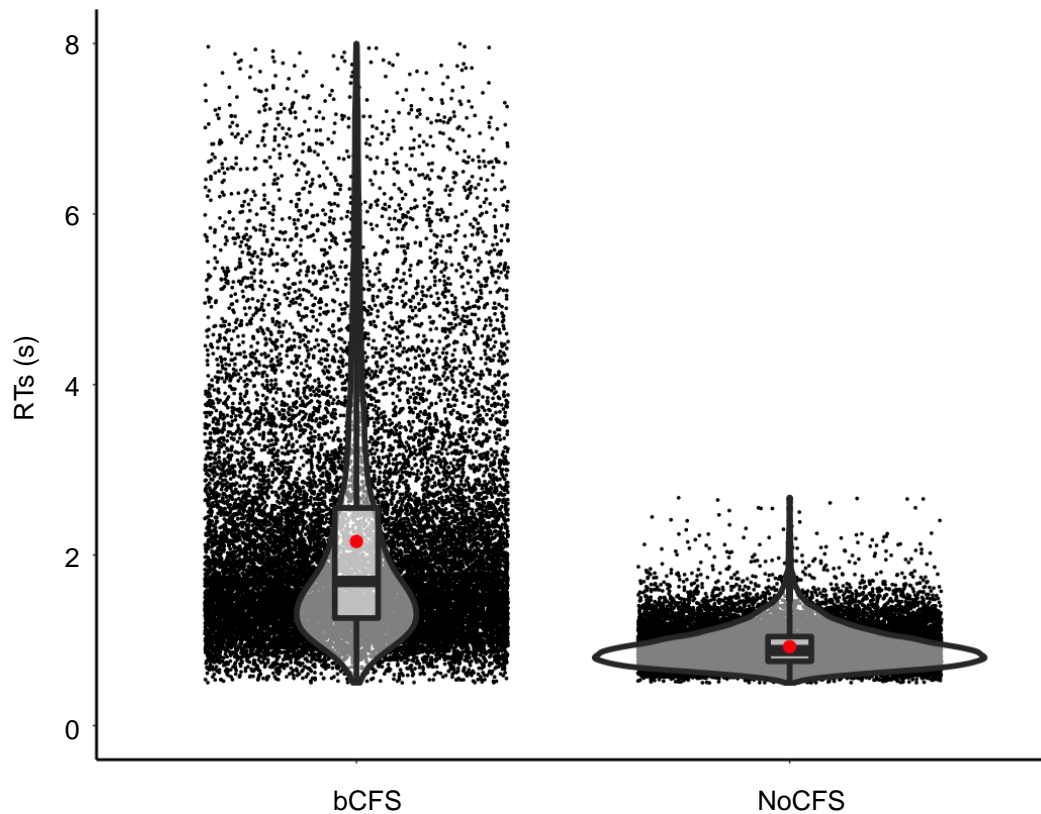
Raw reaction times in the bCFS (left) and NoCFS (right) tasks. The boxplot shows the quartiles of the distribution, the red dot the mean.

Participants' RTs were predicted by their BMI and EAT-26 score, which had different effects depending on stimulus category and across the two tasks, as shown by a four-way interaction between all the predicting factors [$F(1, 30536.7) = 4.4$, $p = 0.03$; find the full model in Supplementary table

2]. To explore whether the interaction between Stimulus Category, BMI and EAT-26 score was significant in both tasks, we run a post-hoc. We found that this three-way interaction was only significant for RTs in the bCFS task (t (30540) = 2.876, $p < 0.01$) and not in the NoCFS task (t (30540) = 0.523, $p = 0.60$). Furthermore, we found that in the bCFS task, the interaction between BMI and EAT-26 score was only significant for food trials (t (65) = 2.292, $p = 0.025$), and was only trending towards significance in the non-food trials (t (65) = 1.691, $p = 0.096$).

This result (Figure 9) suggests that 1) BMI, EAT-26 score and Stimulus Category only impacted responses in the CFS task involving stimulus suppression 2) a high likelihood of eating disorder was associated with shorter suppression in participants with a higher BMI, and with longer suppression in participants with low BMI, and 3) this pattern was more pronounced for food vs. non-food images.

Figure 9
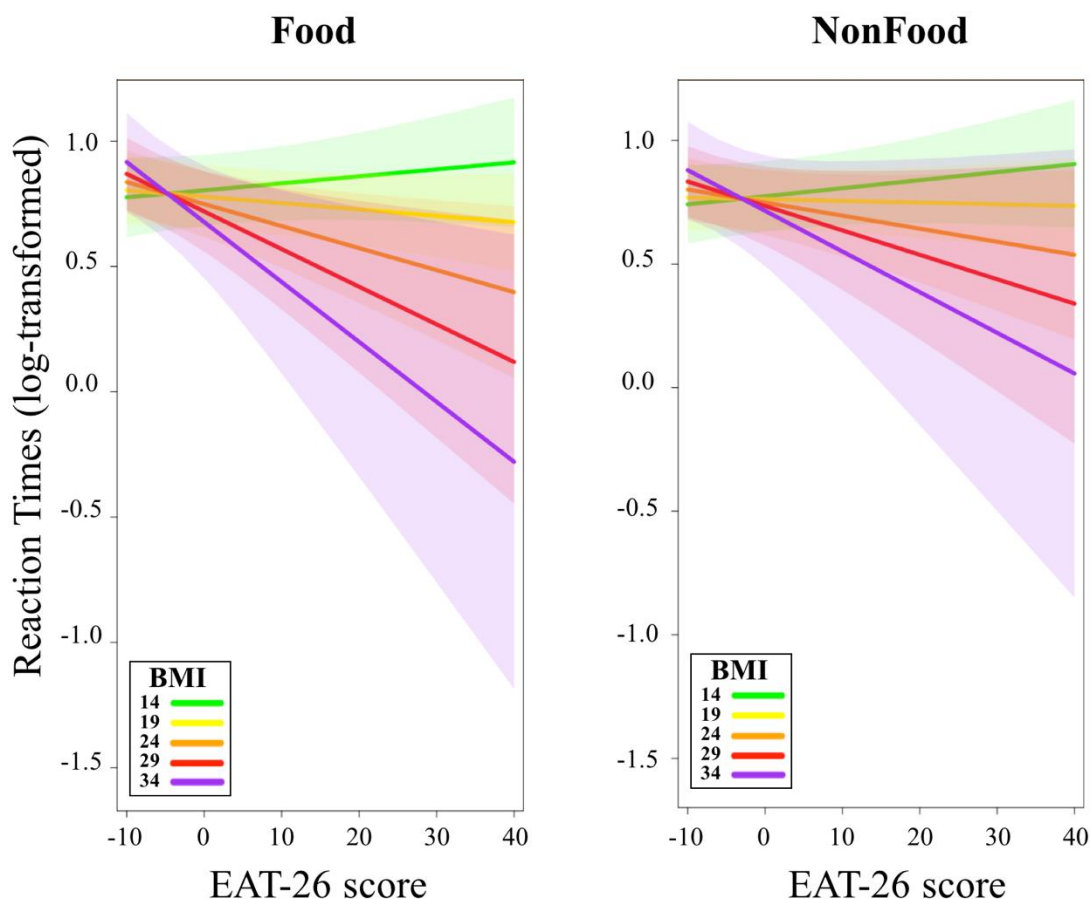
Significant three-way interaction between Stimulus Category, BMI and EAT-26 scores on the log-transformed RTs of the bCFS task. On the left, the influence of BMI and EAT-26 when the stimulus is a food image; on the right when the stimulus is a non-food image. BMI was used as a continuous predictor and is plotted in five groups for better visualization.

Go/No-Go task

Participants' BMI and EAT-26 scores also influenced RTs in the Go/No-Go task. A significant three-way interaction between stimulus type, BMI and EAT-26 scores was found ($F_{(1, 7710.7)} = 19.54$, $p < 0.001$; the complete results of this model are reported in Supplementary table 3). Post-hocs showed that the interaction between BMI and EAT-26 score was only significant in trials with food as a Go cue ($t_{(69)} = 2.49$, $p = 0.01$), where BMI was inversely related to RTs among participants with severe self-reported eating disorders. The same pattern did not reach significance in trials with non-foods as Go cues ($t_{(69)} = 1.1$, $p = 0.27$) (Figure 10).

Figure 10
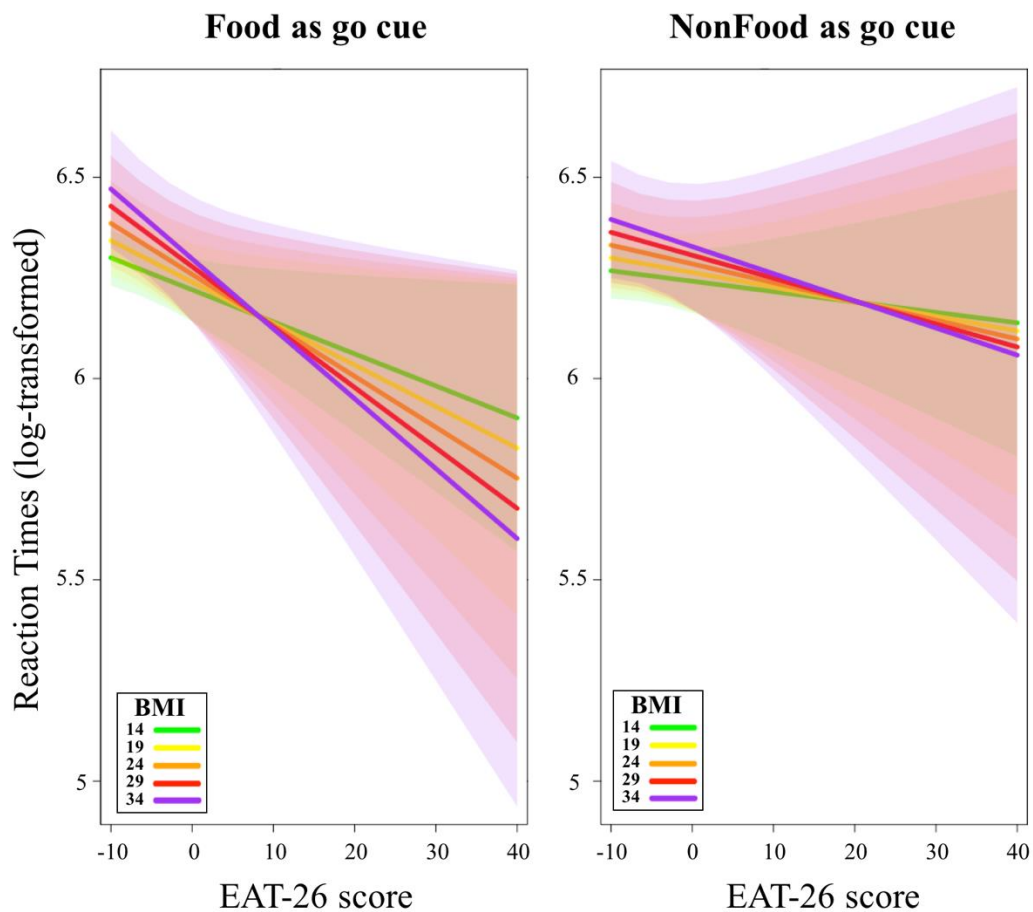
Influence of the BMI and the EAT-26 score on the log-transformed RTs in Go trials of the Go/No-Go task, when the Go cue is a food image (left) and when it is a non-food image (right).

In the analysis on accuracy, a significant three-way interaction between Trial Type, BMI and EAT-26 scores was found (F (1, 11291.2) = 16.512, p < 0.001. Complete results in Supplementary table 4). Post-hocs showed that the interaction between BMI and EAT-26 score was only significant in No-Go trials (t (296) = 3.076, p = 0.002), where BMI was inversely related to accuracy among participants with severe self-reported eating disorders. The interaction between BMI and EAT-26 score was not significant in Go trials (t (98) = 1.479, p = 0.142), see Figure 11.

Figure 11
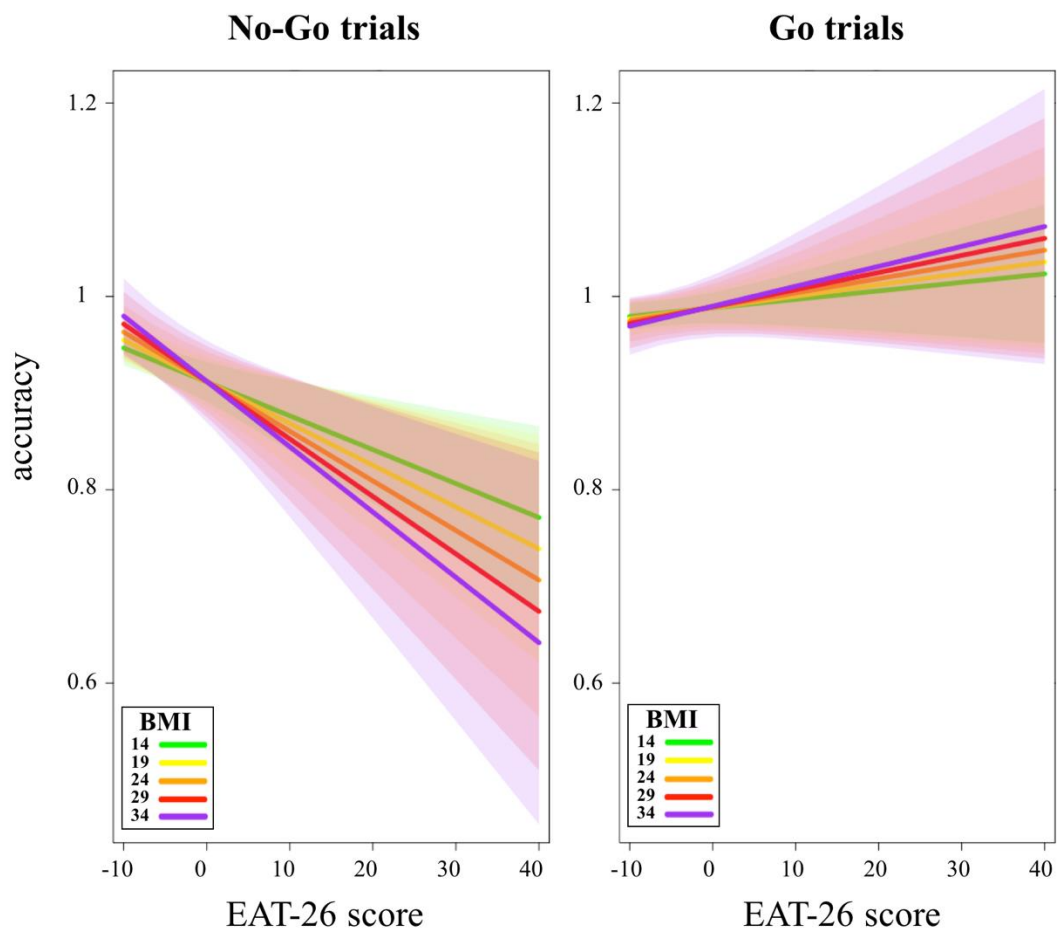
Influence of the BMI and the EAT-26 score on accuracy in the Go/No-Go task, in No-Go trials (left) and Go trials (right).

Discussion

Eating disorders and obesity have both been linked to attentional biases for food stimuli, but have rarely been investigated together in the same studies. However, studying biases for disorders-relevant cues can give us valuable information about the mechanisms at play and the possible underlying neural mechanisms.

In this study, we investigated the influence of eating habits and BMI on the response bias for food images, by measuring the speed of awareness and response inhibition towards food and non-food cues. To the best of our knowledge, this is the first time that subliminal processing of food and non-food images has been investigated using a bCFS paradigm. The main finding was that EAT-26 scores and BMI interacted with each other: among participants with a higher likelihood of having an eating disorder, a lower BMI predicted longer suppression times for foods, while a higher BMI predicted shorter suppression times for foods. While we cannot rule out that different processing speed for foods and non-foods might be influenced by the stimuli low-level features, this finding suggests that eating habits and BMI influence the processing of food images at a preconscious level. It is also in line with the idea that the EAT-26 score is a measure of how much emotions, desires and expectations are invested in food-related thoughts in participants' daily lives. Even though obesity is not an eating disorder, it leads to some of the cognitive biases also found in ED, such as altered attention and inhibition. The present study clearly indicates that preconscious attention allocation might also be affected in people with obesity and ED.

A bias towards food images was also shown in the results of the Go/No-Go task, where the participants' speed in responding to food images was significantly influenced by their EAT-26 scores and BMI, following a pattern similar to the one observed in the bCFS task. Faster reaction times in the Go/No-Go task have been linked to attentional biases (Murphy et al., 1999), emotional preference (Schulz et al., 2007) and salience of the stimuli (Meule et al., 2014). These results fit well with this hypothesis and confirm that people with a high BMI and more severe eating disorder symptoms have a bias towards food already at a preconscious, automatic level of visual processing. Moreover, inhibition, measured as accuracy on the No-Go trials of the Go/No-Go task, was significantly by participants' BMI and EAT-26 scores, regardless of the stimulus type. This result seems to support findings that both ED symptoms and BMI can affect inhibitory control (Bartholdy et al., 2017; Claes et al., 2006; Kulendran et al., 2017).

Taken together, our results suggest that altered attention, due to a different affective salience of food stimuli, is influencing the participants' performance in both tasks. Based on these convergent

results we can speculate that the activity of frontal areas, which are involved in response inhibition and reward learning, as well as in the representation of the affective values of reinforces, is altered by clinically unhealthy eating habits and high BMI. Frontal areas, such as the left orbitofrontal cortex (OFC), have also been found to be involved in the length of suppression times in the bCFS, and the activation of higher-level cortical areas during unconscious processing of complex visual information predicts how fast this information gains access to conscious perception (Schmack et al., 2016). The activity of the OFC has also been associated with the interaction of emotional stimulus processing and response suppression in the Go/No-Go paradigm (Goldstein et al., 2007). Alterations of activity in the OFC has also been linked to high BMI (Killgore & Yurgelun-Todd, 2005), while other frontal regions, such as the prefrontal cortex, have often been linked to obesity and ED (Alonso-Alonso & Pascual-Leone, 2007). Based on this, it may be speculated that the attentional biases found here could be due to altered physiology in frontal neural networks.

Conclusions

Participants with an eating disorder and a high BMI display an attentional bias towards food from a subliminal stage of stimulus processing. These altered attentional mechanisms may contribute to the development and the maintenance of symptoms. Clinical research can profit from using behavioral paradigms to investigate attentional and subliminal processing biases as adequate and useful measures of cognitive changes linked to extreme eating habits and high BMI. To better understand these cognitive changes, ED patients should be investigated together with overweight participants, using participants' eating habits and BMI as continuous predictors of cognitive changes.

Supplementary materials

Supplementary table 1

Group	N	Age	BMI	EAT-26
Healthy controls	25	28.1 (9.6)	22.9 (6.0)	8.4 (7.4)
ED patients	23	31.0 (11.8)	22.7 (8.1)	21.8 (18.3)
Overweight/obese	22	47.0 (8.9)	31.4 (4.2)	5.9 (6.2)

Demographics and clinical data of the bCFS experimental sample after data cleaning.

