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CICLO XXXI

THE IMPULSIVE BRAIN:

NEW INSIGHTS INTO THE NEURAL CORRELATES OF BINGE EATING IN NORMAL WEIGHT POPULATION

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The present work is the result of a project carried out over a three-year period at the Department of General Psychology, University of Padova (Italy), under the supervision of Dr. Chiara Begliomini and a six-months visiting research period at the Department of Neurology, Max Planck Institute for Human Cognitive and Brain Sciences of Leipzig (Germany), under the supervision of Dr. Annette Horstmann.

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LIST OF ABBREVIATIONS

AAL: Automated Anatomical Labeling

ACC: Anterior Cingulate Cortex

AI: Anterior Insula

AN/BP: Anorexia Nervosa Bingeing Purging Type

AN: Anorexia Nervosa

APA: American Psychiatric Association

AR: Art Repair

BA: Brodmann Area

BE: binge eaters

BED: Binge Eating Disorder

BES: Binge Eating Scale

BIS/BAS: Behavioral Inhibition/Behavioral Activation Systems

BIS-11: Barratt Impulsiveness Scale

BMI: Body Mass Index

BN: Bulimia Nervosa

BOLD: Blood Oxygenation Level-Dependent

CAT: Computational Anatomy Toolbox

CSF: Cerebrospinal Fluid

DC: Degree Centrality

DEBQ: Dutch Eating Behavior Questionnaire

DLPFC: Dorsolateral Prefrontal Cortex

dPM: dorsal premotor area

DSM: Diagnostic and Statistical Manual

EAT: Eating Attitude Test

ECM: Eigenvector Centrality

EHI: Edinburgh Handedness Inventory

EPI: Echo Planar Imaging

fMRI: Functional Magnetic Resonance Imaging

FOV: Field of View

FWE: Family Wise Error

FWHM: Full-Width at Half-Maximum

GLM: General Linear Model

GLME: Generalized Mixed Effects

GM: Grey Matter

GMV: Grey Matter Volume

GP: Globus Pallidus

HRF: Hemodynamic Response Function

IFG: Inferior Frontal Gyrus

IPL: Inferior Parietal Lobule

ISI: Inter-Stimulus-Interval

ITI: Inter-Trial-Interval

LC: Locus Coeruleus

LME: Linear Mixed Effects

M1: Primary Motor Cortex

MFG: Middle Frontal Gyrus

MNI: Montreal Neurological Institute

MVPA: Multi-voxel Pattern Analysis

NAc: Nucleus Accumbens

Non-BE: non binge eaters

OFC: Orbitofrontal Cortex

PFC: Prefrontal Cortex

Pre-SMA: Pre-Supplementary Motor Area

REML: Restricted Maximum Likelihood

RFT: Gaussian Random Field Theory

RFX: Random Effects Analysis

ROI: Region of Interest

rsfMRI: resting-state functional Magnetic Resonance Imaging

RTs: Reaction Times

SCA: Seed-based connectivity analysis

SFG: Superior Frontal Gyrus

SG: Supramarginal Gyrus

SMA: Supplementary Motor Area

sMRI: structural Magnetic Resonance Imaging

SN: Substantia Nigra

SPECT: Single Photon Emission Computerized Tomography

SPM12: Statistical Parametric Mapping 12

SSD: Stop Signal Delay

SSRT: Stop Signal Reaction Time

SST: Stop Signal Task

STN: Sub-Thalamic Nucleus

Th: Thalamus

TIV: Total Intracranial Volume

TMS: Transcranial Magnetic Stimulation

TR: Repetition Time

VBM: Voxel-based Morphometry

VTA: Ventral Tegmental Area

WHO: World Health Organization

WM: White Matter

YFAS: Yale Food Addiction Scale

Synopsis

Despite humans are known to embody a unique ability to self-regulate, sometimes they act impulsively (Hofmann et al., 2009). Generally, impulsive behaviors may derive from the co-occurrence of dysfunctional inhibitory processes and strong urges to act (Bari and Robbins, 2013). In more detail, our impulses, if not appropriate to the situation, are usually kept under control by inhibitory mechanisms; however, when inhibition fails, impulsive acts may stem (Bari and Robbins, 2013). Researchers and mental health experts agree that impulsivity can boost the risk for a range of maladaptive behaviors; as an example, over the last decades, mounting evidence has revealed a role of impulsivity at the core of the development of substance addictions (Dawe and Loxton, 2004; Kale et al., 2018; Loxton, 2018).

Drawing upon the similarities between the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV, APA 2000) criteria for addictions and overeating (Gearhardt et al., 2009), a compelling hypothesis is that the same kind of impulsivity aspects that lead people to abuse alcohol or drugs may also lead to an unhealthy relationship with food. In support of this assumption, recent studies have shown that individuals with eating disorders and obesity are more impulsive than healthy people, especially when binge eating behavior (i.e., episodes of loss of control eating) is present (Waxman, 2008). However, given that most of these investigations focused on people with full-blown eating or weight disorders, it is still unclear whether higher impulsivity characterized these individuals also before the dysregulated eating began or if it developed as a result of it. Thus, to date, little is known about the role of impulsivity as a potential risk and predisposing factor for loss of control over eating within the general population.

Based on these premises, the aim of the present thesis is to shed some new light on the role of impulsivity at the roots of binge eating behavior. The overall structure of the thesis takes the form of eight chapters. Starting from the contemporary state of the art, Chapter 1 provides an overview of the definitions of the various facets of impulsivity and their neural correlates. Subsequently, Chapter 2 reviews some of the behavioral and neuroimaging studies exploring the relationship between impulsivity and eating behavior. From the existing state of knowledge, I emphasize the need for an in-depth exploration of the role of different impulsivity-related aspects in normal-weight individuals with binge eating. Hence, at the beginning of Part II, I outline the primary purposes of this project. *First*,

given the well-established impact of eating and weight disorders on cognitive and neurobiological processes (Horstmann et al., 2015; Smith et al., 2011; van den Akker et al., 2014), I decided to focus on a non-clinical population of normal-weight individuals with binge eating. In this way, I aimed to provide a clear account of the role of impulsivity as a hallmark of this behavior, regardless of weight status. *Second*, given that impulsivity comprises several related forms that depend on distinct neuropsychological processes and neural systems (Dalley and Robbins, 2017), I chose to assess this construct multi-modally, with a combination of self-reported, behavioral and neuroimaging measures, in the same study population, to disentangle the relative contribution of each component in the characterization of binge eating (Filbey and Yezhuvath, 2017).