Supplementary table 2

	Sum Sq	Mean Sq	F (df)	p value	
Task	1804.33	1804.33	$F (1, 30578.7) = 15692.4$	< 0.001	***
Stimulus Category	0.06	0.06	$F (1, 83.8) = 0.5$	0.462	
BMI	0.13	0.13	$F (1, 63.9) = 1.2$	0.286	
EAT-26	0.27	0.27	$F (1, 62.8) = 2.3$	0.131	
Task * Stimulus Category	0.11	0.11	$F (1, 30578.9) = 1$	0.322	
Task * BMI	2.11	2.11	$F (1, 30536.6) = 18.3$	< 0.001	***
Stimulus Category * BMI	0.21	0.21	$F (1, 30536.9) = 1.8$	0.181	
Task * EAT-26	0.85	0.85	$F (1, 30537.1) = 7.4$	0.007	**
Stimulus Category * EAT-26	0.55	0.55	$F (1, 30538) = 4.8$	0.029	*
BMI * EAT-26	0.39	0.39	$F (1, 63.3) = 3.4$	0.069	.
Task * Stimulus Category * BMI	0.37	0.37	$F (1, 30536.5) = 3.2$	0.071	.
Task * Stimulus Category * EAT-26	1.46	1.46	$F (1, 30537) = 12.7$	< 0.001	***
Task * BMI * EAT-26	0.35	0.35	$F (1, 30536.9) = 3$	0.082	.
Stimulus Category * BMI * EAT-26	0.18	0.18	$F (1, 30537.2) = 1.6$	0.208	
Task * Stimulus Category * BMI * EAT-26	0.51	0.51	$F (1, 30536.7) = 4.4$	0.035	*

Results of the best fitting model explaining log-transformed RTs of the bCFS and NoCFS

tasks, with Stimulus category, Task, EAT-26 score and BMI as factors.

Supplementary table 3

	Sum Sq	Mean Sq	F (df)	p value	
Stimulus Category	0.04505	0.04505	F (1, 142.7) = 1.4421	0.232	
BMI	0.11663	0.11663	F (1, 54.2) = 3.733	0.059	.
EAT-26	0.00516	0.00516	F (1, 66.9) = 0.165	0.686	
Stimulus Category * BMI	0.01558	0.01558	F (1, 7713.2) = 0.4988	0.480	
Stimulus Category * EAT-26	0.5126	0.5126	F (1, 7711.9) = 16.4075	< 0.001	***
BMI * EAT-26	0.10321	0.10321	F (1, 65.4) = 3.3036	0.074	.
Stimulus Category * BMI * EAT-26	0.61036	0.61036	F (1, 7710.7) = 19.5364	< 0.001	***

Log-transformed RTs of the go trials in the Go/No-Go task predicted by the stimulus category, BMI and EAT-26 score.

Supplementary table 4

	Sum Sq	Mean Sq	F (df)	p value	
Trial Type	8.7	8.7	F (1, 9517.9) = 270.386	< 0.001	***
BMI	0.0	0.0	F (1, 80.6) = 0.016	0.899	
EAT-26	0.2	0.2	F (1, 80.6) = 4.822	0.031	*
Trial Type * BMI	0.0	0.0	F (1, 11298.8) = 0.01	0.919	
Trial Type * EAT-26	0.4	0.4	F (1, 11291.9) = 11.096	< 0.001	***
BMI * EAT-26	0.1	0.1	F (1, 80.6) = 1.841	0.179	
Trial Type * BMI * EAT-26	0.5	0.5	F (1, 11291.2) = 16.512	< 0.001	***

Number of false alarms in the Go/No-Go task predicted by stimulus category, BMI and EAT-26 score.

Obesity, subliminal perception and inhibition:

neuromodulation of the prefrontal cortex

Abstract

Obesity has been linked to low performance in the attention and impulsivity domains. Obese individuals, compared with healthy-weight participants, exhibit increased attentional bias to food cues. Notably, the prefrontal cortex plays a central role in cognitive control over food choices and is less active in obese individuals. By using direct current stimulation (tDCS), the study investigated the role of the right dorsolateral prefrontal cortex (dlPCF) in subliminal visual processing of, and in the inhibition of responses to food pictures, in individuals with healthy vs. obese body mass index (BMI). Obese individuals were expected to show a subliminal food bias and reduced inhibition. Moreover, modulation of the dlPFC by tDCS was expected to impact on this pattern. In a within-subject design, fifty-three participants with a BMI ranging from 17 to 34 received in separate sessions, anodal, cathodal, or sham tDCS over the right dlPCF. Subliminal processing was measured with a breaking Continuous Flash Suppression task (bCFS), and inhibition was assessed with a Go/No-Go task. In both tasks, food-related and unrelated pictures were presented. Data were analyzed using Linear Mixed Models (LMMs).

In the bCFS task, a higher BMI led to longer detection times for both food and nonfood pictures [$p = 0.02$]. In the Go/No-Go task, higher BMI led to slower responses in food Go trials [$p = 0.02$]. Anodal stimulation resulted in shorter detection times in the bCFS task in all participants [$p < 0.001$], but especially in those with higher BMI [$p = 0.01$]. Cathodal stimulation did not interact with participants' BMI in neither the bCFS nor the Go/No-go tasks. The results indicates that an attentional bias for food is not present at a subliminal level of processing, and that it might be present only at a late stage of attentive processing. The study also revealed that obesity might be associated with a generally increased threshold of perceptual awareness. This association has never been reported before. Moreover, these findings indicate that anodal stimulation improves attentional performance of all participants, especially in those with higher BMIs, and particularly at a subliminal level. This is in accordance with the evidence of reduced dlPFC activity in obesity and, more generally, in eating disorders.

Introduction

Over a third of the world's population today is either obese or overweight (Hruby & Hu, 2015). According to the World Health Organization, the worldwide prevalence of obesity has nearly tripled in the last forty years (World Health Organization, 2018). Therefore, it has become of paramount importance to understand mechanisms underlying overeating behaviors. Such an attempt has been endorsed in studies exploring whether altered cognitive functions and brain mechanisms may promote obesity.

In particular, obesity has been linked to low performance in the attention and impulsivity domains (Cook et al., 2017), and obese individuals, compared with healthy-weight participants, have been reported to exhibit increased attentional bias to food cues (Hendrikse et al., 2015). For instance, obese individuals show longer fixation times for foods than non-foods (Castellanos et al., 2009), response facilitation towards targets replacing food probes (Kemps et al., 2016), impaired inhibition of responses to food pictures (Bartholdy et al., 2016a; Kulendran et al., 2017, but see Loeber et al., 2012), and altered implicit attitudes towards food (Craeynest et al., 2005; Roefs & Jansen, 2002). This attentional bias towards food seems to emerge already at an automatic, implicit phase of stimulus processing (Cserjesi et al., 2016; Nijs, Franken, et al., 2010), and seems to have a strong influence on appetitive behavior (Finlayson et al., 2008; Forman et al., 2018; Takada et al., 2018).

The observation that an attentional bias towards food occurs in obese individuals supports the proposed view that obesity is characterized by a disequilibrium between cognitive control and reward sensitivity. Specifically, poor inhibitory control in obesity may favor attention towards food and promote, in turn, hedonic eating (Ziauddeen et al., 2015). Cognitive control is implemented by several regions, among which the dorsolateral prefrontal cortex (dlPFC) plays a key role (Alonso-Alonso et al., 2015). This region has been also implicated in the control over food choices and the top-down cognitive influence on satiation (Gluck et al., 2017). Interestingly, lateral sectors of the prefrontal cortex are active when participants think about the benefits of not eating a food or are asked to voluntarily suppress hunger (Alonso-Alonso et al., 2015). In line with this, obese and overweight individuals show decreased activity of this region (Dong et al., 2015; Gluck et al., 2017). In many studies, transcranial direct current stimulation (tDCS) has been employed to investigate the effect of PFC modulation on obesity-related behaviors, such as food craving and overeating (Fregni et al., 2008; Gluck et al., 2015; Heinitz et al., 2017; Kekic et al., 2014; Ljubisavljevic et al., 2016; Ray et al., 2017; Sauvaget et al., 2015). The common hypothesis is that enhancing dlPFC activity can facilitate cognitive control and help inhibit reward-related neural circuits, ultimately decreasing

appetite and food intake (Fregni et al., 2008; Val-Laillet et al., 2015). However, even if tCDS over the prefrontal cortex has been demonstrated to reduce attentional bias towards food (e.g. Fregni et al., 2008), no study has yet addressed this aspect in obese individuals or at a subliminal level of processing.

Therefore, the aim of this study was to investigate the effects of right dlPCF modulation through tDCS on subliminal and inhibitory processing of food stimuli in obesity. To measure subliminal processing, we used a breaking Continuous Flash Suppression (bCFS) task, a technique that allows to temporarily suppress stimuli from visual awareness, and in which subjective awareness is signaled through button-press (Tsuchiya & Koch, 2005). As shown by previous research, bCFS can be used to investigate subliminal processing of salient stimuli in several clinical populations (Jusyte et al., 2015; Schmack et al., 2016; Sylvers et al., 2011; Z. Yang et al., 2011). Moreover, to measure inhibitory mechanisms, we administered a Go/No-go task. The use of the bCFS and Go/No-Go tasks, combined, allowed us to investigate the effect of tDCS in different stages of food stimuli processing, from subliminal, to explicit. Underweight, healthy, and obese participants completed a bCFS task during sham, anodal or cathodal stimulation of the right dlPFC, in a between-subjects design. A Go/No-Go task was completed immediately following these stimulations. Higher BMI was expected to be associated with altered suppression times in the bCFS task and altered performance in the Go/No-Go task, especially for food stimuli. Anodal stimulation was expected to reduce this association, and cathodal stimulation to strengthen it.

Methods

Participants

Fifty-three participants (11 males) took part in the study. They were enrolled based on their BMI, in order to have a distribution of BMIs from underweight to obese. Exclusion criteria were epilepsy, migraines and the presence of metal parts in the upper part of the body, as well as Daltonism and strabismus. Eating disorders (ED) symptoms were investigated through two questionnaires. The Eating Attitudes Test -26 (EAT-26) (Garner et al., 1982) is used to evaluate the risk of anorexia and bulimia nervosa. It inquiries into how often the individual engages in specific behaviors such as worrying about food, dieting, purging etc (for a more detailed description of this scale, see the methods section in chapter 1). The Binge Eating Scale (BES) (Gormally et al., 1982) inquires specifically on problems in controlling the eating behavior, such as eating too much, too quickly, or

unrelatedly to the feeling of hunger. Each item is comprised by different description of an eating behavior, and participants have to choose the one that best represents them (i.e. "*I don't have any problem stopping eating when I feel full*", "*I usually can stop eating when I feel full but occasionally overeat leaving me feeling uncomfortably stuffed*", "*I have a problem stopping eating once I start and usually I feel uncomfortably stuffed after I eat a meal*", or "*Because I have a problem not being able to stop eating when I want, I sometimes have to induce vomiting to relieve my stuffed feeling*"). Due to exclusion of two participants because of technical failure during testing, the final sample included fifty-one participants, out of which 11.3% was underweight, 62.2% normal-weight and 26.2% overweight (demographical and clinical data are presented in Table 2). This study was approved by SISSA's Ethics Committee (4145-II/16).

Table 2

	Mean (SD)	**range**
Age	24.5 (3.7)	19 – 41
Body Mass Index (BMI)	22.9 (3.8)	16.7 – 34.3
Eating Attitudes Test-26(EAT-26)	7.2 (6.7)	0 – 33
Binge Eating Scale (BES)	10.1 (6.0)	0 - 24

Participants' demographic and clinical data.

Procedure and experimental tasks

Participants responded to an online survey including the screening variables, height, weight, the EAT-26 and the BES. Each participant was tested on three separate sessions, which were at least 48 hours apart, to ensure washout of previous stimulation. A Latin square design was used to randomize and counterbalance the order of stimulation across subjects. A consent form was signed on the first session. Participants were instructed not to eat for two hours before coming to the laboratory. Before testing, they reported their hunger level on a 7-point Likert scale. This was done to control for the effect of hunger, which could influence the salience of food stimuli (e.g., Loeber et al., 2013). Participants then completed a training of the bCFS task, after which the experimenter applied the electrodes, and started tDCS. After a 30 seconds ramp-up period, participants completed the bCFS task, followed by the NoCFS task. To comply with safety limits (Woods et al., 2016), the stimulation lasted twenty minutes, and at its end participants completed the Go/No-Go task. Previous literature has reported effects of offline tDCS stimulation (Horvath et al., 2014; Nozari et al., 2014).

tDCS protocol

Anodal, cathodal or sham tDCS was administered with a battery-driven DC stimulator (Eldith, NeuroConn). One of the electrodes, with an area of 25 cm^2, was positioned over the right dlPFC, defined as the location 8 cm frontally and 6 cm laterally of the vertex. The other electrode, with an area of 70 cm^2, was placed on the right upper arm (Figure 12). Previous studies reported the greatest benefit of tDCS stimulation on ED symptoms from stimulation of the PFC with the anode/right cathode/left montage (Val-Laillet et al., 2015). Placing one electrode on the right dlPFC and the other one on the right arm enabled us to limit as much as possible the stimulation to the dlPFC and to distinguish between the effects of anodal and cathodal stimulation (see also Mengotti et al., 2018). During stimulation, the current intensity was of 1.5 mA (current density of 0.06 mA/cm^2) with a ramping up period of 15 s. The stimulation lasted 20 minutes. During the sham session, the montage was the same as during the anodal stimulation, but the current was supplied only during the first 30 s – enough to elicit a tingling-itching sensation. At the end of each session, participants completed a questionnaire about their sensations experienced during the stimulation (Fertonani et al., 2015). A Chi-squared test showed no difference between the three stimulation sessions in the frequency in which participants thought they were receiving the real or the control stimulation, or reported not being able to tell if the stimulation had been real [$\chi^2(6) = 6.38$, $p = 0.38$].

Figure 12
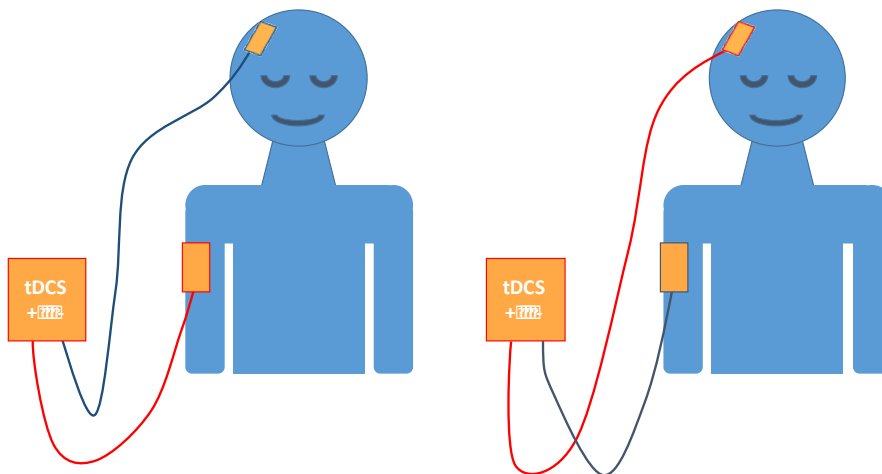

Electrode placement for the cathodal (left) and anodal (right) tDCS stimulation. In the cathodal setup, the cathode (in blue) is placed on the dorsolateral PFC, and the anode on the upper arm; positions are reversed in the anodal montage. The sham stimulation had the same setup as the anodal stimulation, but after the ramping up period of 15 s the current between the electrodes stopped.

Breaking Continuous flash suppression

Unlike the study reported in chapter 1, binocular stimulation was achieved through the use of a mirror stereoscope, which made it possible to show the stimuli in full RGB. Stimuli and distractors were embedded in separate squared frames shown side by side on the screen. By looking through the stereoscope, which was individually calibrated, participants' perception, was that of a single superimposed and perfectly aligned square. The stimulus was displayed in one of the quadrants of a square, while the distractors were displayed over the whole square on the other side. Participants were instructed to indicate via key press on a QWERTY keyboard the position of the stimulus relative to the central fixation cross as fast and as accurately as possible, by pressing with the index fingers 'f' if the stimulus was on the left or 'j' if it was on the right. The order, the position, and the side of the stimuli was randomized so that each participant saw each stimulus once in all four quadrants in a different order. Distractors were shown at 100% contrast and changed at a rate of 10 Hz, while the contrast of the stimuli increased linearly from 0% to 60% over the course of one second, and then stayed at 60% until response. After eight seconds, if no response was given, the trial ended. The bCFS training included 80 trials, while the bCFS task included 160 new trials. Every 30 trials the task paused and participants were allowed to rest. To ensure that the results of the bCFS task are due to processing during suppression, participants performed an equivalent task without suppression (hence NoCFS). This task had the same instructions, number of trials, and stimuli as the bCFS task, but stimuli and distractors were superimposed and shown to both eyes simultaneously. Example trials of the bCFS and NoCFS tasks are shown in Figure 13.

In both the bCFS and the NoCFS tasks, stimuli were displayed on a 17" LCD monitor with a resolution of 1280×1024 pixels and a refresh rate of 60 Hz, positioned 50 cm away from participants. A chin rest was used to minimize head movements. The two squares were of 400*400 pixels each, and stimuli were shown in a 190*190 pixel quadrant. The tasks were programmed in and presented with Python using the Psychopy library (Peirce, 2007) running on a notebook computer with Windows XP.

Figure 13
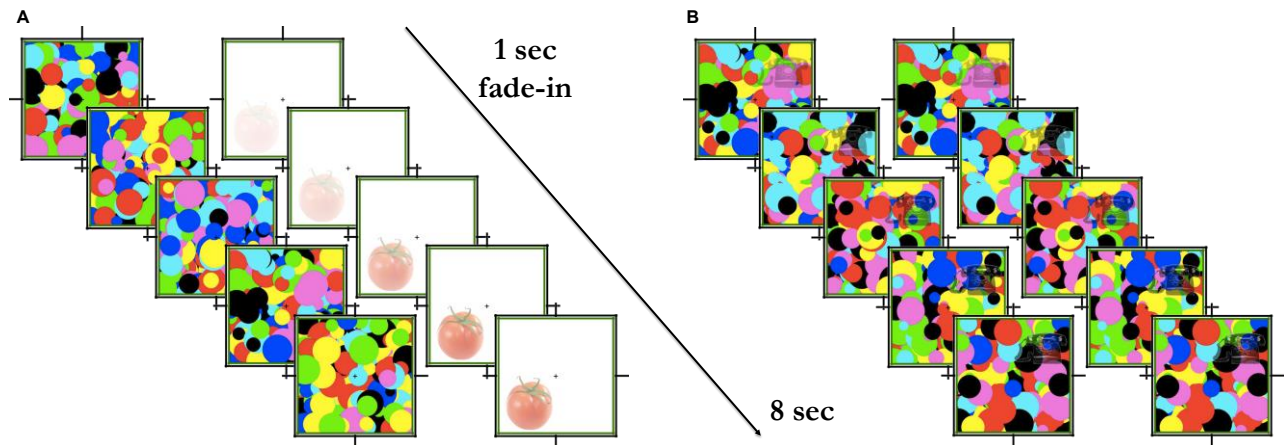
An example trial of the bCFS task (A) and of the NoCFS task (B).

Go/No-Go task

In the Go/No-Go task, the instructions were to respond as quickly as possible to Go stimuli, and to refrain from responding when a No-Go stimulus was presented. In half of the blocks, Go cues consisted of food images and No-Go cues of non-food images, while in the other half the assignment was reversed. There were four blocks of 40 trials each. In each block, 12 out of 40 trials (30%) were No-Go trials. The Go/No-Go task and the stimuli were the same as those used by (Aiello et al., 2017). The order of the blocks was semi-random (ABAB or BABA), and changed across sessions and across participants. An example trial is depicted in Figure 7 in the previous chapter.

Stimuli

In the bCFS and NoCFS tasks, stimuli consisted of 20 images of food and 20 images of non-food items (e.g. animals, man-made objects etc.), selected from (Foroni et al., 2013). Contrary to the study reported in Chapter 1, the use of a stereoscope to achieve binocular rivalry allowed us to present the images in full RGB. Moreover, in this study food and non-food items were matched for brightness [$p = 0.82$] and spatial frequency [$p = 0.09$], since low-level visual features can influence suppression times (Gayet et al., 2014; Gray et al., 2013; E. Yang & Blake, 2012). Food and non-food items also did not differ in valence, familiarity, typicality or arousal [$ps > 0.15$]. The distractor images consisted of a set of 100 pictures with colorful oval shapes of different sizes creating random patterns.

Analyses

Reaction times in the bCFS, NoCFS and RTs and accuracy in the Go/No-Go task were analyzed using linear mixed-effects models (LMMs) using the lmer function (lme4 package) in the software R (version 3.4.3, R Core Team, 2017). In the bCFS and NoCFS tasks, data were cleaned by removing trials with no responses (6.59% across all participants), wrong responses (1.44%), with RTs below 500 ms (0.16%), and with RTs that were more than 2.5 SD from the mean of each subject (0.01%). In addition, six participants were excluded as they failed to respond to two thirds of trials. The final analyses therefore included 44 participants (demographic data of the final sample is reported in Supplementary table 5). RTs of the bCFS, NoCFS and Go/No-Go tasks were log transformed, and fixed factors were mean centered. EAT26 and BES scores were used as covariates to control for eating disorders symptoms. Random intercepts for Participant, Session, Stimulus and Stimulus Location were included in all models. After initial inclusion, these predictors were removed one by one, and the resulting model was compared to the initial more complicated one by using the anova function (lmerTest package, Kuznetsova et al., 2017) and the AIC criterion − a reduction of which suggests better model fit (Bolker et al., 2009). When the AIC of two models did not differ significantly, the model with less factors was chosen. In addition, once non-significant factors had been removed, non-significant high-level interactions were pruned. All post-hoc interactions that included continuous factors were analyzed according to (Aiken & West, 1991).

The final model investigating the effect of stimulation on bCFS and NoCFS included Task (bCFS, NoCFS), Stimulation (Anodal, Cathodal and Sham) and BMI as factors. In the analyses of the Go/No-Go task, the final model investigating the effect of stimulation on RTs included Stimulus Category (Food, Non-Food) and BMI as factors; the model on accuracy included Trial Type (Go, NoGo) and Stimulation as factors. All comparisons between initial and final models are reported in Supplementary table 6.

Results

To ensure that eventual RT differences are not caused by learning effects, the RTs of the three training sessions were compared. No difference between RTs in the training sessions emerged [$F_{(2)}$ = 0.40, p = 0.67]. Moreover, no significant difference of hunger was found between sessions [$F_{(2)}$ = 0.58, p = 0.56].

bCFS and NoCFS tasks

Results showed a main effect of Task [F (1, 40344) = 43764, $p < 0.001$], indicating longer RTs in bCFS compared to NoCFS, confirming that suppression did occur during the bCFS task (for an overview of RTs during bCFS and NoCFS tasks, see Figure 14). We also found a main effect of Stimulation [F (2, 40343) = 34, $p < 0.001$], reflecting faster reaction times during anodal stimulation compared to sham [t = 8.23, $p < 0.001$] and to cathodal stimulation [t = 4.38, $p < 0.001$], and a reduction of RTs in cathodal compared to sham stimulation [t = 3.83, $p = 0.001$].

Figure 14
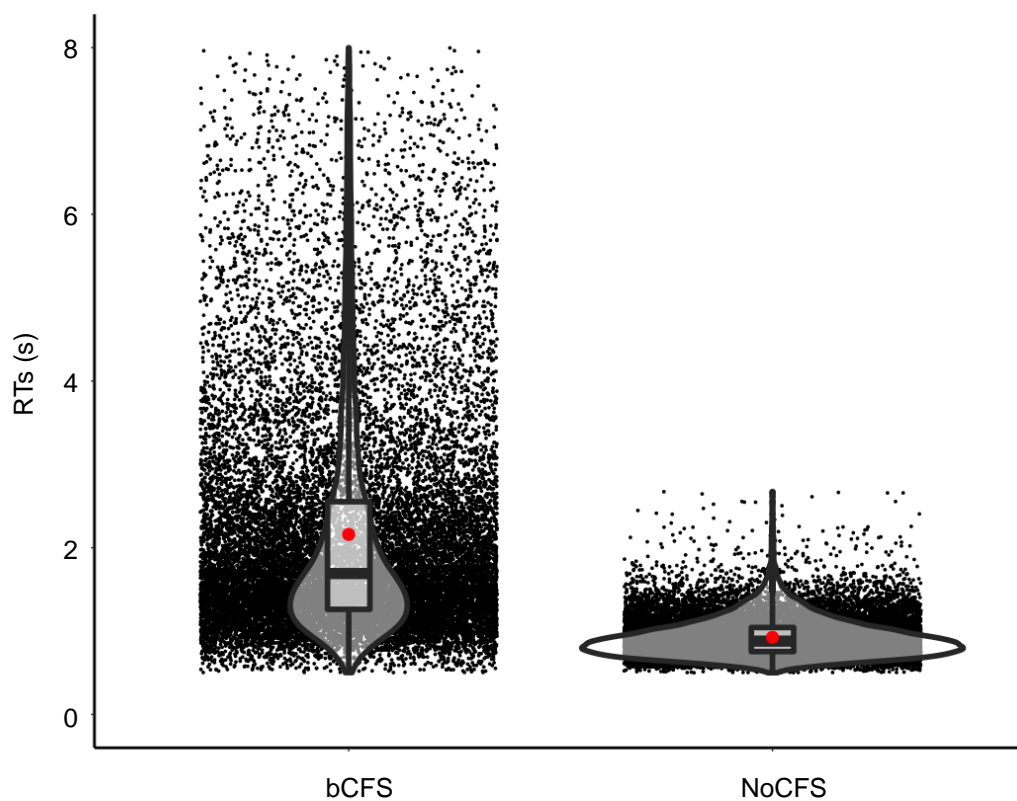
Reaction times in the bCFS task (left) and NoCFS task (right). The boxplot shows the quartiles of the distribution, the red dot the mean.

In addition, a significant Task x Stimulation interaction was found [F (2, 40343) = 9, $p < 0.001$]. Post-hoc showed faster RTs in the bCFS task, during both the anodal [$t = 8.49, p < 0.001$] and the cathodal [$t = 4.96, p < 0.001$] stimulation, with a stronger effect of the anodal compared to the cathodal stimulation [$t = 3.54, p < 0.001$]. Conversely, in the NoCFS task only the anodal stimulation caused significant shorter RTs compared both to the sham [$t = 3.08, p = 0.002$] and the cathodal

stimulation [$t = 2.67$, $p = 0.008$], and RTs during cathodal stimulation did not significantly differ from sham [$t = 0.20$, $p = 0.67$].

A significant Task x BMI interaction was also observed [$F (1, 40344) = 363$, $p < 0.001$]. Post-hoc analyses revealed that higher BMI led to slower RTs in the bCFS task [$p = 0.02$] but not in the NoCFS task [$p = 0.91$]. Moreover, although a significant difference between bCFS and NoCFS was present in both low and high BMIs, it was higher in high BMIs [low BMIs $t = 134.67$, $p < 0.001$; high BMIs $t = 161.45$, $p < 0.001$, see Figure 15 Panel A]. Interestingly, we found a significant Stimulation x BMI interaction [$F (2, 40347) = 14$, $p < 0.001$]. Post-hoc tests showed that BMI's effect was stronger during anodal stimulation than during either sham or cathodal stimulations [$ps > 0.001$]. Exploring this effect, we found that anodal stimulation significantly shortened RTs for both low BMIs and high BMIs compared to sham stimulation, but this effect was greater in high BMIs [low BMIs $t = 2.97$, $p = 0.003$; high BMIs $t = 8.47$, $p < 0.001$]. See Figure 15 Panel B and Supplementary table 7.

Figure 15
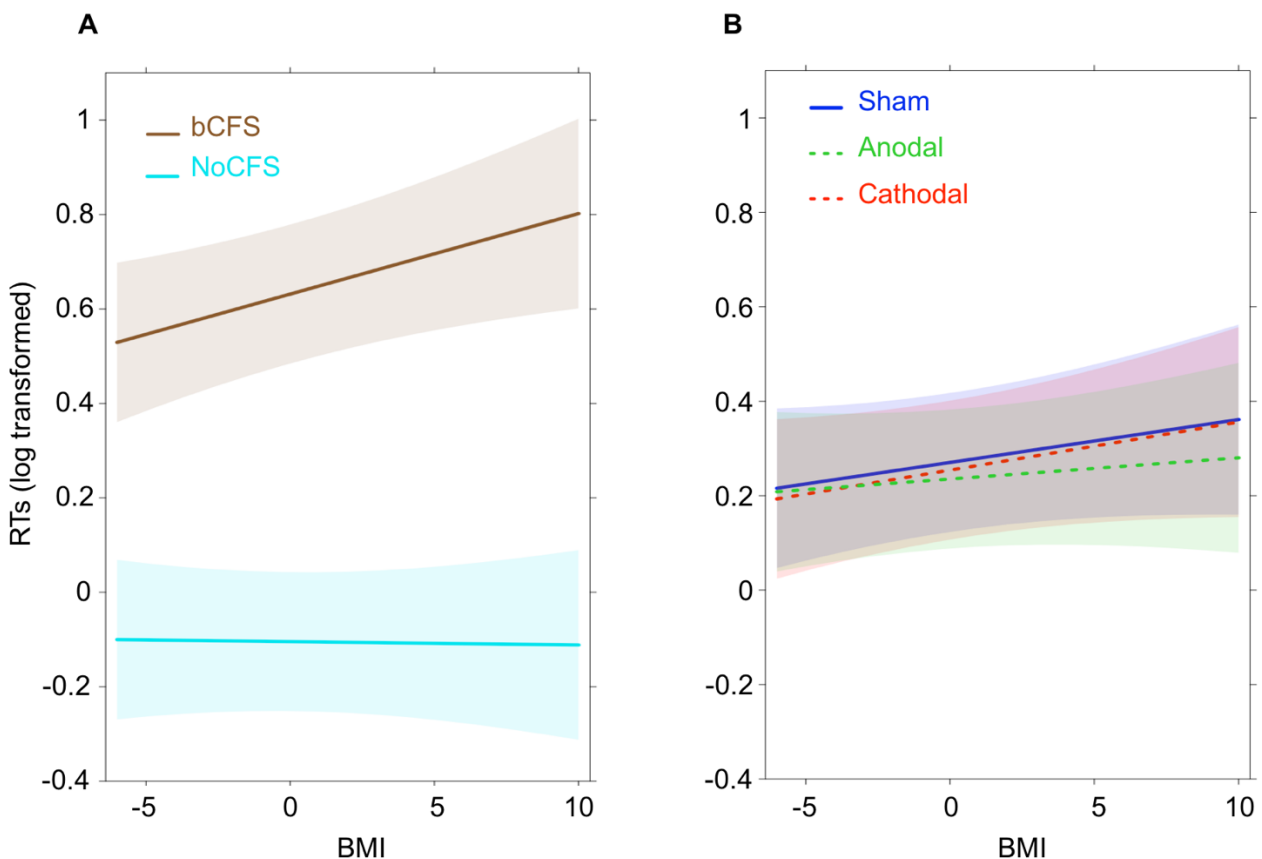
Fit lines of the model addressing the effect of the stimulation on RTs of the bCFS and NoCFS tasks. A) Task by BMI effect. A higher BMI significantly predicted longer suppression times in the bCFS task, but not in the NoCFS task. B) Stimulation by BMI effect. Anodal stimulation shortened RTs both in high and low BMIs, with a greater effect on high BMIs. Cathodal stimulation does not differ from Sham stimulation.

Go/No-Go

In the analysis of the RTs of Go trials, we observed a main effect of BMI [F (1, 49) = 4.2, p = 0.046], reflecting a correlation between higher BMI and slower RTs, and a significant interaction between Stimulus Category and BMI [F (1, 16431.7) = 10.5, p = 0.001] (Supplementary table 8). Participants' BMI significantly affected their reaction times to foods [p = 0.02] but not to non-foods [p = 0.09]. In particular, the difference between foods and non-foods was significant for low BMIs [p = 0.045] but not for high BMIs [p = 0.88]. See Figure 16.

In the analysis on accuracy, we found a significant effect of Trial Type [F (1, 9393.9) = 649.06, $p < 0.001$] meaning higher accuracy for Go trial compared to NoGo trials. No other effect reached the significance level (Supplementary table 9).

Figure 16
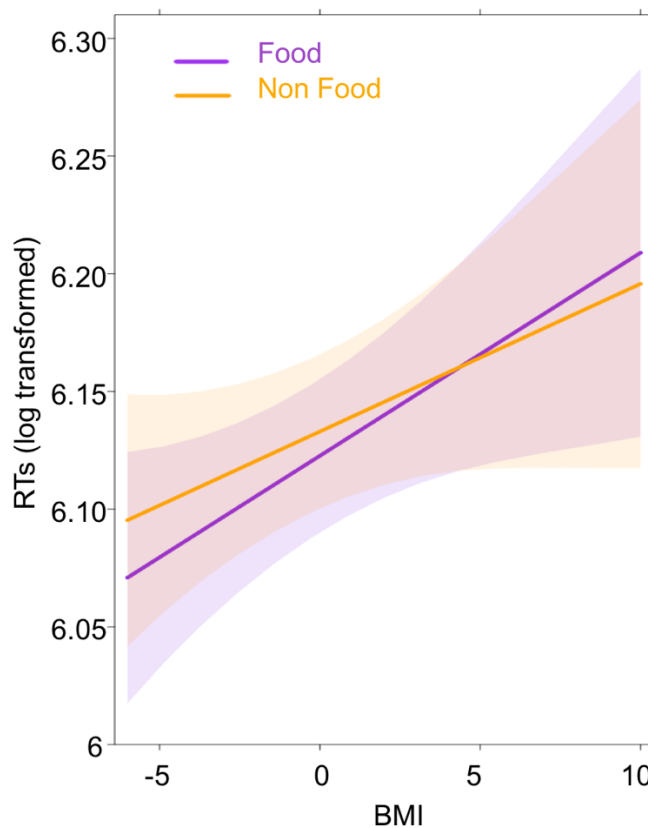
Fit lines of the model on the effect of anodal stimulation on the Go trials of the Go/No-Go task. A higher BMI predicts slower RTs on food trials, but not in non-food trials.

Discussion

This study investigated the alteration of subliminal perception and inhibitory processes in obesity, and their susceptibility to modulation of the right dlPFC through tDCS. Longer suppression times were found in the bCFS task in individuals with high BMI. Notably, we also found an influence of BMI on suppression times in the study reported in Chapter 1 (see Supplementary table 2). This result is in line with the hypothesis that an attentional deficit characterizes obese individuals (Cook et al., 2017; Prickett et al., 2015). Further, it extends this evidence by showing, for the first time, that this impairment may also affect subliminal perception. However, the exact identification of mechanisms involved is yet to be obtained, and future studies are required to investigate them further. Interestingly, using a different methodology such as visual masking, a higher threshold of perceptual awareness has been reported in multiple sclerosis and linked to white matter damage and altered connectivity between distant cortical areas (Reuter et al., 2007, 2009). Numerous studies have reported white matter alterations in obese individuals, especially in the corpus callosum and fornix (se for instance Kullmann et al., 2015; Xu et al., 2013).

It is important to note that, against our expectations, we did not observe a bias for food stimuli at the subliminal level. Indeed, in the study reported in chapter 1, we observed faster awareness of food stimuli in obese individuals with higher self-reported eating-disorder symptoms.

The lack of a difference between processing of foods and non-foods in the current experiment could be ascribed to different motivations. First, it is possible that a difference in the experimental stimuli has brought on this result. The stimuli used in this study differed from the ones used in the study in chapter 1, as the use of a stereoscope in this study allowed us to used full RGB pictures. Pictures in study 1 were chosen based on their recognisability from shape only. Moreover, pictures in study 1 were not matched for spacial frequency, which has been shown to influence suppression times (Gray et al., 2013). We cannot therefore rule out that the difference in the processing of foods and non-foods in study 1 might be due to low-level features. Second, another possibility could be that foods and non-foods are processed differently at a subliminal level only in a clinical sample. Nijs & Franken (2012) have indeed proposed that enhanced attentional bias for food may only be present in obese individuals showing an eating disorder. While in the study reported in chapter 1 we enrolled ED patients and frankly obese participants, the sample of this study is not comprised of clinical patients. It is therefore possible that in a non clinical population, a bias for food stimuli does not occur at the subliminal level, and emerges only at a later stage, or that it may appear only when the task requires explicit categorization of foods vs. non-foods. This possibility is corroborated by the fact

that the current literature on food bias in obesity has mostly been based on paradigms in which food was consciously perceived by participants (Kemps et al., 2014; Nijs & Franken, 2012). Interestingly, in the present study, a higher BMI predicted longer RTs on food Go trials in the Go/No-go task, which seems to favor this argument. Finally, another factor that might affect these results is hunger. Castellanos et al. (2009) only reported differences in attentional bias for foods between obese and normal-weight individuals after satiation and our participants fasted for two hours before the testing. In the study reported in chapter 1, no instruction had been given to participants about eating before the task, as patients were tested during their stay at a rehabilitation center. However, the presence of a food effect in the Go/No-Go task in the current study excludes the possibility that a lack of subliminal bias for foods can be ascribed to participants' satiation, as the tasks were performed during the same session. All in all, these results suggest that while a higher BMI predicts a bias towards food only at late attentive stages, or when categorizing stimuli as foods or non-foods, it does not predict a food bias at a subliminal level, except from individuals with eating disorders.