The second part of the thesis cover four experiments of my PhD project, in which, by comparing two groups of normal-weight individuals with and without binge eating, I aimed to explore:

- General trait impulsivity, as assessed by self-reported questionnaires (Chapter 3);
- Response inhibition abilities toward food, measured with a food-specific Go/No-Go, GNG (Chapter 4) and a food-specific Stop Signal Task, SST (Chapter 5);
- Task-related brain activity during the execution of both the GNG and the SST (*Task-based functional MRI studies*; Chapters 4 - 5);
- Functional brain connectivity at rest (*Resting-state functional MRI study*; Chapter 6);
- Brain morphometry (*Voxel-based morphometry study*; Chapter 7).

A more complete account of the main aims, hypotheses and measures of each experiment will be provided in the introductory part of the *Experimental Work*.

In conclusion, the last chapter (Chapter 8) will draw upon the entire thesis, tying up the various theoretical and empirical strands in order to discuss the main findings of the experiments and their implication to future studies into this area.

To the best of my knowledge this is the first research investigating impulsivity, with multiple behavioral and neuroimaging measures, in normal-weight non-purging individuals with binge eating. I strongly believe that this project may offer an important opportunity to advance the understanding of the role of impulsivity at the roots of binge eating. Moreover, it may provide valuable insights for prevention and treatment interventions, addressing impulsivity with specific training approaches, psychotherapy and novel neuro-modulatory techniques (i.e., real-time fMRI neurofeedback).

Sinossi

L'impulsività è un concetto multidimensionale che si riferisce alla tendenza a reagire in modo rapido e non controllato ad alcuni stimoli senza considerare le conseguenze negative che ne possono derivare. In generale, un comportamento impulsivo può essere definito come la risultante dell'interazione di due fattori: un controllo inibitorio disfunzionale e un forte impulso ad agire (Bari e Robbins, 2013). Più nello specifico, se nella maggior parte dei casi i nostri impulsi sono tenuti a bada da un'efficiente capacità inibitoria, quando questa fallisce, il risultato può essere la messa in atto di azioni non pianificate, rischiose o inappropriate alla situazione.

Ad oggi esiste un generale consenso sulla relazione tra impulsività e lo sviluppo di un ampio range di comportamenti maladattivi, come ad esempio l'abuso di sostanze (Kale et al., 2018; Hogart, 2011). Recentemente, sulla base dell'ipotesi che iperalimentazione e dipendenza da sostanze condividano caratteristiche comportamentali e neurobiologiche comuni (Gearhardt et al., 2009), alcuni ricercatori hanno ipotizzato che gli stessi tratti 'impulsivi' che predispongono alle dipendenze, siano anche coinvolti nel discontrollo nei confronti del cibo (o *binge eating*). Diverse ricerche hanno fornito un preliminare supporto a questa tesi, riportando una chiara associazione tra impulsività, obesità e disturbi alimentari, soprattutto quando episodi di abbuffate erano presenti (Waxman, 2009). Purtroppo però lo studio di persone con una storia di disturbo alimentare o del peso può fornirci limitate informazioni sul motivo per cui alcune persone – e non altre – tendano a perdere il controllo nei confronti del cibo. Soprattutto non si chiarisce il ruolo dell'impulsività nel discontrollo alimentare: è un tratto pre-esistente e potenzialmente di rischio per lo sviluppo delle abbuffate o è invece la risultante del perpetuarsi di questi comportamenti?

Sulla base di queste premesse, il presente elaborato intende mettere in luce il ruolo dell'impulsività alla base del comportamento di *binge eating*. La struttura della tesi si sviluppa in otto capitoli divisi in due parti: una sezione teorica e una sperimentale. Nella prima sezione, partendo dallo stato dell'arte, il Capitolo 1 si concentra sulla definizione delle diverse componenti dell'impulsività e sulle loro basi neurobiologiche. Seguendo la stessa struttura, poi, il Capitolo 2 si sofferma sugli studi che hanno indagato l'impulsività e i suoi correlati in relazione al comportamento alimentare.

Dall'analisi della letteratura ho quindi messo in luce lo scopo del progetto di dottorato: l'indagine di diverse componenti dell'impulsività in individui normopeso il cui comportamento

alimentare risulta caratterizzato dalla presenza di episodi di *binge eating*. In particolare, visto l'impatto di disturbi alimentari e del peso sui processi cognitivi e neurobiologici (Horstmann et al., 2015; Smith et al., 2011; van den Akker et al., 2014), ho deciso di condurre il mio progetto considerando una popolazione sana normopeso. In questo modo, i risultati possono fornire importanti informazioni per la comprensione del ruolo dell'impulsività come caratteristica alla base di questo comportamento, indipendentemente dalla presenza di una diagnosi conclamata di disturbo alimentare o del peso. Inoltre, poiché il termine impulsività racchiude in sé varie componenti, sottese da diversi substrati neurobiologici (Dalley e Robbins, 2017), ho scelto di indagare questo costrutto usando molteplici misure (questionari, compiti comportamentali, e tecniche di neuroimmagine), nella stessa popolazione, al fine di comprende il contributo relativo di ogni dimensione nella caratterizzazione del binge eating (Filbey and Yezhuvath, 2017).

La seconda parte della tesi [*Experimental Work*] si compone quindi dei quattro studi del progetto di dottorato, nei quali, confrontando due gruppi di persone con e senza episodi di binge eating, ho esplorato i seguenti aspetti:

- Impulsività di tratto, tramite questionari autosomministrati (Capitolo 3)
- Capacità di inibizione della risposta motoria nei confronti del cibo, attraverso due paradigmi: Go/No-Go, GNG (Capitolo 4) e Stop Signal Task, SST (Capitolo 5)
- Attività cerebrale durante l'esecuzione di entrambi i compiti, GNG e SST (*task-based fMRI study*; Capitolo 4 e 5)
- Connettività funzionale a riposo (*resting-state fMRI study*; Capitolo 6)
- Morfometria cerebrale (*Voxel-based Morphometry study*; Capitolo 7)

Una descrizione dettagliata di obiettivi, ipotesi e misure di ogni esperimento verrà ripresa nell'introduzione alla parte sperimentale (Parte II, *Experimental Work*).