As for the effects of the tDCS stimulation in the bCFS and NoCFS tasks, we found that anodal stimulation significantly reduced RTs in all participants compared to sham and cathodal stimulation. This result accords well with studies showing benefits of anodal stimulation of the PFC on visual attention (Leite et al., 2013; Vierheilig et al., 2016) and cognitive performance (Coffman et al., 2014; Hussey et al., 2015). Moreover, while anodal stimulation significantly reduced RTs in both tasks, we found that it had a stronger effect on the bCFS task, i.e. at a subliminal level. Interestingly, PFC lesions have shown to affect the threshold for conscious access and PFC has been suggested to contribute to conscious perception of masked stimuli (Del Cul et al., 2009). Finally, the greater effect of stimulation on participants with a high BMI is consistent with the fact that these individuals have a decreased activity of this area (Dong et al., 2015; Gluck et al., 2017), and might therefore be showing greater effect of the anodal stimulation boost.

When considering the effect of the cathodal modulation on the bCFS and NoCFS tasks, contrary to our predictions, no inhibitory effect was found. Cathodal inhibition effects are usually found on motor tasks, but they are rarely observed on cognitive tasks (Fertonani et al., 2010; Fregni et al., 2005; Kraft et al., 2010), which has been attributed to cognition relying on bilateral, rich brain networks, that can compensate contralaterally (Jacobson et al., 2012). In addition, cathodal stimulation unexpectedly shortened RTs in the bCFS task. Other studies have shown similar effects of anodal and cathodal stimulation (see for instance Brückner & Kammer, 2017). Nonetheless, cathodal stimulation's effect did not interact with participants' BMI, suggesting that it does not have a specific effect on obesity-related cognitions and behaviors.

In the Go/No-Go task, we did not find any significant effects of stimulation. The lack of a strong influence of stimulation on Go/No-Go might be due to the fact that participants did not perform this task during the stimulation, but at its end. Indeed, even if tDCS effects can be effective after the stimulation has ended (Horvath et al., 2014; Nozari et al., 2014), many studies report no effect of offline tDCS stimulation on Go/No-Go performance (Conley et al., 2016; Cosmo et al., 2015; Filmer et al., 2017; McLaughlin et al., 2017; Sallard et al., 2018, but see Boggio et al., 2007). More studies are needed to address this issue. Moreover, we did not observe that BMI was associated to a higher rate of errors in this task. Admittedly, not all studies are consistent with the idea that BMI *per se* is associated with increased inhibitory deficits (Aiello et al., 2018; Bartholdy et al., 2016a).

In conclusion, higher BMI leads to longer suppression times in the bCFS task. This effect is not food-specific, and suggests that an elevated threshold for conscious perception may characterize obesity. This topic is open to future investigation, since visual information outside of awareness may influence conscious experience, decision making and goal pursuit behavior (Finlayson et al., 2008; Forman et al., 2018; Takada et al., 2018). Conversely, higher BMI is associated with an attentional food bias at later stage of attentional processing, as observed in the Go/No-Go task, and inhibitory deficits (Bartholdy et al., 2016a; Kulendran et al., 2017; Loeber et al., 2012). Anodal stimulation on the right PFC reduces RTs, probably due to its effects on cognitive control and attention. This effect is particularly strong on the bCFS task, suggesting an influence of anodal stimulation on subliminal processing, and in participants with high BMI.

As early processing of food has been shown to have a role in the unconscious regulation of appetite and food choice (Finlayson et al., 2008; Takada et al., 2018), it is possible to speculate that the reported beneficial effects of anodal tDCS on craving and food intake (Kekic et al., 2014; Val-Laillet et al., 2015) may be modulated by its effects on cognitive control and attention (Gluck et al., 2015; Heinitz et al., 2017), starting at a subliminal level. Future research should investigate how subliminal perception may affect eating choices in obese individuals, and test the effects of anodal modulation on this process.

Acknowledgements

Supplementary materials

Supplementary table 5

	Mean (SD)	**range**
Age	24.2 (3.8)	19 – 41
Body Mass Index (BMI)	23.1 (3.8)	16.7 – 34.3
Eating Attitudes Test-26(EAT-26)	7.4 (8.0)	0 – 33
Binge Eating Scale (BES)	10.4 (6.1)	0 - 24

Demographic data of participants included in the analysis of the bCFS and NoCFS tasks.

Supplementary table 6

RTs of bCFS and NoCFS tasks	initial model AIC (31) = 31008	$\chi^2(16) = 10.31, p = 0.85$
	final model AIC (15) = 30987	
RTs on Go trials of Go/NoGo task	initial model AIC (18) = -9774.6	$\chi^2(10) = 16.47, p = 0.09$
	final model AIC (8) = -9778.1	
Accuracy of Go/NoGo task	initial model AIC (30) = -18617	$\chi^2(20) = 31.92, p = 0.04$
	final model AIC (10) = -18625	

Comparison between initial and final models.

Supplementary table 7

	Sum Sq	**Mean Sq**	**F (df)**	**p value**	
Task	5454	5454	$F(1, 40344) = 43764$	>0.001	***
Stimulation	8.4	4.2	$F(2, 40343) = 34$	>0.001	***
BMI	0.2	0.2	$F(1, 43) = 1$	0.250	
Task * Stimulation	2.2	1.1	$F(2, 40343) = 9$	>0.001	***
Task * BMI	45.3	45.3	$F(1, 40344) = 363$	>0.001	***
Stimulation * BMI	3.5	1.8	$F(2, 40347) = 14$	>0.001	***

Effects of the model on RTs in the bCFS and NoCFS tasks.

Supplementary table 8

	Sum Sq	Mean Sq	F (df)	p value	
Stimulus Category	0.03	0.03	F (1, 136.6) = 1.2323	0.269	
BMI	0.13	0.13	F (1, 49) = 4.1978	0.046	*
Stimulus Category * BMI	0.33	0.33	F (1, 16431.7) = 10.547	0.001	**

Effect of the model on RTs on Go trials in the Go/No-Go task.

Supplementary table 9

	Sum Sq	Mean Sq	F (df)	p value	
Trial Type	17.3	17.3	F (1, 9393.9) = 649.06	>0.001	***
BMI	0.12	0.06	F (2, 22412.1) = 2.28	0.102	
Trial Type * BMI	0.14	0.07	F (2, 23834.1) = 2.67	0.069	.

Effect of the model on accuracy in the Go/No-Go task.

The neural substrates of suppression: a Voxel-Based Morphometry study

Abstract

Food is a salient stimulus and as such it is preferentially attended. From early stages of stimulus processing, obesity and eating disorders influence attention and inhibition towards food. Subliminal processing of food is also altered in individuals with a high BMI and ED symptoms, and a higher BMI has been linked to a higher threshold for visual awareness. In this study we explore the neural correlates of suppression and inhibition of food and non-food stimuli. Fifty-three participants completed a breaking Continuous Flash Suppression (bCFS) task and a Go/No-Go task with food and non-food stimuli. We collected whole-brain structural magnetic resonance images and used voxel-based morphometry to measure grey matter (GM) density. We find that higher GM density in visual (left calcarine and occipital cortex) and reward areas (bilateral caudate nuclei) is associated with longer suppression times in the bCFS task, while higher GM density in control areas is associated to shorter suppression times in the bCFS task (left frontal gyrus) and faster reaction times in the Go/No-Go task (left frontal pole). Higher hypothalamic and lower postcentral cortex GM density are associated with higher Body Mass Index and more severe self-reported eating disorder symptoms. Moreover, some areas in the reward and control circuit (left orbitofrontal cortex, left insula, right dorsolateral prefrontal cortex, bilateral temporal areas) are differentially correlated to suppression times in participants with a high BMI. In conclusion, the reward and control circuits are involved in subliminal processing, and altered suppression times are associated with morphological alterations of these regions.

Introduction

From an evolutionary perspective, food is a salient stimulus, as it is crucial for our survival. Given its relevance, it is not surprising that it can preferentially attract attention compared to other stimuli (Brignell et al., 2009), especially in hungry individuals (Loeber et al., 2013). In addition, it seems to be preferentially processed in individuals with eating disorders and obesity (Brooks, Prince, et al., 2011; Hendrikse et al., 2015; Kulendran et al., 2017), as we have previously discussed in the 'Attentional biases' paragraph in the introduction. In tasks such as priming, eye-tracking, dot-probe and modified Stroop tasks, obese and ED patients have been frequently reported to show increased attentional approach, and later avoidance, of food stimuli (Werthmann et al., 2015). Food salience has also been investigated with tasks that measure behavioral inhibition, such as the Go/No-Go task. Evidence shows that healthy participants respond more quickly and make more commission errors to food cues compared to non-food cues (Teslovich et al., 2014), and that eating disorders patients and obese participants show a worse performance than controls (Price et al., 2015; Wu et al., 2013, but see Loeber et al., 2012; Kulendran et al., 2017).

In the studies reported in chapters 1-2 of this thesis, I have investigated attention towards food at a subliminal level of processing using a breaking Continuous Flash Suppression task (bCFS), and inhibition towards foods using a Go/No-Go task. bCFS is a technique of binocular rivalry that allows to temporarily suppress stimuli from visual awareness, and to measure the processing times of different stimuli at a subliminal level of processing (Tsuchiya & Koch, 2005). Importantly, it has been shown that personal features alter the relevance of the stimuli influence suppression times (Schmack et al., 2016) and that clinical disorders, such as anxiety and depression, can influence suppression times of disorder-related stimuli (Capitão et al., 2014; Z. Yang et al., 2011; for an in-depth excursus on the applications of bCFS, see the Introduction section "Continuous Flash Suppression and clinical findings"). In these studies, I have found that participants with high self-reported eating disorders symptoms and a concomitant high BMI, show a faster processing of food pictures presented at a subliminal level, as measured by the bCFS task, and shorter RTs in food trials in the Go/No-Go task. Furthermore, I have also observed that a higher BMI per se is associated with a heightened threshold of visual awareness, regardless of the stimulus presented.

In this study, I aim at investigating the neural basis of these phenomena. Previous literature has shown that during the subliminal processing of images rendered invisible by the CFS protocol, stimuli can activate areas in the limbic system, such as the amygdala (Pasley et al., 2004), an area involved in the detection of behaviorally relevant stimuli and the conjunction of a stimulus

representation with its behavioral relevance. Suppressed relevant stimuli have also been shown to selectively activate higher level areas, such as areas devoted to reaching and grasping when viewing tools (dorsal pathway: V7, intraparietal sulcus and lateral occipital complex) (Fang & He, 2005). Additionally, suppression times in the CFS task can be predicted by neural activity in visual areas (right, and to a less extent left, fusiform gyrus), and by activity in the left orbitofrontal cortex (OFC); nobly, this area is involved in the reward circuit, affective salience evaluation, value-based decision-making, and representation of the affective value of reinforces (Schmack et al., 2016) and that, together with the PFC, is involved in the control of food intake (Rolls, 2004).

Studies on the neural activation during Go/No-Go tasks find that response inhibition is connected to activation of the pre-supplementary motor area, which is involved in the motor response inhibition and selection, and of the left fusiform gyrus, which is connected and modulated by higher-order parietal and prefrontal regions, whose activity likely reflects stimulus classification and attentional mechanisms. In fact, higher level areas involved in executive control and attention, such as the right dorsolateral prefrontal and inferior parietal lobule, are recruited under conditions of increased working memory demand (Simmonds et al., 2008). Importantly, individual performance in this task has been connected to brain activity in the left frontal and parietal cortex, that is areas devoted to attention orientation and inhibition (Hirose et al., 2012).

A growing research body has shown that processing of food stimuli recruits areas associated with reward processing (insula and OFC), emotional processing (insula and amygdala), working memory (amygdala, hippocampus, thalamus, posterior cingulate cortex, and caudate), executive functioning and decision making (such as prefrontal cortex, caudate cingulate gyrus, OFC, thalamus) and visual processing (thalamus and fusiform gyrus) (García-García et al., 2013; Pursey et al., 2014). In accordance with these observations, obese individuals show altered activity in response to food in areas connected to reward (striatum and OFC), taste information processing (anterior insula and lateral OFC), motivation and emotion (OFC and posterior cingulate cortex) (Rothemund et al., 2007), exhibiting a suboptimal modulation of the affective/emotional aspects of the rewards value of foods, and a heightened drive to eat in response to food cues (Stoeckel et al., 2009).

The activity of these regions in response to foods result altered also in ED patients. For instance, hypoactivation of areas devoted to the assessment of food's reward value, and integration of reward value and interoceptive signaling (hypothalamus, amygdala and anterior insula) has been observed in anorexic patients (Holsen et al., 2012), while diminished activity in impulse control-related cortical areas (prefrontal, frontal, and insular cortex) has been reported in BED patients (Kessler et al., 2016; for a review see Steward et al., 2018).

The aim of this study, therefore, is to investigate whether altered gray matter in regions involved in reward and controls is associated with altered subliminal attention and inhibition toward food in obesity and ED.

Methods

Participants

Fifty-three participants (thirteen males) aged 19-33 years ($M = 23.2$, $SD = 2.9$) with normal or corrected-to-normal eyesight took part in the study. Participants were recruited on a volunteer basis through advertisement on different internet platforms. Potential participants were screened for conditions incompatible with MRI scanning, such as metal prostheses, as well as for Daltonism and strabismus. Moreover, they responded to an online questionnaire, assessing their satisfaction with their eating habits through four questions on a 7-point Likert scale (example questions: '*How do you rate your eating behavior?*'; '*How much influence does your relationship with food have on your daily life?*'). Half of the final sample (twenty-six participants) was more satisfied than unsatisfied with their eating habits, while the other half (twenty-seven participants) was more unsatisfied than satisfied. Participants filled the EAT-26 questionnaire, assessing their risk of having an eating disorder (Dotti & Lazzari, 1998; for a full description of the questionnaire see chapter 1; Garner et al., 1982), and reported their BMI. The sample included 11% underweight, 68% normal weight, 15% overweight and 6% obese participants. 21% of participants showed an EAT-26 score above the clinical cutoff, showing that our recruitment method had indeed attracted a rate of participants with dysfunctional eating habits higher than in the normal population. The demographical data of the experimental sample is reported in Table 3.

Table 3

	Mean (SD)	**range**
Age	23.2 (2.9)	19 – 33
Body Mass Index (BMI)	22.9 (4.5)	15.3 – 41.9
Eating Attitudes Test-26(EAT-26)	11.4 (12.1)	0 – 56

Demographic data of the experimental sample.

This study was approved by SISSA's Ethics Committee and by the regional Friuli Venezia Giulia Ethics' Committee.

Procedure and experimental tasks

Participants were tested at Udine's Santa Maria della Misericordia Hospital. Before starting the experiment, participants completed a questionnaire evaluating their compatibility with MRI scanning and signed a consent form. The experimental procedure consisted in the behavioral testing (questionnaires and experimental tasks), and in the MRI scanning.

Experimental tasks

Participants completed the bCFS and the Go/No-Go task, always in this order. For the bCFS task, the experimental setup was the same used in the study reported in chapter 2. Binocular stimulation was achieved through the use of a mirror stereoscope, and stimuli were shown in full RGB. Stimuli were displayed in one of the quadrants of a square, while the distractors were displayed over the whole square on the other side. Participants were instructed to indicate via key press the position of the stimulus relative to the central fixation cross as fast and as accurately as possible. The order, the position, and the side of the stimuli was randomized so that each participant saw each stimulus twice in all four quadrants in a different order. Trials ended after eight seconds if no response was given. Participants then performed an equivalent task without suppression (NoCFS). This task had the same instructions, and stimuli as the bCFS task, which are described in full in the Stimuli section in Chapter 2, but stimuli and distractors were superimposed as to not elicit suppression. Participants performed 40 trials of training, and 320 trials of the bCFS task and NoCFS task each, with a break every 30 trials. The total testing time was of about one hour and 15 minutes. Example trials of the bCFS and NoCFS tasks are shown in Figure 13 in the previous chapter. Refer to the Breaking Continuous flash suppression paragraph of chapter 2 for further details.

The protocol of the Go/No-Go task was the same that has been used in the study reported in Chapter 1 and Chapter 2. Participants were instructed to respond as quickly as possible to Go stimuli, and to not to respond to No-Go stimuli. There were four blocks of 40 trials each, in half of which Go cues consisted of food images, and No-Go cues of non-food images, while in the other half the assignment was reversed. In each block, 30% of trials were No-Go trials. An example trial is depicted in Figure 7 in Chapter 1.

MRI data acquisition and preprocessing

To collect a high-resolution 3D T1-weighted anatomical images [brain scan acquired along the AC-PC plane, 170 sagittal slices, FOV = 176 × 240 × 240 mm, voxel size = 1 × 1 × 1 mm, reconstruction matrix = 256 x 256, flip angle = 12°, TR = 8.1 ms, TE = 3.7 ms] a 3 Tesla Philips Achieva scanner was used. Data preprocessing was done in Matlab, using the SPM12 and CAT12 toolboxes (Friston et al., 2017; Gaser & Danhke, 2016). Scans were spatially normalized using the DARTEL algorithm and SPM12 tissue probability maps were used to segment the scans into gray matter (GW), white matter (WM) and cerebrospinal fluid (CSF) and for spatial registration, after which the Total Intracranial Volume (TIV) was calculated. Data were then smoothed with an 8 mm FWHM gaussian kernel.

Analyses

Behavioral analyses

We investigated the effect of the participants' BMI and EAT-26 scores on RTs in the bCFS and Go/No-Go tasks, and on accuracy in the Go/No-Go task, using linear mixed-effects models (LMMs). All analyses were run using the software R (version 3.4.3, R Core Team, 2017). LMMs were tested using the lmer function (lme4 package, Bates et al., 2015). Reaction times in the bCFS and NoCFS tasks were cleaned by removing trials with no responses (15.01% across all participants), wrong responses (1.66%), with RTs below 500 ms (0.11%), and with RTs that were more than 2.5 SD from the mean of each subject (0.02%). Seven participants were excluded from the analyses, as they did not respond to more than half of the trials. The final sample therefore included 46 participants (demographic data are reported in Supplementary table 10). In the analysis of the RTs of the Go trials in the Go/No-Go task, only correct responses that did not deviate more than 2.5 SD from each participants' mean were included (wrong responses = 1,89%, outlier responses = 0.03%). As in the analyses reported in the previous chapters, RTs in the bCFS, NoCFS, and Go/No-Go task were log-transformed, and BMI and EAT-26 scores were mean centered.

The initial model investigating the effect of participants' BMI and EAT-26 score on the reaction times of the bCFS and NoCFS tasks, derived from the experimental hypothesis, included Task (bCFS, NoCFS), Stimulus Type (Food, NonFood), BMI, and EAT-26 score as predictors, and Participant, Stimulus, and Stimulus Location as random intercepts. To verify that all predictors and all interactions significantly improved the model fit, non-significant interactions and predictors were

removed from the model, and the resulting model and the initial one were compared, on the basis of the AIC criterion (Bolker et al., 2009), using the anova function (lmerTest package, Kuznetsova et al., 2017). All factors and interactions that did not significantly improve the initial model were pruned. To confirm that high-level interactions explained more variance than the combination of the lower-level interactions between, we compared the AIC of models with and of models without the high-level interactions, and only included high-level interactions that improved the models' fit.

The final model included Task, BMI, and EAT-26 and their interactions as predictors. The comparison between the initial and final model is reported in Supplementary table 11.

In the analysis on the effect of BMI and EAT-26 on the RTs in the Go/No-Go task, the initial model included Stimulus Type, BMI, and EAT-26 score as predictors, and Participant and Stimulus as random intercepts. The final model included only Stimulus Type, BMI, and their interaction as predictors. The initial model on accuracy in the Go/No-Go task included Trial Type (Go, NoGo), Stimulus Type, BMI, and EAT-26 score as predictors, and Participant and Stimulus as random intercepts, while the final model included Trial Type, Stimulus Type, EAT-26, and their interaction as predictors. All comparisons between initial and final models are reported in Supplementary table 11.

VMB analyses

The VBM analyses were structured to investigate three main experimental questions. First, we wanted to explore whether participants' performance in the bCFS and Go/No-Go tasks significantly predicted gray matter (GM) density in certain brain areas. Secondly, we wanted to investigate whether our independent predictors, namely participant's BMI and EAT-26 scores, were correlated to participants' GM density. Finally, we wanted to explore whether the brain areas whose GM density was predicted by participants' performance in our experimental tasks, and the ones predicted by participants' BMI and EAT-26 scores overlapped or were part of the same circuit, with a particular interest in areas involved in the reward and control network for food intake.

To answer these experimental questions, we run a series multiple regressions using SPM 12 (Friston et al., 2017). In all models, age, gender, and TIV were covaried. The first model investigated the correlation between GM density and performance in the bCFS task. The dependent variable was calculated as the mean suppression times in the bCFS task for each participant, normalized by their RTs in the NoCFS task, to account for differences in response times that are not due to longer suppression. To investigate the correlation between GM density and performance in the Go/No-Go task, we run two models, using the mean RTs in Go trials per participant as predictor in one, and the

number of false alarms (FA), i.e. wrongly given responses on No-Go trials, in the other. Finally, to explore the correlation between GM density and participants' BMI and EAT-score, both independently of each other, and cumulatively, we entered them as separate predictors in the same model. The same models were also run only on the data derived from food trials of the bCFS and Go/No-Go tasks, to investigate whether performance in the tasks predicted GM density in the same areas when only considering food trials.

In addition, to further investigate the relationship between suppression times in the bCFS task and participants' BMI, we run an analysis to assess whether in participants with a high BMI, compared to participants with a low BMI, suppression times in the bCFS task were connected to GM density in different areas. For this purpose, we split our participants into a group with a high and one with low BMIs, based on a median split. We run a full factorial model with suppression times as a behavioral covariate, to assess whether a significantly different regression slope predicted GM density in the two groups, based on their performance in the bCFS task. The same model was also run with data coming from food trials only.

A correction for multiple comparisons based on False Discovery Rate (FDR) was applied to all regressions.
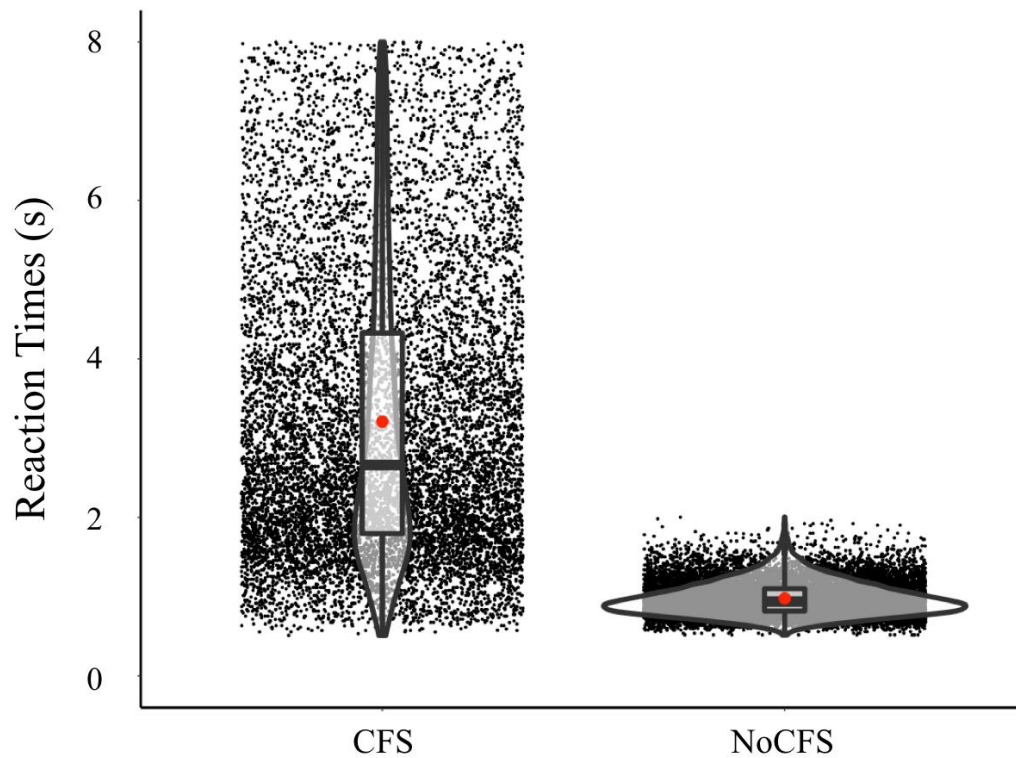
Results

Behavioral results

bCFS and NoCFS task

In the analysis on the RTs, we found a main effect of Task [F (1, 25691.7) = 50493, $p <$ 0.001], indicating longer RTs in bCFS compared to NoCFS, confirming that suppression had occurred during the bCFS task. Raw RTs of the bCFS and NoCFS tasks are depicted in Figure 17. The complete results are reported in Supplementary table 12.

Figure 17

Raw reaction times in the bCFS and NoCFS tasks.

We also found a main effect of BMI [F (1, 42) = 5, p = 0.025] and of EAT-26 scores [F (1, 42.1) = 5, p = 0.015], reflecting slower reaction times in participants with a high BMI, and with a high EAT-26 score, respectively. Results also showed a significant Task x BMI interaction [F (1, 25682) = 386, p < 0.001], depicted in the left panel of Figure 18. Higher BMI led to slower RTs in the bCFS task [p < 0.001] but not in the NoCFS task [p = 0.82]. Although the significant difference between bCFS and NoCFS was present in both low and high BMIs, it was higher in high BMIs [low BMIs t = 144.25, p < 0.001; high BMIs t = 170.18, p < 0.001]. Moreover, we observed a Task x EAT-26 interaction [F (1, 25687.5) = 379, p < 0.001], depicted in the right panel of Figure 18: that higher EAT-26 scores led to slower RTs in the bCFS task [p < 0.001] but not in the NoCFS task [p = 0.73]. The significant difference between bCFS and NoCFS was present in individuals with both low and high EAT-26 scores, but it was greater for those with high EAT-26 scores [low EAT-26 t = 143.76, p < 0.001; high EAT-26 t = 171.84, p < 0.001].

Figure 18
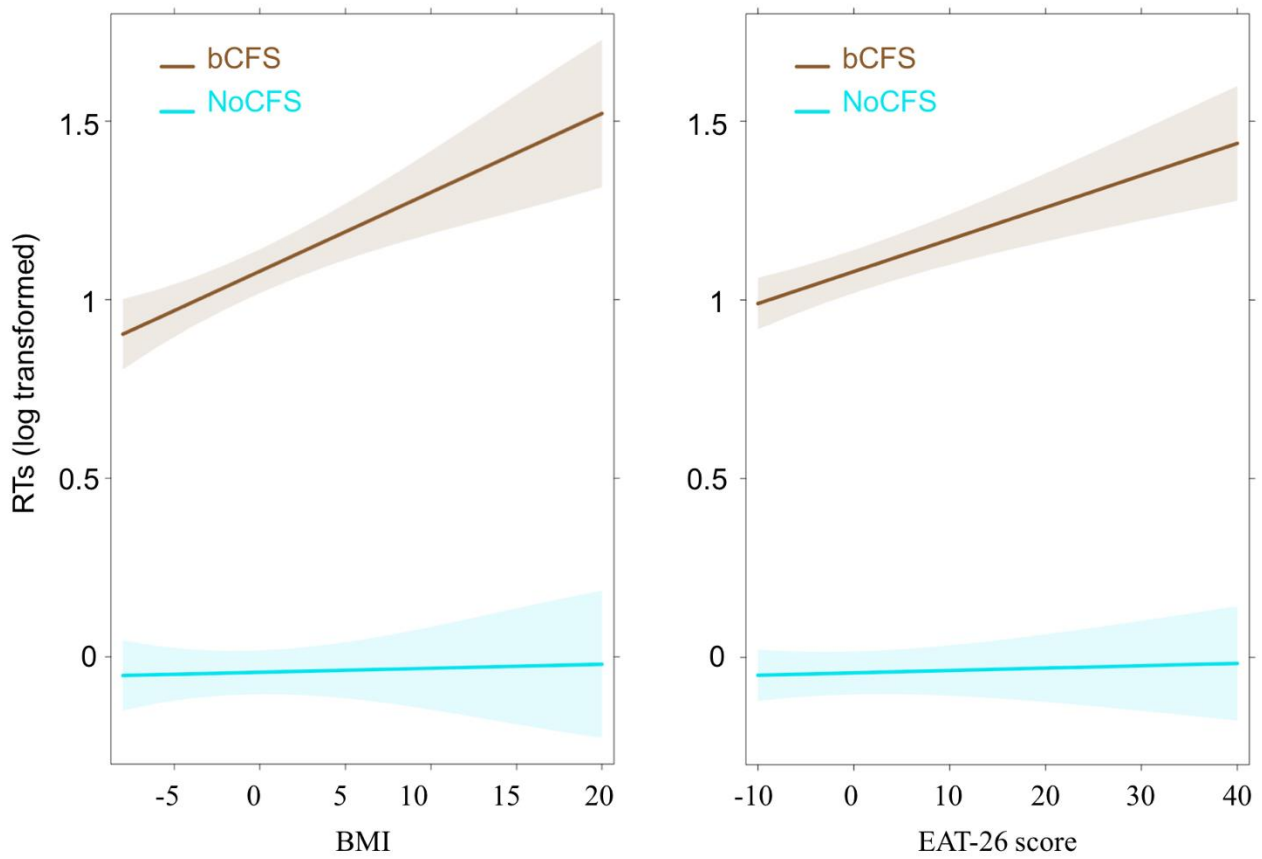
The interaction effect between task and BMI (left) and task and EAT-26 scores (right). A higher BMI predicts longer RTs in the bCFS task, but not in the NoCFS task; higher EAT-26 scores also predict longer suppression times in the bCFS task, but not in the NoCFS task.

Finally, a significant three-way interaction between Task, BMI, and EAT-26 scores [F (1, 25682.1) = 42, $p < 0.001$. See Figure 19] was observed. Post-hoc tests revealed that BMI * EAT-26 interaction failed to reach the significance level in the bCFS task ($p = 0.099$), and was not significant in the NoCFS task ($p = 0.76$).

Figure 19
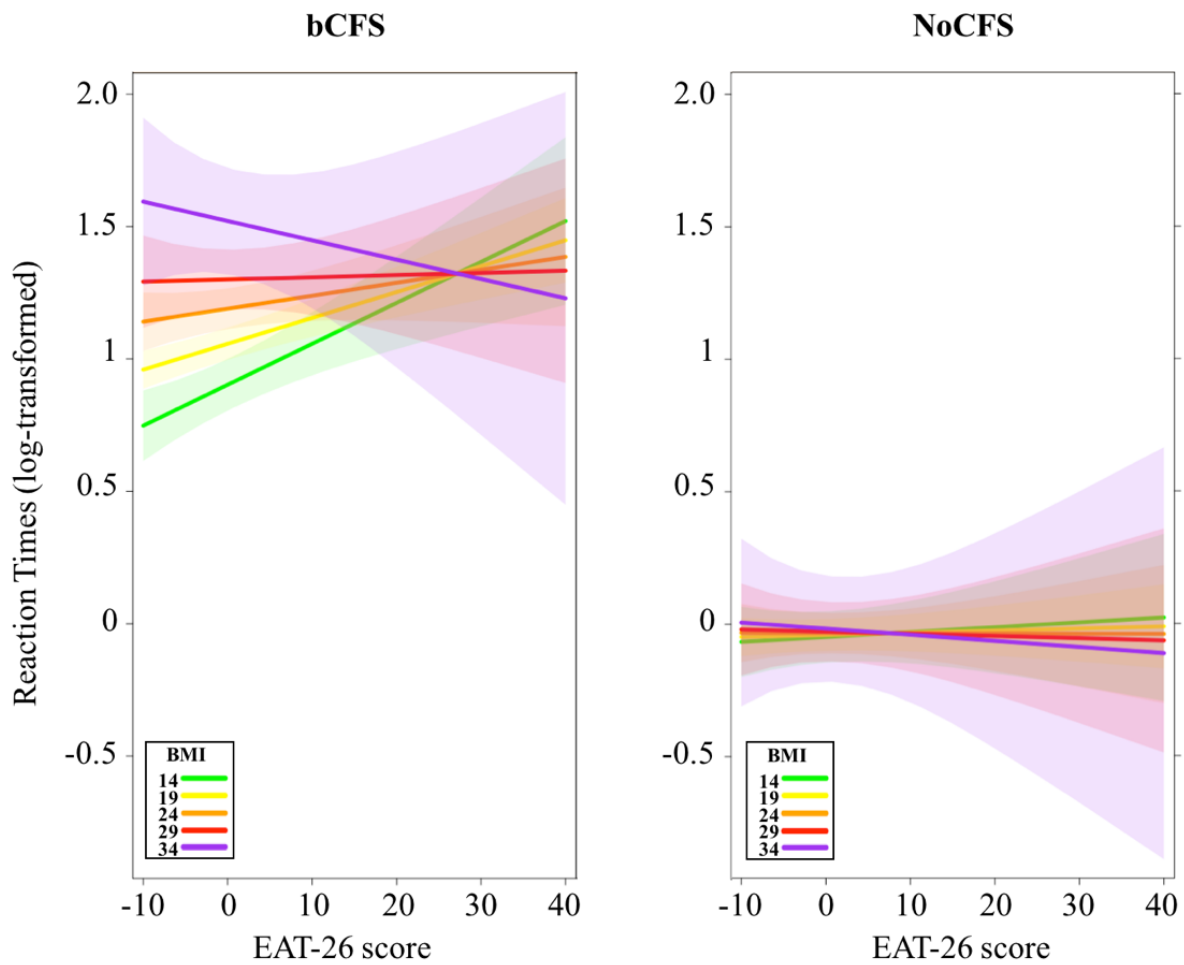
Fit lines of the interaction between BMI (plotted in colors) and EAT-26 scores (on the X axis) in the bCFS (left) and NoCFS (right) tasks.

In conclusion, both a high BMI and a high EAT-26 score significantly predicted longer RTs, in particular in the bCFS task; a significant three-way interaction showed that the interaction between BMI and EAT-26 scores was significantly stronger in the bCFS than in the NoCFS task, but post-hoc tests revealed that their interaction failed to reach the significance level in either task.

Go/No-Go task

In the analysis on the RTs in the Go trials, the main effects did not reach significance level [all $ps > 0.09$]. However, we found an interaction effect of Stimulus Type * BMI [$F (1, 5465.7) = 4.2, p = 0.04$], indicating that while in food trials BMI did not exert a significant effect on RTs [$p = 0.27$], it tendentially slowered RTs in non-food trials [$p = 0.08$]. The result is depicted in Figure 20.

Figure 20
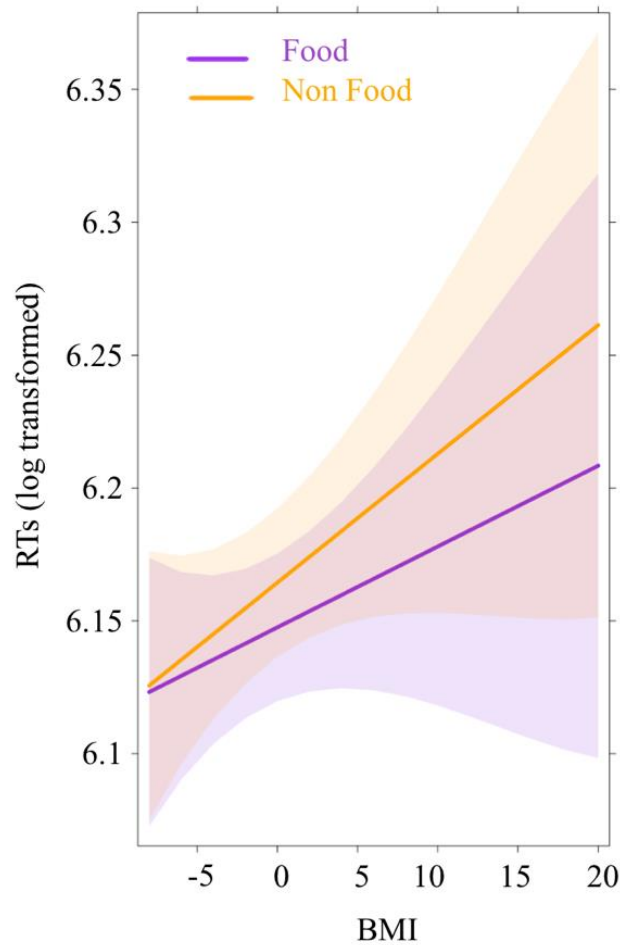
Fit lines of the Stimulus Type * BMI interaction, in the analysis of the Go trials of the Go/No-Go task.

Importantly, the difference between food and non-food was only significant in high BMIs [$p = 0.02$], but not in low BMIs [$p = 0.42$].

The analysis on accuracy revealed a main effect of Trial Type [$F (1, 4116.2) = 216.2$, $p < 0.001$], indicating overall lower accuracy in No-Go trials. Results also showed an interaction between Trial Type and Stimulus Type [$F (1, 4080.3) = 7.6$, $p = 0.006$] and Trial Type and EAT-26 scores [$F (1, 8364.8) = 7.9$, $p = 0.005$]. While in Go trials, accuracy did not change between food and non-food trial [$p = 0.45$], in No-Go trials participants made more false alarms in No-Go trials depicting non-foods, (i.e. in blocks when they were instructed to respond to foods) than on No-Go trials depicting foods [$p = 0.012$]. Moreover, while EAT scores did not influence accuracy on Go trials [$p = 0.68$], higher EAT-26 scores significantly predicted lower accuracy in No-Go trials [$p = 0.038$].

Finally, we found a significant three-way Trial Type * Stimulus Type * EAT26 interaction [F (1, 8364.8) = 12.9, $p < 0.001$], depicted in Figure 21. We observed that in both in Go and No-Go trials the difference between food and non-food was not significant for low EAT-26 scores [all $ps >$ 0.18], and significant for high EAT-26 scores, with a stronger effect in the No-Go trials [low EAT-26 scores $t = 2.5$, $p = 0.012$; high EAT-26 scores $t = 3.43$, $p < 0.001$].