In conclusione, il Capitolo 8, sulla base del cappello teorico introduttivo e dei risultati degli esperimenti, propone una discussione generale dei risultati e le loro possibili implicazioni per future ricerche in questo campo.

Credo che questo progetto possa fornire importanti spunti per l'approfondimento della comprensione dei meccanismi alla base del discontrollo alimentare e il ruolo dell'impulsività come fattore prodromico allo sviluppo di questo comportamento.

In generale, questo lavoro e gli studi che ne deriveranno potranno essere d'aiuto per la definizione di interventi di prevenzione e trattamento rivolti a persone a rischio di sviluppo di comportamenti alimentari disfunzionali, all'interno della popolazione generale.

PART I

THEORETICAL BACKGROUND

Chapter 1
IMPULSIVITY & INHIBITION

"Can you resist the dessert tray when eating out at restaurants? Do you enjoy the thrill of pulling the arm on a slot machine in anticipation of the results? Do you succumb to purchasing candy or magazines in the checkout line of the grocery store?" (Stevens, 2017).

All these questions pertain to different aspects of the construct of impulsivity. Although a firm definition of impulsivity continues to be debated in the literature (Evenden, 1999; Smith et al., 2007; Whiteside and Lynam, 2001), there is a general agreement on the description of impulsivity as a multi-dimensional trait, characterized by different facets that can be gathered into the classic definition of "*actions poorly conceived, prematurely expressed, unduly risky or inappropriate to the situation that often result in undesirable consequences*" (Daruna and Barnes, 1993). As such, impulsivity can be either part of everyday life situations as well as be peculiar of a number of psychopathologies (behavioral and drug addictions, personality disorders, obsessive-compulsive disorder etc.; Robbins et al., 2012). It arises in common behaviors when, for example, we have to make a split second decision on whether to cross the street or not, or to buy a chocolate bar during checkout at the grocery store. But it may also be a characteristic feature of pathological conditions when the inability to withhold responses becomes compulsive, inappropriate to the situation and persists even without an obvious relationship with the overall goal (Stevens et al., 2017). Importantly, in addition to its description as a key feature of many psychiatric disorders, impulsivity has also been described as a possible risk factor for some of these conditions. For example, trait impulsivity has been shown to predict the chances of initiating smoking or become a heavy drinker (Grano et al., 2004). Therefore, given its potentially negative implications (e.g., progression from impulsivity to compulsivity; see Robbins et al., 2012), taking the investigation of impulsivity a step further by studying its cognitive and neurobiological underpinnings, can provide fruitful insights into its mechanisms, as well as provide hints for possible interventions to treat impulsivity in its pathological forms (Stevens et al., 2017).

The overall goal of this section is to provide an overview of the various dimensions of impulsivity and the measures that have been used to investigate them. This Chapter aims at providing

a clear outline of those aspects that will be used in Chapter 2 to discuss their possible role in the development of the tendency to lose control over eating behavior in the general population.

1.1 FRACTIONATING IMPULSIVITY

The efforts to define and measure the multidimensional construct of impulsivity have been complicated by the large number of theoretical models of personality in which this construct has been conceptualized (Eysenck and Eysenck, 1991; Cloninger et al. 1987, Gray et al., 1970). In fact, while there tends to be general agreement on its classic definition (see Daruna and Barnes, 1993), the complex nature of impulsivity is mirrored by the several heterogeneous dimensions that this term captures (Sperry et al., 2016). Most of these dimensions are related to different, even if overlapping, aspects, such as the tendency toward maladaptive behavior, the inability to inhibit responses, the performance of automatic urges or the propensity to avoid delay (Gullo and Potenza, 2014). For this reason, it is now commonly accepted that relying on a unitary definition of the impulsivity construct and the use of only one generic term (i.e., impulsivity) is outdated and misleading (VanderVeen et al., 2013). Hence, in the study of this broad concept, it is critical to clarify the nature of its various components, as they relate to specific contexts and conditions, and to investigate them with precise measures and multimodal approaches (Craighead and Nemeroff, 2004).

1.1.1 The Dual-process models of impulsivity

In the attempt to identify these components, theories concurred with a two-factor structure as a good starting point in defining impulsivity (Swann et al., 2002; Dawe et al., 2004). The first factor is related to *reward sensitivity*, responsible for the attraction of individuals toward unsafe decisions. It could be thought as a motivational aspect that drives individuals toward choices with the lure of reward, despite negative outcomes. For instance, in the case of drug abuse, reward sensitivity would account for the initial attraction to the substance and for the maintenance of the addiction by keeping the benefits of the substance in forefront of the person's mind, masking the downsides (Dawe et al., 2004). The second factor refers to *rash impulsiveness*. This component is closely linked to the lack of inhibitory control or response inhibition, hence the inability of the individual to stop from acting out a certain behavior or response (e.g., taking the drug). Maladaptive behaviors are more likely to persist in persons who display rash impulsiveness, because of their diminished ability to inhibit approach tendencies (Dawe et al., 2004). These dimensions, with independent cognitive and neurobiological substrates (Dalley et al., 2011), may intervene in different stages of the impulsive behavior as well as

operate in tandem (Dawe and Loxton, 2004; Davis et al., 2013). Nevertheless, even though both factors are known to be involved in impulsive behaviors, some authors maintain that inhibitory control is one of the major top-down processes involve in self-regulation (Aron, 2007), associated with executive control capacity (Bari and Robbins, 2013). Failure of inhibitory control will indeed reduce the capability to self-regulate and weaken control over impulsive and unwanted behaviors (Hofmann et al., 2008).

1.1.2 Impulsivity and Inhibition

Drawing upon this assumption, authors have underlined the strong link between impulsivity and inhibitory control (Bari and Robbins, 2013; Hoffman et al., 2008). Impulsivity has been indeed generally regarded as the consequence of defective inhibition. In more detail, an impulsive action could be defined as the result of deficits in the ability to inhibit responses (i.e., lack of inhibitory control) when strong urges (or impulses) arise (Hofmann et al., 2009).

The concept of inhibition (or inhibitory control), and its relation with impulsivity, has been extensively described in Bari and Robbins' model (2013; Figure 1.1). This model elucidates the different facets of inhibitory control, a construct that refers to a wide range of dimensions, both at the behavioral and the cognitive level (Bari and Robbins, 2013). Inhibitory control represents indeed a loose collection of behavioral and cognitive processes that are all crucially involved in self-regulation: defective general inhibitory control may indeed lead to unwanted, impulsive and eventually maladaptive acts (Fuster, 2008). As an example, deficits in cognitive control can affect our ability to disengage attention from irrelevant material, increasing unwanted thoughts and rumination (Joormann, 2010). Whereas, defective behavioral inhibition can lead to an inability to inhibit our actions (e.g., drinking or eating more than we wanted to, despite the negative consequences; Smith and Mattick, 2013; Svaldi et al., 2014). This latter aspect of inhibitory control (i.e., behavioral inhibition) is strongly correlated with measures of trait impulsivity (Logan et al., 1997; Enticott et al., 2006) and it appears to have a pivotal role, at the core of the impulsivity construct (Barkley, 1997; Bari and Robbins, 2013).

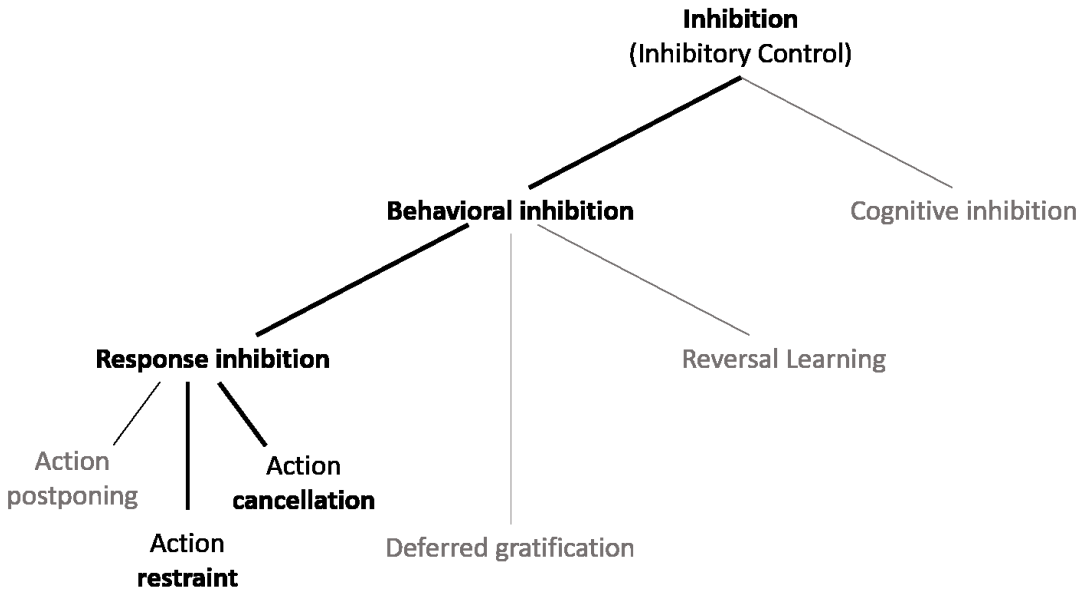


Figure 1.1. Diagram of a subdivision between behavioral and cognitive inhibition with corresponding behavioral tasks used to measure impulsive behaviors, proposed by Bari and Robbins (2013). In the diagram I highlighted the terms that are of interest in the context of our project. Image adapted from: Bari and Robbins (2013).

In the model, Bari and Robbins (2013) outlined three components of behavioral inhibition: (i) the ability to inhibit responses (i.e., impulsive action), (ii) the ability to delay gratification (i.e., impulsive choice) and (iii) reversal learning. Among these factors, response inhibition has been suggested to serve as an endophenotype, or a 'proxy', for the study of impulsivity and its neurobiological underpinnings (Aron, 2007; Aron and Poldrack, 2005). Nevertheless, addressing the diversity of its components, by means of specific paradigms and measures, will help disentangle the relative contribution of each aspect in the development and maintenance of impulsive behavior.

The next paragraph will provide an overview of some of the most widely used measures to assess impulsivity (paragraph 1.2). Given that trait impulsivity and inhibitory control play a crucial role in impulsive behavior (Aron, 2007), particular attention will be placed in the description of rash impulsiveness (paragraph 1.2.1) and response inhibition abilities (paragraph 1.2.2); whereas, reward sensitivity will be discussed in the context of its possible impact on inhibitory control abilities (paragraph 1.2.3). Furthermore, an account of the neurobiological underpinnings of these dimensions will be outlined in paragraph 1.3.

1.2 TRAIT AND STATE IMPULSIVITY

Impulsivity is one of those personality traits that can be both self-assessed and observable (Reynolds et al., 2006). Accordingly, the leading methods for the measurement of impulsivity include self-reported measures (e.g., personality questionnaires) and behavioral laboratory paradigms (e.g., response inhibition tasks; de Wit, 2009). On one hand, self-reported measures rely on the individual self-perceptions of behavior and assess behavioral tendencies averaged across situations and times, thus they give a comprehensive account of the stable patterns of behavior (Nettle and Penke, 2010). On the other, behavioral tasks can be more reliable than self-reported questionnaires to predict specific behaviors in various situations, measuring overt behavior related to certain dimensions of impulsivity (Reynolds et al., 2006). Thus, the firsts are thought to be more appropriate to measure '*trait impulsivity*', while the seconds are more suitable for the assessment of the so-called '*state impulsivity*'. The definitions of trait and state impulsivity will be elucidated in the next paragraphs (paragraphs 1.2.1 and 1.2.2). Nonetheless, it must be said that the distinctions between subtypes of impulsivity (i.e., trait and state impulsivity) has to be considered more quantitative than qualitative, with the measures assessing different but still interrelated forms of this construct (Bari and Robbins, 2013).