Figure 21
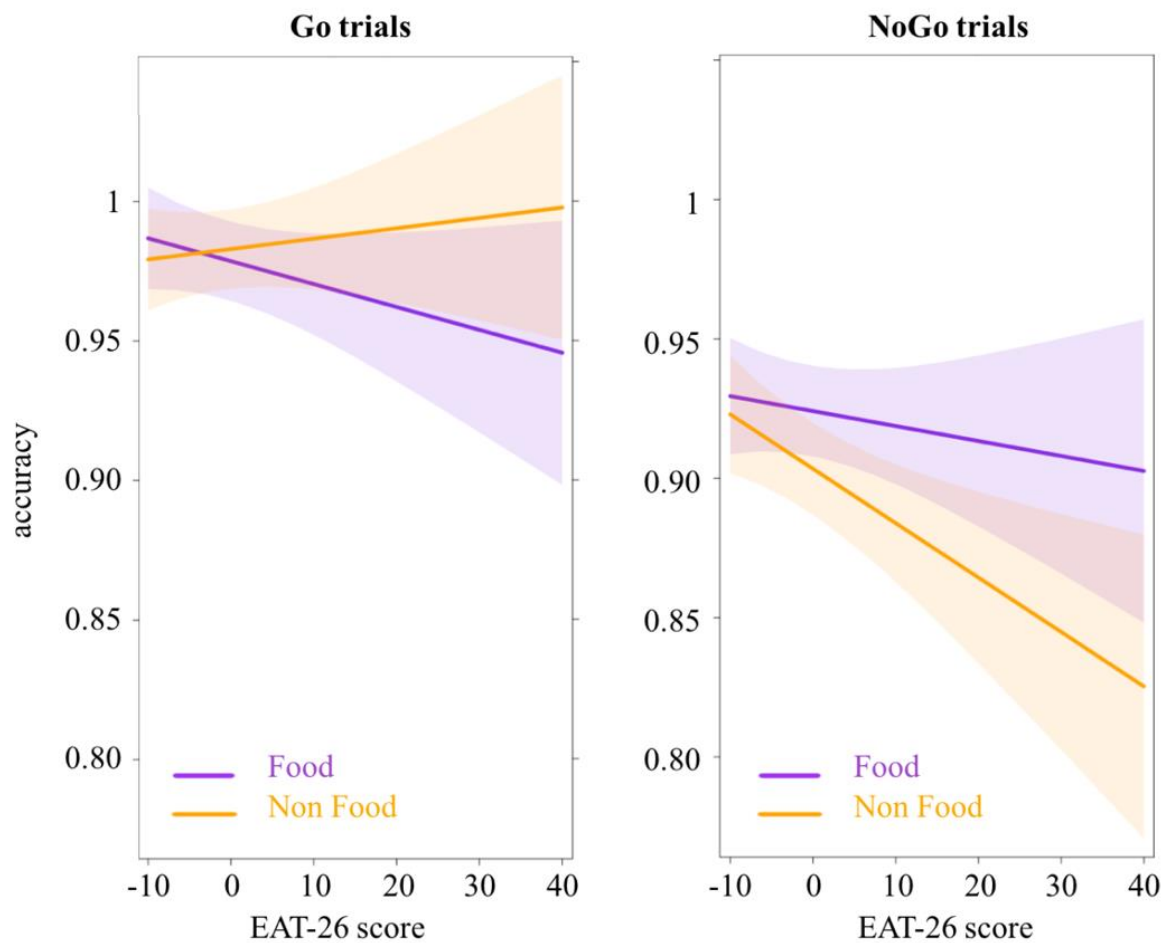
Three-way interaction between Trial Type, Stimulus Type, and EAT-26 score on accuracy in the Go/No-Go task.

To sum up, the analyses showed two main findings: first, participants with a high BMI responded significantly slower on Go trials only when they were instructed to respond to non-food images; second, a higher EAT-26 score predicted lower accuracy for Go trials and for No-Go trials. Importantly, participants with higher EAT-26 scores were less accurate in non-food No-Go trials, i.e. when they were instructed to respond to food images, compared to food No-Go trials.

VBM results

Correlation between grey matter density, task performance, BMI and EAT-26 scores

We assessed a relationship between voxel-wise GM density and the strength of suppression in the bCFS task. We found a positive correlation between suppression times and GM density in right occipital visual areas (calcarine cortex, occipital fusiform gyrus, inferior occipital gyrus, occipital pole) and in the bilateral caudate nuclei, i.e. the longer the suppression times, the higher was GM density in these areas. A cluster in the left occipital visual areas (left calcarine cortex) did not survive FDR correction. On the other hand, suppression time were negatively correlated with GM density in the left dorsolateral PFC (left middle frontal gyrus): i.e. the longer the suppression times, the lower GM density in this region. The same areas were found correlated with suppression times when using data from the food trials only. Results are depicted in Figure 22.

Figure 22
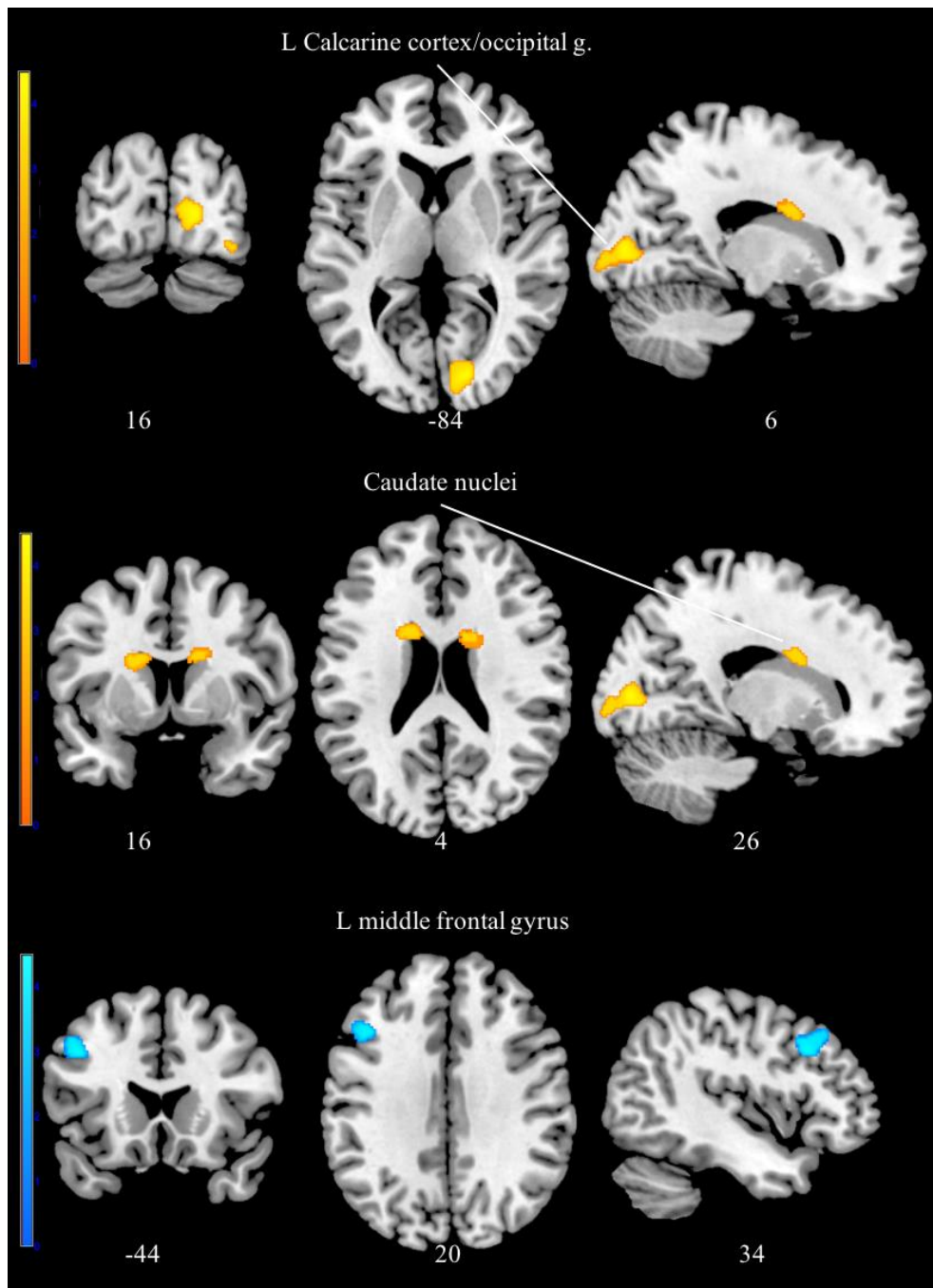
In warm colors, areas in which GM density correlated positively with suppression times in the bCFS task; in cold colors, areas in which GM density correlated inversely with suppression times in the bCFS task.

The analysis of RTs in the Go trials of the Go/No-Go task showed that faster RTs were associated to higher GM density in the left frontal pole (Figure 23). No correlation was found between GM density and the number of false alarms in the Go/No-Go task. The same results emerged when running the analysis only on food trials.

Figure 23
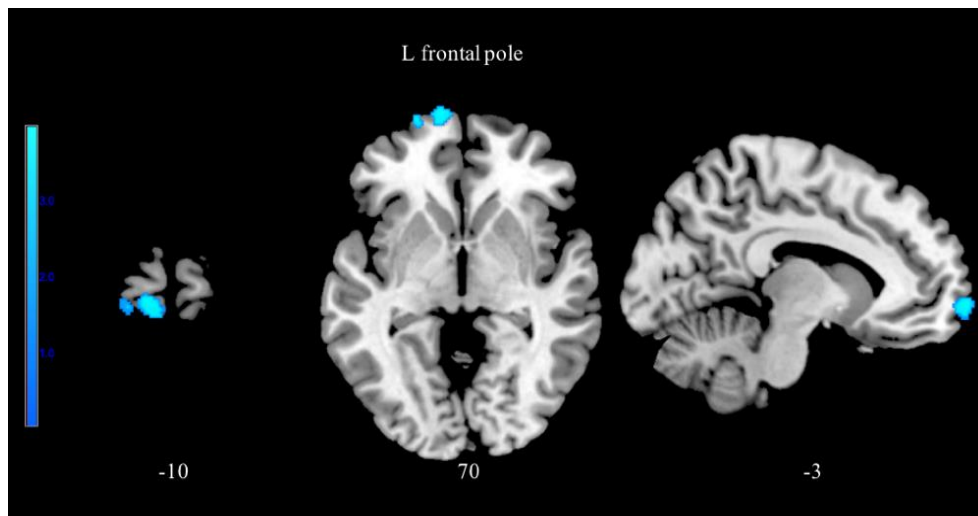
Area in which GM density inversely correlated with RTs in the Go/No-Go task.

The multiple regression with BMI and EAT-26 scores as predictors showed that participants' BMI positively correlated to GM density in the bilateral hypothalamus and ventral thalamus. In addition, it negatively correlated with GM density in the left postcentral gyrus. An inverse correlation between EAT-26 and GM density in the right postcentral gyrus did not survive FDR correction. Higher BMI and EAT-26 scores together were found to be positively associated with GM density in the bilateral hypothalamus and ventral thalamus, and inversely correlated with GM density in the left postcentral gyrus, in an area similar, but more extended, to the one correlated with participants' BMI (Figure 24).

All results are reported in Table 4.

Figure 24
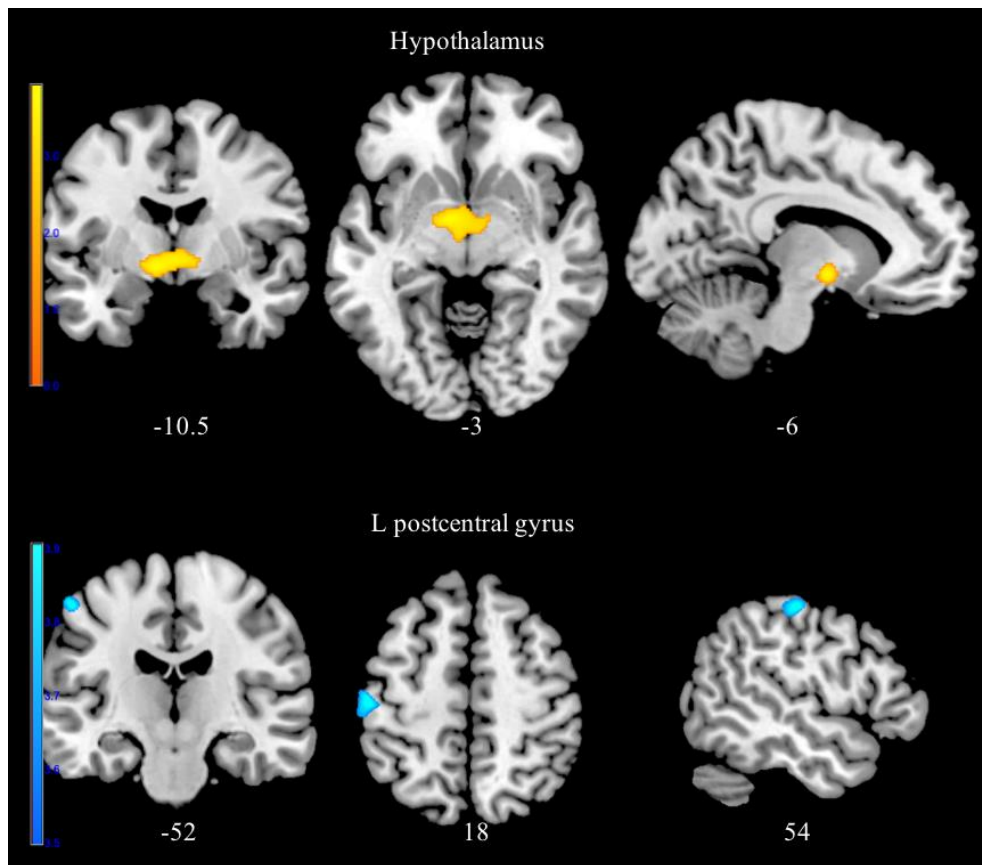
In warm colors, the area in which GM density significantly correlated with the participants' BMI; in cold colors, the area in which GM density inversely correlated with the participants' BMI.

Table 4

Contrast	H	Brain region	p value (FDR)	N voxels	MNI coordinates x	y	z	T	Z
CFS dir	R	Calcarine / OFG / IOG / Occipital p.	< 0.001	996	16	-84	6	4.92	4.41
	L	Caudate	0.025	199	-20	10	21	3.80	3.54
	R	Caudate	0.028	172	16	4	26	3.59	3.36
CFS ind	L	Middle Frontal g.	0.002	352	-44	20	34	4.47	4.07
GNG RTs ind	L	Frontal p.	0.014	235	-10	70	-3	3.96	3.67
BMI dir	R/L	Hypothalamus / ventral thalamus	< 0.001	575	-10.5	-3	-6	5.05	4.49
BMI ind	L	Postcentral g.	0.040	140	-52	-18	54	3.76	3.49
BMI&EAT dir	R/L	Hypothalamus / ventral thalamus	< 0.001	513	-6	-2	-6	4.83	4.33
BMI&EAT ind	L	Postcentral g.	< 0.001	339	-52	-20	56	4	3.69

VBM correlation results.

Group differences in the correlation between GM density and suppression times

In the analysis of the relationship between suppression time and differences in GM density in the high and low BMI group, we found a correlation between suppression times and the bilateral temporal, right frontal, and left orbitofrontal regions, as well as in the left operculum and insula. Clusters in the right superior temporal gyrus, right frontal pole, right insula, and putamen did not survive the FDR correction. This indicates that in these regions, the association between performance at the bCFS task and GM density is significantly different in participants with a high BMI and those with a low BMI. As the beta values of the regression slope between GM density and suppression times are more negative in the high BMI group, and are close to zero in the low BMI group, this means that higher GM density in these areas associated with shorter suppression times in the high BMI group, but not in the low BMI group. The analysis performed only on food trials yielded correlations with GM density in the same areas, with the addition of the right insula, which had not reached full significance in the analysis using data from all trials.

Results are reported in Table 5, and visually represented in Figure 25.

Table 5

H	Brain region	*p* value (FDR)	N voxels	MNI coordinates X	Y	Z	T	Z	β low BMI	β high BMI
R	Temporal lobe/ Middle Temporal g.	< 0.001	585	50	6	-28	4.37	3.98	0.020	-0.044
L	Orbital g.	< 0.001	547	-27	30	-16	5.08	4.50	0.007	-0.042
L	Operculum/insula	0.001	425	-36	4	18	4.16	3.81	0.006	-0.033
L	Inferior Temporal g./ Temporal pole	0.001	357	-42	3	-48	4.50	4.07	0.008	-0.042
R	Middle Frontal g.	0.009	231	52	18	40	3.96	3.66	0.004	-0.039
L	Inferior Temporal g.	0.015	193	-51	-30	-22	4.13	3.79	0.013	-0.043

VBM group analysis results.

Figure 25
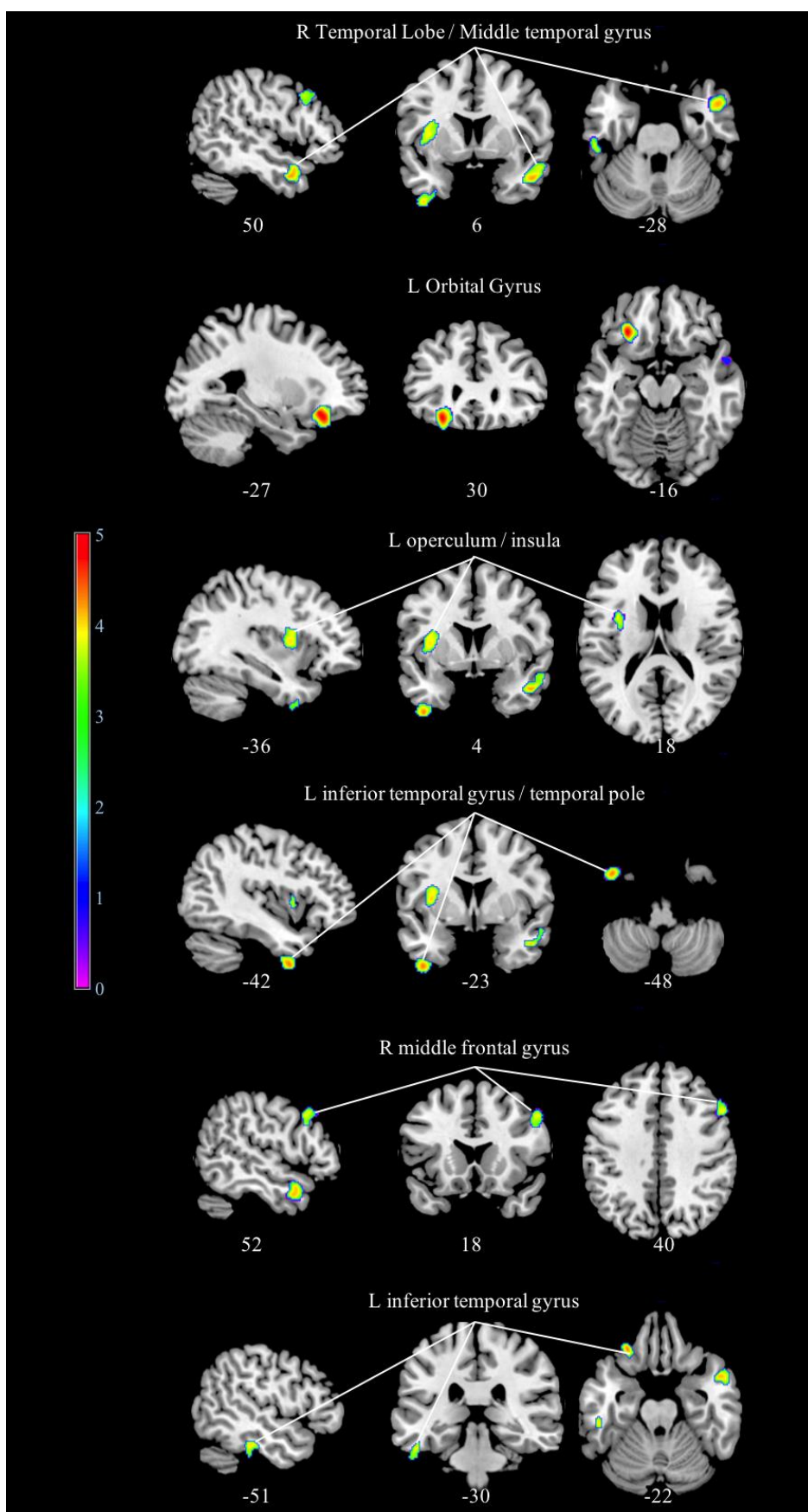
Different GM density association with bCFS performance in the high and low BMI groups.