1.2.1 Trait Impulsivity: definition and measures

Rash spontaneous impulsiveness refers to the "*acting on the spur of the moment without being aware of any risk involved*" (Eysenck et al., 1984). This tendency is thought to reflect '**trait-impulsivity**', namely impulsivity as a stable personality characteristic of the individual (Bari and Robbins, 2013). The most widely used measures to assess impulsivity as a trait are self-reported questionnaires, which have been defined as "*convenient and reliable methods for assessing stable individual differences, drawing on subjects' experiences over a far greater span of time than is available in the laboratory*" (Deyoung and Gray, 2009). In clinical settings, self-reported measures have been effective in predicting the development of some risky impulsive behaviors, such as alcohol use (Kirisci et al., 2007). High *trait* impulsivity, indeed, is thought to predispose individuals to impulsive behaviors, which in turn may lead to further *state* impulsivity, thus a more stable failure to control and inhibit behavior (Balodis et al., 2009).

Measures of trait impulsivity

In both clinical and non-clinical research, two examples of frequently adopted questionnaires are the Barratt Impulsiveness Scale (BIS-11; Patton, 1995) and the Behavioral Approach/Inhibition System (BIS/BAS; Carver and White, 1994). The BIS-11 brought research of impulsivity to gain huge impetus and it has been influential in shaping current theories of impulse control, playing a role also in the study of the biological, psychological, and behavioral correlates of impulsivity (Reise et al., 2013). The value of this scale lies in the ability to capture the heterogeneity of the impulsivity term. As such, it involves different subjective evaluations of one's performance and behavior that refers to three aspects (or subscales): 'motor', 'attentional,' and 'non-planning' impulsivity (see Appendix A). These subscales cover three key components of trait impulsivity, more specifically: *motor* impulsivity refers to the tendency to act without forethought; *attentional* impulsivity concerns the inability to focus attention and concentrate; *non-planning* impulsivity refers to the lack of future orientation (Patton, 1995). Patton et al (1995) suggested that these subfactors would be helpful in defining the general impulsivity trait and its relationship with different clinical syndromes (e.g., impulsive, personality and mood disorders). Accordingly, the BIS-11 has been used in a variety of clinical contexts, revealing high levels of impulsivity in different psychopathologies such as substance abuse, attention deficit hyperactivity disorder (ADHD), mood and eating disorders (Stanford et al., 2009; Meule, 2013; Lane et al., 2007; Bond et al., 2004; Peluso et al., 2007). Unfortunately, despite researchers agreed on impulsivity as a multi-dimensional construct, the majority of the studies using BIS-11 have reported only total scores, ignoring the subscales' scores (Stanford et al., 2009). However, because of the complexity of the impulsivity construct, it is critical to assess the relative contribution of each subscale to accurately characterize the level of impulsiveness of each individual. A more detailed investigation of the subscales would in fact bring uniformity in the impulsivity definition and would help clarify its relation with different psychopathologies (Stanford et al., 2009).

Additional information for the assessment of impulsivity traits could derive from the BIS/BAS questionnaire (Carver and White, 1994). This self-reported measure refers back to Gray's theory of regulation of behavior (Gray, 1970) according to which two core systems are involved in behavioral regulation: the *inhibition* and the *activation* systems. The first one deals with aversive motivation and avoidance, inhibiting behavior that potentially leads to negative outcomes; whereas, the latter deals with appetite motivation and approach behavior and it is strongly sensitive to signals of reward (Gray, 1970). In line with this model, Carver and White (1994) developed the BIS/BAS questionnaire (Appendix A), which measures the relative contribution of these two different systems in behavioral

regulation: the behavioral inhibition system (BIS) and behavioral activation system (BAS). The BIS subscale provides a measure of the sensitivity to possible negative events when they occur, hence, the sensitivity of the inhibition system that Gray (1970) refers to as the individual difference in the "*proneness to anxiety*" (Leone et al., 2001). Whereas, the BAS subscale includes three dimensions: drive, fun seeking and reward responsiveness. Even if distinct in three categories, all BAS items deal with potentially rewarding events and how the individual responds to them (Leone et al., 2001). A support for the validity of the BIS/BAS scale includes a variety of correlations with psychological measures (Brenner et al. 2005). Hypo- or hyperactivity of the BAS and BIS have been indeed implied in internalizing and externalizing behavioral disorders (Brenner et al., 2005). For example, overactivity of the BIS has been associated with anxious personality traits (Gray and McNaughton, 2000), which may in turn predispose to anxiety disorders (McNaughton and Corr, 2004). Underactive BIS might be responsible for disinhibition, observed for example in ADHD (Quay, 1997). Lastly, depressive symptoms have been linked to an underactive BAS, leading to lower appetitive motivation (Fowles, 1988). Thus, this scale may give useful hints when trying to give a complete account of self-regulation and impulsive behavior, in which both the tendency to inhibit and to approach play cardinal roles.

In sum, both questionnaires give the opportunity to furthering our understanding of different but overlapping aspects of impulsive behavior, confirming its non-unitary nature. The use of both measures is of extreme importance given the assumption that impulsive behaviors may derive from the co-occurrence of a lack of inhibitory abilities together with enhanced approach tendencies (Hofmann et al., 2008). In addition, given that self-reported measures are believed to provide a good measure of potential stable traits and personality characteristics (Bari and Robbins, 2013), understanding the relationship between these trait aspects and different psychopathologies may prospectively result in more effective diagnosis and treatment (Stanford et al., 2009). Nevertheless, these measures can be potentially contaminated by subjective bias (e.g., past life events; lack of insights of inhibitory control deficits); thus, to circumvent these issues, behavioral tasks may be used to provide additional information of individual's behavior.

1.2.2 State Impulsivity: definition and measures

In contrast to self-reported measures, behavioral tasks can be useful to detect more narrowly defined components of impulsivity, such as response inhibition abilities (Bari and Robbins, 2013). Inhibition is considered to be one of the core components of executive control (Aron, 2007). This mechanism has been initially described by Logan (1985) in his '*executive control model*', according to

which inhibition is a top-down process where a high order system interacts and controls a lower order system (Logan, 1985). The lower order or subordinate system relies on the higher order one, both for instructions and resources, such as the higher order executive system can stop the choice to act out an intention of the subordinate system and replace it with a new intention (Band and van Boxtel, 1999). In this context, dysfunctional response inhibition (or response impulsivity) refers to an impairment of the ability to stop responses, following changes in the environmental circumstances (Fineberg et al., 2014).

This aspect has been further described in the context of Bari and Robbins' model (2013; paragraph 1.1.2; Figure 1.1), in which the authors placed a particular focus on response inhibition, as an endophenotype for the study of impulsivity (Aron, 2007; Aron and Poldrack, 2005). In fact, the easy assessment of observable motor responses with a variety of tasks allows to obtain indices of the underlying cognitive processes and to investigate the possible consequences of their failure (Bari and Robbins, 2013). In line with this assumption, different studies have used behavioral paradigms (e.g., Go/No-Go, GNG; Stop Signal Task, SST; or Stroop Task) to assess response inhibition abilities in clinical populations. Impaired response inhibition has been revealed in various conditions characterized by impulsive behaviors and traits, such as bipolar disorder (Fleck et al., 2011), substance abuse (Colzato et al., 2007) and ADHD (Lipszyc et al., 2010). In addition, poor response inhibition during childhood has been shown to predict later drug abuse (Nigg et al., 2006), pathological gambling (Slutske et al., 2012) and increased criminal activity (Moffitt et al., 2011).

Measures of response inhibition

A number of different paradigms are used to study response inhibition in the laboratory. Most of the studies in literature adopted different paradigms interchangeably, relying on a unitary and misleading 'inhibition' definition (Littman et al., 2017). However, alike impulsivity, also response inhibition is thought to be a non-unitary construct (Bari and Robbins, 2013; Figure 1.1) and behavioral investigations provide further support to this view (Stuss and Alexander, 2007).

Based on the temporal interval in which inhibition occurs, a distinction within the different stages of the inhibition process can be made: namely, the restraining of the action (*action restraint*) and its cancellation (*action cancellation*; Eagle et al., 2008). This distinction is better clarified in light of the behavioral tasks generally adopted to investigate these aspects, namely the GNG and SST (Figure 1.2a and 1.2b). These two paradigms have been dissociated based on the form of response

inhibition that they require (Eagle et al., 2008; Schachar et al., 2007) and their neural underpinnings (see paragraph 1.3.2; Swick et al., 2011).

In the GNG task for example, individuals are required to respond to one class of stimuli and to withhold their responses to another set of stimuli (Figure 1.2a). Therefore, participants perform motor responses to go cues but should refrain from responding when a no-go cue is presented. The proportion of go and no-go trials can be manipulated to set the prepotency of responding so that restraining the action in response to no-go cues is more difficult when go trials are frequent (e.g., 75% go trials; 25% no-go trials).

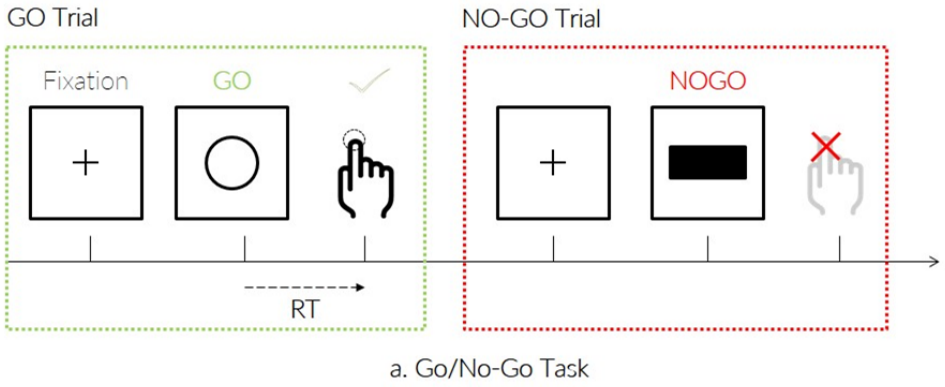


Figure 1.2a. Examples of go and no-go trials in the Go/No-Go paradigm. Abbreviations: RT= Reaction Time.

Conversely, in the SST responses are required for each trial unless a stop signal (e.g., a tone) is delivered (Logan et al., 1997; Figure 1.2b). In fact, on a minority of the trials (usually around 25%) a signal is presented after a certain delay (Stop Signal Delay, SSD): for these trials an already ongoing motor response has to be inhibited.

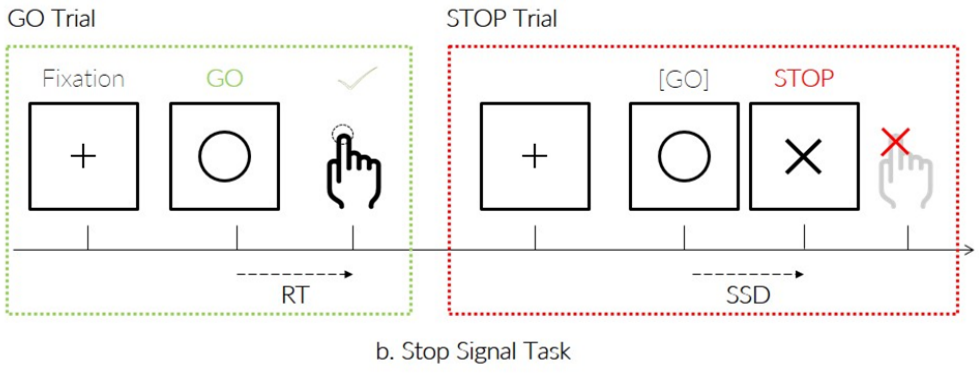


Figure 1.2b. Examples of go and stop trials in the Stop Signal Task. Abbreviations: RT= Reaction Time; SSD= Stop Signal Delay.

The key difference between GNG and SST lies on the temporal location of the no-go and the stop signal, respectively. In the GNG task the no-go stimulus can be presented instead of the go stimulus or simultaneously, so that both the go and the stop process are triggered simultaneously. This means that the action is interrupted during the planning phase. This form of inhibition has been referred to as '*action restraint*' and is argued to reflect a decision-making rather than an inhibition process (Eagle et al., 2008; Schachar et al., 2007). On the other hand, in the SST, as the go stimulus is always presented prior to the stop signal, the go process is already ongoing when the stop signal comes, and the action must be cancelled during its execution (Logan et al., 1997). This form of inhibition has been referred to as '*action cancellation*' and has been argued to reflect a 'true' stopping action (Eagle et al., 2008; Schachar et al., 2007).