Discussion

This study investigated the neural correlates of performance at the bCFS and Go/No-Go tasks, and their connection to the participants' BMI and EAT-26 scores.

In line with the results of the studies reported in the previous chapters, we observed that both participants' BMI and EAT-26 scores influenced suppression times at the bCFS task. Moreover, these two factors significantly interacted with each other: the higher the BMI and EAT-26 scores, the faster the suppression times. However, we did not find that BMI and EAT-26 scores influence food and non-food processing differently, unlike our findings reported in chapter 1. The lack of a food-specific effect could be due to the difference in the experimental stimuli that were used or to the characteristics of the participants tested. Differently from the stimuli of the study reported in chapter 1, the stimuli used here were shown in full RGB, and matched for spatial frequency, a feature that has been shown to influence suppression times (Gray et al., 2013). It is therefore possible that the difference in the processing of foods and non-foods reported in study 1 might be due to low-level features. Another difference with respect to study 1 lies in the sample of participants: the participants in this study did not include a clinical sample, and it is possible that foods and non-foods are processed differently at a subliminal level only in a clinical sample, as suggested by Nijs & Franken (2012). We do find a bias for food images at a later stage of stimulus processing, as measured by the participants' performance at the Go/No-Go task. We found that the participants' BMI and EAT-26 scores influence participants' RTs and accuracy, respectively, and that their influence depends on the type of stimulus, with higher BMIs leading to longer RTs in non-food Go trials compared to food Go trials, and higher EAT-26 scores to lower accuracy, especially for non-food No-Go trials (i.e. in blocks with food Go cues).

Our anatomical analyses yielded some interesting results. Stronger suppression correlated with higher GM in visual areas. This could indicate that a higher suppression power of distractors might be due to the different processing of the visual features in low-level visual areas. Interestingly, we also found that longer suppression times were associated with higher GM density in the caudate nuclei, a key structure implicated in reward-dependent behaviors (Balleine et al., 2007; Nakamura & Hikosaka, 2006) and in the elicitation of correct action schemas based on the evaluation of outcomes (Grahn et al., 2008). Similarly, Schmack at al. (2016) have found that suppression times can be predicted from activity in the orbitofrontal cortex, also part of the reward circuit, and speculate that the pre-conscious representation of the stimulus' affective salience influences the speed of visual awareness, through top-down modulation of visual areas. It can be therefore hypothesized that

reciprocal connections between visual areas and the reward circuit influence suppression times. Furthermore, we found that shorter suppression times correlated with higher GM density in the left dorsolateral PFC, an area deputed to top-down control, working memory, attention, inhibition, emotion regulation (Golkar et al., 2012; Paneri & Gregoriou, 2017) and that directly modulates the caudate nuclei (Tanaka et al., 2006). As greater GM density in the left PFC correlates with shorter suppression times, it is possible to hypothesize that greater attention, inhibition ability and modulation of the reward circuit are necessary for faster processing of visual stimuli in the bCFS task. We can therefore conclude that suppression mechanisms in the bCFS task rely on neural substrates that are involved in the reward and control systems, and that the behavioral measure of suppression time can be informative of the imbalance of these circuits.

As to the Go/No-Go task, our result shows that a faster performance is associated to higher GM density in the left frontal pole. This area, deputed to high-level monitoring and task switching (Burgess et al., 2007), also incorporates information to guide goal-directed behavior, by integrating information through connections to higher-order sensory association cortex, other prefrontal regions that process goals and action plans, monitor action outcomes and motivate behaviors, and regions that process information about stimuli, values, and emotion (Orr et al., 2015). A negative association between frontal GM density and performance in the Go/No-Go task was also reported by Li et al. in alcohol-dependent patients (Li et al., 2010); the the best of our knowledge, no study to date has investigated the GM density correlated of the food Go/No-Go task performance.

As for the neural correlated of BMI and EAT-26 scores, our results show participants' BMI, and the conjunct increase of BMI and EAT-26 scores, correlate with higher GM density in the bilateral hypothalamus and ventral thalamus. The hypothalamus and ventral thalamus are key regions in the regulation of appetite (Tataranni et al., 1999), that are active when viewing food stimuli (Killgore et al., 2003), and whose functioning is altered in obesity and ED (Berthoud & Morrison, 2008; Holsen et al., 2012). Matsuda et al. (1999) find that paraventricular and ventromedial hypothalamic nuclei, involved in the regulation of appetite and in the recognition of the feeling of fullness, are more active in obese individuals than in healthy controls after glucose ingestion. It is possible that a higher GM density in this region reflects an altered ability to recognize the feelings of hunger and fullness, with consequent dysregulation of food intake. The participants' BMI, and the conjunct increase of BMI and EAT-26 scores, also correlated with lower GM density in the left postcentral gyrus, a region associated with the gustatory cortex where the somatosensory maps of the mouth, lips, and tongue are located, that has been shown to be active in participants viewing low-calorie foods (Killgore et al., 2003). Interestingly, a similar finding has been reported by Pannacciulli

et al. (2006) in a VBM study, addressing differences in GM density between obese and lean individuals.

Summing up, better performance on the bCFS and Go/No-Go tasks are related to higher GM density in frontal areas known to be involved in control, that project and modulate lower-level areas. We therefore speculate that the influence of the participants' BMI and EAT-26 scores on their performance on the bCFS and Go/No-Go tasks can be attributed to alterations in the reward and control circuits. This hypothesis is supported by the results from the analysis of the relationship between suppression time and differences in GM density in the high and low BMI group. Many key areas of the reward circuit, such as OFC, bilateral temporal areas, and the operculum and insula, as well as the right dlPFC, a key region in control whose functioning has been linked to the etiology of obesity (Alonso-Alonso & Pascual-Leone, 2007), are only associated to better performance in the bCFS among participants with a high BMI, but not among the ones with a low BMI. This suggests that the higher threshold of awareness in participants with a higher BMI might be linked to an altered functioning of the control and rewards systems, and of their reciprocal modulation. It is interesting to note that when analysis is restricted to food trials, we also find an effect on the right anterior insula, an area regarded as the primary taste cortex that has a strong association with the rewarding/hedonic aspects of food, and has been shown to be activated differently in obese individuals and ED patients (Frank et al., 2013).

In conclusion, areas of the reward and control circuit are correlated with task performance at the bCFS and Go/No-Go tasks. The relation, at a behavioral level, of the participants' BMI and EAT-26 scores and performance at these tasks can be linked to an altered functioning of the reward system, and malfunctioning modulation of control areas such as the dlPFC over lower-level areas.

Supplementary materials

Supplementary table 10

	Mean (SD)	**range**
Age	23.0 (2.9)	19 – 33
BMI	23.1 (4.8)	15.3 – 41.9
EAT-26	11.5 (12.4)	0 – 56

Demographic data of the participants included in the bCFS and NoCFS analyses.

Supplementary table 11

RTs of bCFS and NoCFS tasks	initial model AIC (20) = 25715	$\chi2(8) = 7.42$, $p = 0.49$
	final model AIC (12) = 25706	
RTs on Go trials of Go/NoGo task	initial model AIC (11) = -4913.8	$\chi2(4) = 2.64$, $p = 0.62$
	final model AIC (7) = -4919.2	
Accuracy of Go/NoGo task	initial model AIC (19) = -4367.5	$\chi2(8) = 31.92$, $p = 0.66$
	final model AIC (11) = -4377.6	

Comparison between initial and final models.

Supplementary table 12.

	Sum Sq	**Mean Sq**	*F* **(df)**	*p* **value**	
Task	7906	7906	$F\,(1,\,25691.7) = 50493$	< 0.001	***
BMI	0.9	0.9	$F\,(1,\,42) = 5$	0.025	*
EAT26	1	1	$F\,(1,\,42.1) = 6$	0.015	*
Task * BMI	60.5	60.5	$F\,(1,\,25682) = 386$	< 0.001	***
Task * EAT26	59.4	59.4	$F\,(1,\,25687.5) = 379$	< 0.001	***
BMI * EAT26	0.2	0.2	$F\,(1,\,42) = 1$	0.322	
Task * BMI * EAT26	6.6	6.6	$F\,(1,\,25682.1) = 42$	0.000	***

Results of the model predicting RTs in the bCFS and NoCFS tasks.

Supplementary table 13.

	Sum Sq	Mean Sq	F (df)	p value	
Stimulus Type	0.1	0.1	F (1, 130.5) = 2.9	0.090	.
BMI	0.0	0.0	F (1, 51) = 2.2	0.148	
Stimulus Type * BMI	0.1	0.1	F (1, 5465.7) = 4.2	0.041	*

Results of the analysis of the RTs on Go trials of the Go/No-Go task.

Supplementary table 14

	Sum Sq	Mean Sq	F (df)	p value	
Trial Type	7.4	7.4	F (1, 4116.2) = 216.2	< 0.001	***
Stimulus Type	0.1	0.1	F (1, 164.6) = 2.3	0.133	
EAT26	0.1	0.1	F (1, 52.9) = 1.9	0.176	
Trial Type * Stimulus Type	0.3	0.3	F (1, 4080.3) = 7.6	0.006	**
Trial Type * EAT26	0.3	0.3	F (1, 8364.8) = 7.9	0.005	**
Stimulus Type * EAT26	0.0	0.0	F (1, 8331.3) = 0.1	0.760	
Trial Type * Stimulus Type * EAT26	0.4	0.4	F (1, 8364.8) = 12.9	0.000	***

Results of the analysis on accuracy in the Go/No-Go task.

Appendix

Foreword

This thesis is comprised of three studies that have used the same paradigms, the bCFS, NoCFS, and Go/No-Go tasks, with different populations and methods. In all studies, we aimed at assessing the influence of the participants' BMI and EAT-26 scores on their task performance. We consistently do find a BMI and EAT-26 scores influence on task performance; however, some differences in the experimental designs and population tested have led to partially different results in the three studies. Moreover, depending on the population and the aims of each single study, we have chosen the most appropriate model to analyze the data. In the current appendix, we report some summary statistics of our three experimental samples, to give an overview of our participants' characteristics across the three studies, and we report an analysis run on the Go/No-Go data of the three studies, which have used the same experimental paradigm.

Experimental samples

Participants in the three experiments were recruited following different criteria, which resulted in very different characteristics of the experimental samples. In the first study reported in this thesis, a third of the participants were recruited at an eating-disorders clinic, with the criterion that they should be currently under treatment for an ED, another third at a dietician's practice, with the criterion that they should be overweight or obese, and the remaining third at a university campus. The resulting sample, as reported in Table 6, was made up by more than 45% of overweight and obese individuals, and 22% of participants whose EAT-26 score was above the cutoff, indicating a risk for eating disorders. In our second experiment, reported in chapter 2, participants were recruited exclusively at a university campus, with the only criterion of having a wide range of BMIs in the final sample. The experimental sample was therefore comprised of 27% of overweight or obese individuals, 62% of normal weight individuals and 11% of underweight individuals. Only 7% of individuals resulted at risk for eating disorders. Finally, in our third experiment, reported in chapter 3, participants were recruited after an online survey, in order to have half of our experimental sample generally satisfied with their relationship with their eating habits and their body, and the other half generally unsatisfied. The experimental sample therefore included 21% of overweight or obese individuals, but the percentage of individuals at risk for an ED was similar to the one reported in study 1, going up to 21%.

Table 6

	N	Underweight	Normal	Overweight & obese	BMI	EAT-26 score	Over EAT-26 cut-off
Study 1	74	12.5%	41.7%	45.8%	M = 25.9(7.4)	M = 12.4(13.7)	22.2%
					median = 24	median = 7	
Study 2	53	11.3%	62.2%	26.2%	M = 23.2(4.5)	M = 7.8(8.2)	7.5%
					median = 22.4	median = 4	
Study 3	53	11.3%	68%	20.7%	M = 22.9(4.5)	M = 11.4(12)	20.8%
					median = 22	median = 8	

Demographic and clinical data of the experimental samples of study 1, 2, and 3.

The three experiments therefore draw on different samples, which might in part explain the partial differences in the results. As this thesis aims at considering individuals' characteristics as part of a spectrum, rather than analyzing each group separately, it can be of interest to analyze data from all the experiments pulled together. This is unfortunately not possible in the case of the bCFS and NoCFS tasks, as the paradigm used in study 1 is different from the one used in studies 2 and 3, as discussed in the relative chapters. The following paragraph reports the analysis of the Go/No-Go task, run on the data from the 3 experiments pulled together.

Go/No-Go data analysis over three studies

Methods

As mentioned above, this analysis includes all participants form the three experiments reported in this thesis (n = 183; sample characteristics reported in Table 6). Only the trials from the blocks of sham stimulation were included from study 2. The experimental paradigm is explained in full in the Go/No-Go task section in chapter 1. As in the analyses reported throughout this thesis, we used RTs in the Go trials, and accuracy on all trials as depended variables of the analysis. RTs were cleaned by removing trials with no response and all trials more than 2.5 SD away from each participant's mean, and log transformed. Continuous predictors were mean centered. As in previous

chapters, the final model of the analysis was obtained by removing factors and interaction effects that did not significantly increase the model fit, according to the AIC criterion.

The model for the analysis of RTs on Go trials included Stimulus Type (Food, NonFood), BMI and EAT-26 scores as predictors. All predictors and interaction improved the model fit, and were left in the model. The initial model for the analysis of accuracy included Trial Type (Go, NoGo), Stimulus Type, BMI and EAT-26 scores as predictors. The final model did not include BMI, as it did not improve the model's fit. Stimulus Type was included in the final model even if it only marginally improved its fit [$p = 0.059$] as it significantly interacted with the other predictors.

Results

The model on the RTs of Go trials yielded a significant main effect of BMI [$F(1, 172) = 24.1$, $p < 0.001$], reflecting a correlation between longer RTs for higher BMIs. We also found a significant interaction between Stimulus Type and EAT-26 scores [$F(1, 29860.4) = 18.5$, $p < 0.001$]: even if EAT-26 scores did not significantly affect RTs neither in food trials nor in non-food trials [all $ps > 0.35$], for high EAT-26 scores, food trials were significantly shorter than non-food trials [$p = 0.03$], but not for low EAT-26 scores [$p = 0.86$]. A significant interaction between BMI and EAT-26 scores [$F(1, 172) = 5.6$, $p = 0.02$] indicated that the two predictors interacted in influencing RTs, and a further three-way Stimulus Type * BMI * EAT-26 scores interaction showed that this pattern differed for food and nonfood trials [$F(1, 18520.3) = 28.3$, $p < 0.001$]. Post-hoc tests showed that the BMI * EAT-26 scores interaction was only significant for food go trials [$t = 3.1$, $p = 0.002$], but not for non-food trials [$p = 0.13$]. In food trials, participants' BMI had a significant effect only for low EAT-26 scores [$t = 5.9$, $p < 0.001$], but not for high EAT-26 scores [$p = 0.33$]. This indicates that in individuals with a low EAT-26 score, a high BMI leads to longer RTs, but this effect is not present in individuals with a high EAT-26 score. This interaction is depicted in Figure 26, and complete results are reported in Supplementary table 15.

Figure 26
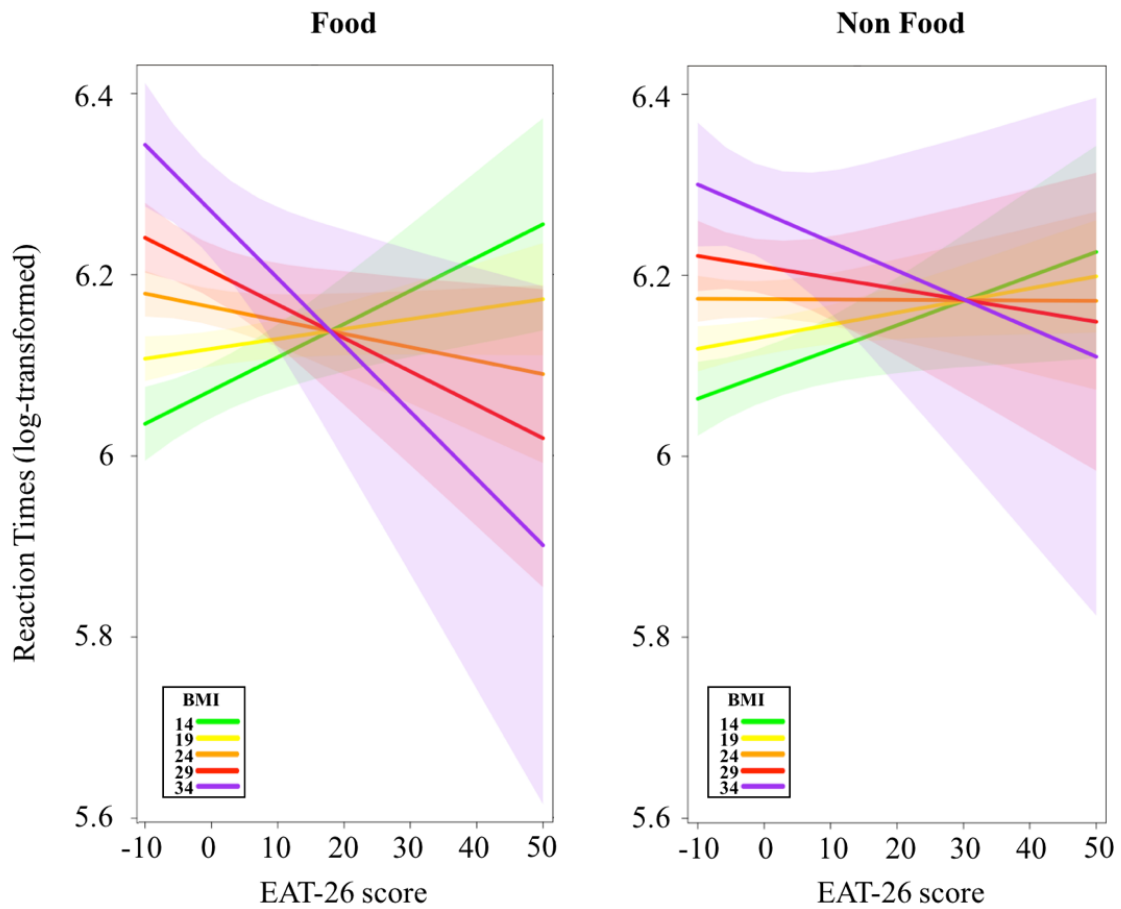
Food   **Non Food**

Fit lines of the association between RTs in the Go/No-Go task and participants' EAT-26 scores and BMI, in food trials (left) and non-food trials (right).