For both GNG and SST the outcome measures are represented by reaction times to go stimuli, percentage of commission errors (i.e., false alarms) and omission errors (i.e., response not given), all of which provide a measure of the efficiency of the inhibition process. In addition, in the SST a measure of the latency of the stop process can be calculated. In fact, the SSD – the interval between the go and the stop stimuli – can be varied using an adaptive procedure, based on the participants' performance (Logan et al., 1997). In such cases, the performance is modeled as a 'race' between the go and the stop processes and the stop signal reaction time (SSRT) can be computed. This measure estimates how quickly participants can cancel an already-initiated response and provides a measure of the latency of the stop process (Logan et al, 2014).

By describing these differences it comes across that using these two tasks should interchangeably is not appropriate, leading to a potential misuse of the concept of inhibition and to inconsistencies across studies and authors (Friedman and Miyake, 2004; Littman et al., 2017). Nevertheless, as long as participants are encourage to response as quickly as possible, both tasks are likely to involve motor cancellation processes and to provide a measure of '**state impulsivity'**, an extent of the ability to inhibit responses to specific stimuli in definite situations. The term "*state*" impulsivity, in contrast with "*trait*" impulsivity, derives from the notion that response inhibition can be highly dependent to state dependent variations. Among these variations, a crucial role could be played by the personal motivational state when reward parameters of the task are manipulated (Herrera et al., 2014), a scenario that will be better discussed in the next paragraph.

The impact of reward in response inhibition

One of the aspects defined in the two-factor model of self-regulation (Dawe et al., 2004) is reward sensitivity. Its importance lies on the notion that individual's motivations and approach tendencies toward specific stimuli may affect the ability to inhibit responses (Hoffman et al., 2009). Consequently, people who are more sensitive to reward may be more likely to approach rewarding stimuli, being less able to inhibit responses or delay gratification (Avila, 2001).

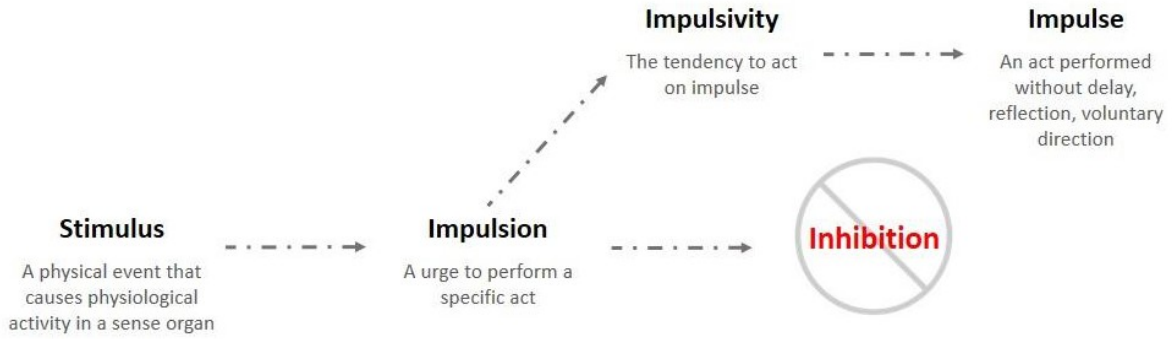


Figure 1.3. Schematic representation of the inhibition process, adapted from Bari and Robbins (2013). Definitions are quoted or adapted from English and English (1958).

Figure 1.3 better contextualize the possible role that certain stimuli may have in the activation of inappropriate urges (Bari and Robbins, 2013). The need to inhibit an action would not be present if there was no '*impulsion'*, hence a (dispositional or triggered) urge to perform that specific action (Bari and Robbins, 2013). This impulsion can be triggered by the paradigm itself (e.g., by increasing the ratio between go and no-go trials, thus making the act of responding more automatic and more difficult to stop), by dispositional variables (i.e., reward sensitivity) or by the stimuli used in the tasks (i.e., rewarding stimuli). Hence, even though response inhibition is a reliable and easy way to measure the ability to withhold or stop an observable motor act, we need to carefully consider the events and variables that may nourish the impulsion, i.e. the urge to act (Herrera et al., 2014). Not only the stimuli (e.g., rewarding stimuli, such as food or money), but also the individual differences in the approach tendencies toward that specific stimuli (e.g., individuals reward sensitivity) need to be taken into account.

In line with these considerations, some authors have investigated the influence of individual differences in reward sensitivity on inhibitory functions (Fuentes-Claramonte et al., 2016), while others have used modified versions of response inhibition tasks, using stimuli with a positive or negative valence in addition to the neutral ones (e.g., Veling and Aarts, 2011).

A first example derives from a recent study that aimed to assess the influence of reward sensitivity on behavioral performance and brain activation with functional Magnetic Resonance Imaging (fMRI) during a SST task (Fuentes-Claramonte et al., 2016). Authors observed that reward sensitivity was associated with more errors and with a more variable performance (in terms of reaction times) during the go trials. They concluded that high reward sensitivity was associated with an increased distractibility, given that increased performance variability has been interpreted as a marker of attentional fluctuations (Adams et al., 2011; Fuentes-Claramonte et al., 2016). In support of this result, the authors revealed a general pattern of increased activity of the motor 'go networks' (motor and pre-motor brain regions) during the presentation of the stop signal, in individuals with high reward sensitivity. Thus they posited that in these individuals – compared to those with low reward sensitivity – the motor network was less suppressed, and this in turn was reflected by a greater engagement in motor responses, thus in a tendency to act even when not required (Fuentes-Claramonte et al., 2016).

In line with these considerations, a second study tested whether the exposure to need-rewarding stimuli (e.g., a bottle of water when in need for water) evoked a preparatory motor impulse (even when it is not required) during a GNG task (Veling and Aarts, 2011). The aim was to investigate under what conditions the perception of rewarding cues (e.g., food, money etc.) would prepare the action, engaging the motor system, and if this process of action preparation would interfere with the inhibition of responses (Veling and Aarts, 2011). The results showed that in those individuals who were relatively high in need for water (and hence, who perceive water as a rewarding), the presentation of the rewarding stimulus during no-go trials caused slower reaction times in the following go trials, compared to those preceded by no-go trials with control objects. Consequently, when confronted with rewarding stimuli, participants probably needed to inhibit unintentionally prepared motor impulses and subsequently, this inhibition put a brake on the motor system and slowed down responding to the following action probes (Veling and Aarts, 2011).