The analysis of accuracy yielded a significant main effect of Trial Type [$F_{(1, 14206.5)}$ = 623.84, $p < 0.001$] and EAT-26 scores [$F_{(1, 822.4)}$ = 26.62, $p < 0.001$], indicating overall higher accuracy for Go trials than for NoGo trials, and overall lower accuracy for increasing EAT-26 scores. We also found a significant Trial Type by EAT-26 scores interaction [$F_{(1, 27895.1)}$ = 10.75, $p = 0.001$] and a further three-way interaction between Trial Type, Stimulus Type and EAT-26 scores [$F_{((1, 27895.1)}$ = 5.61, $p = 0.02$]. Post hoc tests showed that higher EAT-26 scores led to lower accuracy both on the Go [$t = 2.8$, $p = 0.006$] and on the NoGo trials [$t = 5.4$, $p < 0.001$], but with a stronger effect on the NoGo trials. Importantly, the difference between food and non-food was only significant in NoGo trials [$t = 2$, $p = 0.047$], and not in Go trials [$p = 0.19$] and, within NoGo trials, only for high EAT-26 scores [$t = 2.55$, $p = 0.01$], and not for low EAT-26 scores [$p = 0.68$]. Results are depicted in Figure 27. Complete results are reported in Supplementary table 16.

Figure 27

Go trials   NoGo trials
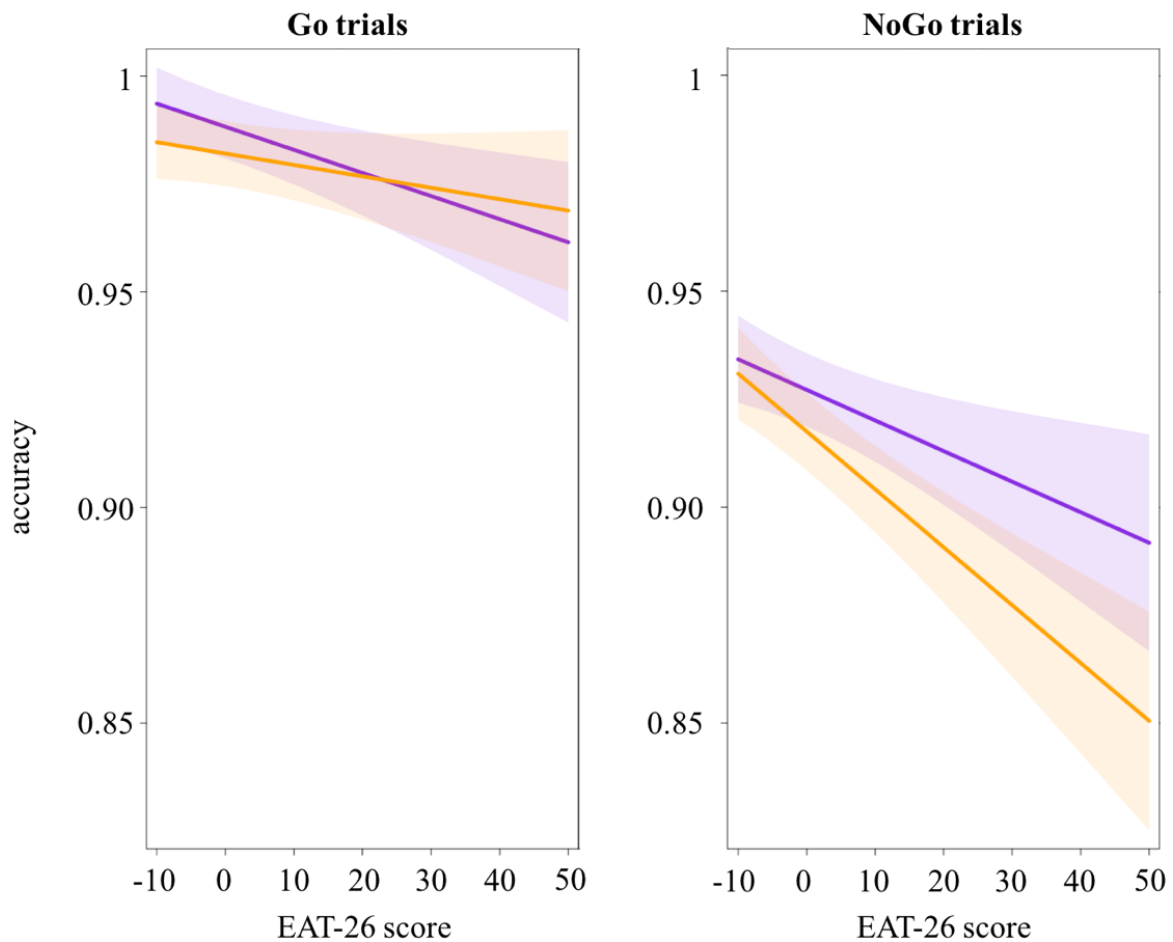
Fit lines of the association between accuracy the Go/No-Go task and the participants' EAT-26 scores, in Go trials (left) and NoGo trials (right).

Discussion and conclusions

These results are in line with the results reported in the previous chapters. In the analyses of RTs, we find that higher BMI leads to slower responses, a result that has already emerged in study 1, which has the largest number of overweight and obese participants. Indeed, the participants' BMI has been found to be a significant factor in the analyses of all studies, and in all four analyses, we find that it significantly interacts with the type of stimulus participants are responding to (i.e. foods or non-foods). Notably, in study 2 and 3, where the participants' EAT-26 scores are not included in the model, participants respond faster to food images than to non-food images for low BMIs and high BMIs. In study 1 and in the overall analysis, which include the participants' EAT-26 scores as a predictor, the participants' BMI interacts with the participants' EAT-26 scores only in food trials. From these overall analysis, conducted on a large sample of participants, it is possible to conclude that higher BMI and EAT-26 scores significantly reduce RTs in the Go trials when participants are

responding to food images. The fact that BMI and EAT-26 scores influence participants' performance especially in block in which they are responding to food images suggests that impaired inhibition might be food specific. However, results in the literature about performance of obese individuals and ED patients in food Go/No-Go task vary (Bartholdy et al., 2016b), and, as pointed out by Meule (2017), Go/No-Go task in which food is either the go signal, or the no-go signal, are of difficult interpretation, as it can be argued both that a food-specific inhibition would particularly affect trials in which food is the go cue, or that it would have a greater effect in trials where food is the no-go cue.

In experimental samples with a higher prevalence of participants with high EAT-26 scores, i.e. in study 1 and 3, EAT-26 scores also influence the participants' accuracy, especially in NoGo trials. The overall analysis shows that this effect is particularly strong in blocks where participants are responding to food Go cues, and should withhold responses in non-food trials. The participants' BMI only seems to influence accuracy in the analysis of study 1, possibly because the sample included the highest percentage of overweight and obese participants.

In conclusion, the participants' BMI and EAT-26 scores significantly influence their performance in the Go/No-Go task, especially in blocks with foods as Go cues.

Supplementary materials

Supplementary table 15

	Sum Sq	Mean Sq	F (df)	p value	
Stimulus Type	0.0	0.0	F (1, 136.8) = 1.5486	0.215	
BMI	0.6	0.6	F (1, 172) = 24.1382	< 0.001	***
EAT26	0.0	0.0	F (1, 172.1) = 0.1104	0.740	
Stimulus Type * BMI	0.0	0.0	F (1, 18512.1) = 0.7739	0.379	
Stimulus Type * EAT26	0.4	0.4	F (1, 18514.2) = 15.7056	< 0.001	***
BMI * EAT26	0.1	0.1	F (1, 172) = 5.5738	0.019	*
Stimulus Type * BMI * EAT26	0.7	0.7	F (1, 18520.3) = 28.3259	< 0.001	***

Complete results of the linear mixed model on RTs during Go trials in the Go/No-Go task data from the three experiments reported in chapter 1, 2, and 3.

Supplementary table 16.

	Sum Sq	Mean Sq	F (df)	p value	
Trial Type	19.3	19.3	F (1, 14206.5) = 623.84	< 0.001	***
Stimulus Type	0.1	0.1	F (1, 144.9) = 3.08	0.081	.
EAT26	0.8	0.8	F (1, 822.4) = 26.62	< 0.001	***
Trial Type * Stimulus Type	0.0	0.0	F (1, 13867.4) = 0.47	0.494	
Trial Type * EAT26	0.3	0.3	F (1, 27895.1) = 10.75	0.001	**
Stimulus Type * EAT26	0.0	0.0	F (1, 27883.9) = 0.9	0.343	
Trial Type * Stimulus Type * EAT26	0.2	0.2	F (1, 27895.1) = 5.61	0.018	*

Complete results of the linear mixed model accuracy in the Go/No-Go task data from the three experiments reported in chapter 1, 2, and 3.

General discussion

The aim of my thesis was to pinpoint the processes implicated in eating disorders and obesity, and their underlying neural substrates. To this end, in particular, I investigated the subliminal processing, attention, and inhibition towards foods and non-foods in eating disorders patients, obese individuals, and asymptomatic participants. I followed an inclusive dimensional approach and considered the participants' BMI and eating disorder symptoms as continuous predictors of the participants' performance, with no categorical distinction into diagnostic labels. In all three studies, I have used the participants' EAT-26 scores as a measure of self-reported eating disorders symptomatology (Garner et al., 1982), using the validated Italian version (Dotti & Lazzari, 1998). EAT-26 is a measure that is sensitive to various aspects of ED symptomatology that characterize anorexic, bulimic, and binge-eating disorder patients: its items inquire into various symptoms and behaviors, such as the pathological avoidance of certain foods, shape preoccupations, body-image disturbances, binge eating behaviors, and effort to control the amount of food eaten. Its final score is considered indicative of the likelihood of having an eating disorder, and studies have shown its efficacy in detecting ED risk also in samples including overweight and obese individuals (Hadjigeorgiou et al., 2012; Woo, 2014).

In these three studies, I set out to investigate whether ED symptomatology and BMI influence subliminal processing of food and non-food images, by using the bCFS paradigm, and whether they influence inhibition towards foods and non-foods by using the Go/No-Go task. Moreover, I have investigated how does tDCS stimulation influence subliminal processing times and inhibition, what are the neural substrates of suppression and inhibition, and how do they relate to the participants' BMI and ED risk. I have chosen to concentrate on *attention*, in the for of subliminal processing alterations, and *inhibition* because they are key aspects of these disorders. On one hand, *attention* towards food has been shown to be altered in ED patients and obese individuals: more specifically, it has been proposed that early attentional biases are indicative of alterations of early, automatic attentional components, associated with more involuntary, less controlled mechanisms, whereas later attention components are thought to reflect the slower top-down mechanisms of voluntary or more controlled processing (Nijs & Franken, 2012; Werthmann et al., 2015). The study of subliminal processing can be informative as to what happens outside of awareness, especially as this implicit phase of stimulus processing has a strong influence on eating choices (Finlayson et al., 2008; Forman et al., 2018; Takada et al., 2018). On the other hand, *inhibition* is also a central characteristic of ED ad obesity; indeed, it has been suggested that a model of eating disorders as a spectrum of impulse control disorders – with anorexia nervosa restrictive subtype at one end, and binge eating disorder symptoms at the other – would provide a more informative classification and better treatment possibilities (Brooks et al., 2012).

From the results of the studies, I can conclude that the ***participants' BMI and risk for eating disorders do influence both the subliminal processing of stimuli, and inhibition***, at later stage of stimulus processing. However, I failed to consistently find a food specific alteration of subliminal processing, as only Study 1 reported a significantly different effect of BMI and EAT-26 scores between foods and non-foods (compare Figure 9 with Figure 15A and Figure 19). This could be due to several reasons.

First, in Study 1 we recruited a clinical population which was comprised of participants showing more ED symptoms, and a higher percentage of overweight and obese individuals (see the 'Experimental samples' section reported in the Appendix). It is therefore possible that a food-specific food bias at a subliminal level is only present in a clinical population. As early attentional biases are indicative of automatic attention components, this result could support the theory (also proposed by Nijs & Franken, 2012), that only individuals with problems in the regulation of food intake might show an enhanced attentional bias for food. This finding would take this theory one step further, with the postulation that only individuals at ED symptoms show a food bias at a subliminal phase of stimulus processing. Another possibility is that the differences in the experimental stimuli between study 1 and studies 2-3 might have influenced this result. The experimental stimuli used in the first study depicted foods with overall higher caloric content than the ones used in Studies 2-3 [M_{study1} = 193 kcal (168), $M_{study2,3}$ = 175 kcal (173)], although this difference was not statistically significant [p = 0.69], and it is possible that only salient, high-caloric foods lead to a difference in subliminal processing. Furthermore, unlike the stimuli used in study 2 and 3, stimuli in study 1 were not matched for spatial frequency, a characteristic that has been shown to influence suppression times (Gray et al., 2013). However, it is important to point out that comparing the spatial frequency of both food and non-food pictures used in study 1 with the ones used in studies 2 and 3, we did not find a significant difference [all ps > 0.49]. In addition, if the difference in subliminal processing between foods and non-foods were due only to low-level visual features, it is unlikely that it would have interacted with participants' characteristics, such as BMI and EAT-26 scores. It is therefore likely that a ***difference in processing between foods and non-foods is only present at a subliminal level in a clinical population***. Future research should confirm these results, by replicating them with different sets of stimuli. It would also be interesting to investigate how a subliminal processing bias influences conscious attitudes towards food, and food-related decision making processes.

At a later stage of stimulus processing, as measured by RTs during Go trials in the Go/No-Go task, we consistently find an influence of the participants' BMI and their EAT-26 scores on the RTs

in the Go trials when participants are responding to food images (see the 'Results' section of the Appendix, Figure 26). RTs on go trials of affective Go/No-Go tasks have been interpreted as reflecting an attention/response bias or as an approach tendency (Meule et al., 2014; Murphy et al., 1999), but these interpretations are speculative (Meule, 2017). As responding fast makes it more difficult to refrain from responding to no-go trials, longer suppression times can also be interpreted as an attempt not to make mistakes on difficult blocks. Moreover, I observed that the participants' self-reported ED symptoms, in groups with a higher prevalence of participants with high EAT-26 scores, influence their accuracy. Individuals with high self-reported ED symptoms tend to respond faster, and make more mistakes, in blocks when they are asked to respond only to food cues (see Figure 27). As Meule points out in his opinion piece (2017), it is not trivial to interpret the results of an affective Go/No-Go task, as participants are responding to a salient stimulus in half of the blocks and refraining from responding to a salient stimulus on the other half of the blocks. For what regards food in particular, some authors find that more mistakes are made in blocks in which food serves as the no-go cue by hungry participants and by participants with high impulsivity and food craving (Loeber et al., 2012; Meule & Kübler, 2014), a result that goes in the opposite direction of the results found in this thesis. However, it is possible to speculate that finding blocks with food as the no-go cue more difficult would lead the participants with a high ED score to respond slower and to make fewer mistakes, a result which is congruent with what we find. Whichever the interpretation, what emerges from these results is *that higher ED symptoms significantly interferes in task performance at the Go/No-Go task*, possibly because the inhibition mechanisms are affected by the stimuli salience.

In addition to these findings, a novel result has emerged from these studies: *higher BMI leads to a heightened threshold for visual awareness, which is independent of type the of stimuli*. This result is consistent throughout the three studies and in line with the hypothesis that an attentional deficit characterizes obese individuals (Cook et al., 2017; Prickett et al., 2015), and extends this evidence by showing that this impairment may also affect subliminal perception. In multiple sclerosis, a higher threshold of perceptual awareness has been linked to white matter damage and altered connectivity between distant cortical areas (Reuter et al., 2007, 2009), and numerous studies have reported white matter alterations in obese individuals, especially in the corpus callosum and fornix (see for instance Kullmann et al., 2015; Xu et al., 2013). Interestingly, modulation of the right dorsolateral PFC in the study reported in chapter 2 has proven efficacious in reducing this effect, leading to shorter suppression times especially in individuals with a high BMI (see Chapter 2, Figure 15). The dorsolateral PFC has a key role in attention and working memory, and its dysfunctional

activation has been proposed as a key element in the etiology of obesity (Alonso-Alonso & Pascual-Leone, 2007). Furthermore, in individuals with a high BMI, we found a correlation between suppression times and grey matter density in the right PFC and in areas involved in the reward network, such as the insula and the orbitofrontal cortex. Based on these results, it is possible to speculate that the same areas that are involved in the unbalance between the reward and control systems are also involved in affecting the length of suppression in the bCFS task. Future research should investigate whether a higher threshold of visual awareness characterizes obesity using other paradigms, such as visual masking; moreover, it would be interesting to further explore whether modulation of the prefrontal cortex affects attentional biases in obesity at a conscious level of stimulus processing, a hypothesis that we have tested but couldn't confirm, using different paradigms, and exploring the possible difference in the effects following online and offline stimulation.

Future research should address many issues that we have just touched upon in my thesis. First of all, to explore the effects due to the *stimuli* used, it would be interesting to see if these results can be replicated using other sets of stimuli. It would also be interesting to explore if highly salient stimuli, such as high-calorie foods chosen by the participants before the task, would have a stronger influence on suppression times. Also relatedly to the stimuli used, it should be explored how individual liking and wanting of certain foods might affect suppression times. In addition, to explore the effect of the *characteristics of the participants' sample*, it would be of interest to see if our result that the processing of foods at a subliminal level is affected only in a clinical sample can be replicated. Moreover, if would be interesting to explore whether the activation of the PFC trough tDCS improves subliminal stimulus processing in a clinical sample depending on the stimulus type, and how a subliminal food bias relates to the processing of stimuli above the threshold of awareness. Another sample-related factor that should be explored is whether there are gender differences in the subliminal processing of stimuli, an issue that we have not considered in our studies, but has been shown to be very important in obesity and ED. Furthermore, it would be interesting to replicate in a clinical sample, and in participants with a wider range of BMIs, our results that grey matter density differences in key areas of the reward and control system correlate with suppression times.

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