In sum, these findings support the assumption that reward sensitivity and rewarding cues may intervene in the process of response inhibition (Herrera et al., 2014). On one hand, high reward sensitivity may have an effect over executive functions, manifested as increased performance variability, rather than inhibitory deficits per se (Fuentes-Claramonte et al., 2016). On the other hand, the presentation of rewarding stimuli in no-go trials may unintentionally activate motor programs (and thus an approach behavior), instrumental in obtaining these objects (Veling and Aarts, 2011). Overall, these pieces of evidence confirm the complex and multi-faceted nature of impulsivity,

highlighting the importance of the (internal or external) variables that may create the urges (or impulses) to respond (Bari and Robbins, 2013). As a consequence, taking into account the interaction between motivational dispositions and cognitive processes may help better characterize cognitive or behavioral deficits in pathologies that feature impulsive or disinhibited behavior (Fuentes-Claramonte et al., 2016).

1.2.3 A Comprehensive Assessment of Impulsivity

Both self-reported and behavioral measures have been extensively used in research contexts for the investigation of impulsive behavior in relation to several clinical and non-clinical conditions (Reynolds et al., 2006). However, there is still conflicting evidence as to which aspects of trait impulsivity can be directly associated with response inhibition (Enticott et al., 2006; Reynolds et al., 2006). The little knowledge about the relation between self-reported and behavioral measures is probably due to the fact that they are rarely used together in the same study (Reynolds et al., 2006). Indeed, the majority of the impulsivity literature comes from separated fields: personality studies tend to view impulsivity as a trait (as measured by self-reported instruments), experimental investigations often rely on response paradigms, while neurobiology investigates pharmacological interventions and brain activity. Unfortunately, these different fields have historically remained largely independent (Eveden, 1999). Thus, a comprehensive account of impulsivity may be best predicted by the combination of different measures and approaches (self-reported, behavioral and neurobiological) in the same individuals.

In order to provide additional information for the discussion of the impulsivity construct, in the following paragraph I will review the evidence from neuroimaging investigations, with particular focus on structural and functional Magnetic Resonance Imaging (MRI) approaches.

1.3 THE NEUROBIOLOGY OF IMPULSIVITY

In the last decades, a major interest in cognitive neuroscience has been placed on the neural underpinnings of behavioral inhibition, due to the fact that impulsivity is a common characteristic of many psychiatric and neurological populations (e.g., substance abuse; obsessive-compulsive disorder; Parkinson disease; mood disorders; Dalley and Robbins, 2017; Rossi et al., 2017). The interest about behavioral inhibition's correlates goes back to the time of Luria (1973) who proposed a role of the frontal lobes for the regulation of behavior according to current goals and aims. Luria (1973) attributed the highest function of the brain to the frontal lobes. To summarize with his words: "*the frontal lobes not only perform the function of synthesis of external stimuli, preparation for action, and formation of programs, but also the function of allowing for the effect of the action carried out and verification that it has taken a proper course*" (Luria, 1973, p. 93). From Luria's work on, the evidence of the dependency of behavioral inhibition on the integrity of the frontal lobes has been consistent over time and authors (Brutkowski and Mempel, 1961; Mishkin, 1964; Stanley and Jaynes, 1949). However, considerable research has underlined that the non-unitary construct of impulsivity might be mediated by diverse neural mechanisms (Swick et al., 2011; Bari and Robbins, 2013; Whelan et al., 2012). Data point toward the assumption that impulsivity derives from several distinct neurocognitive mechanisms, each with specific neuroanatomical and neurochemical bases, and that different brain networks may contribute to distinct aspects of impulsivity (Whelan et al., 2012). More specifically, the facets of impulsivity seem to be the products of reciprocal interactions between and within both frontal and subcortical regions (Leshem, 2016).

Given the vast debate on the number and identity of domains into which impulsivity might fractionate, in this chapter I will focus on the evidence of response inhibition, covering the most important task-based fMRI investigations, and of the underpinnings of trait impulsivity, with resting-state fMRI and structural MRI studies.

1.3.1 MRI investigations

"The brain controls all the complex functions in the human body. Structurally, the brain is organized grossly into different regions specialized for processing and relaying neural signals; functionally, the brain is subspecialized for perceptual and cognitive processes. Working in concert, these subspecialized areas orchestrate complex bodily functions and allow human behavior" (Lv et al., 2018).

In order to investigate the brain, both functionally and structurally, researchers have adopted many neuroimaging techniques, among which one widely used is MRI. During the past decade, the application of MRI techniques has indeed seen a rapid increase.

MRI is a non-invasive and safe technique that uses a magnetic field and radio waves to produce detailed images of the brain. On one hand, functional MRI (fMRI) is used to measure and map brain activity. The fMRI measures the MR signal, which varies as an indirect effect related to the changes in blood flow that follow those in neural activity. In more detail, neural activity triggers a large change in blood flow and this leads to the blood being more oxygenated as neural activity increases (i.e., Blood Oxygen Level Dependent (BOLD) signal; Ogawa et al., 1990). This has an effect on the MR signal, captured by fMRI. The fMRI has been extensively used to investigate brain functional activity and cognitive processes, both during the execution of behavioral tasks (i.e., task-based fMRI; Worsley and Friston, 1995, Heeger and Ress, 2002) or during task-free, resting conditions (i.e., resting state fMRI, rsfMRI; Fox and Raichle, 2007). The first method, namely *task-based fMRI*, is commonly adopted to identify brain regions that are functionally involved in specific tasks conditions (e.g., visualization of pictures, motor responses etc.). As opposed to task-based fMRI, *rsfMRI* is acquired in the absence of a stimulus or a task, at rest. Based on the BOLD signal fluctuations, the same as for task-based fMRI (Wang et al., 2018), rsfMRI is used to explore the intrinsically functionally connectivity of brain regions and networks (Logothetis, 2008).

On the other hand, structural MRI provides information about brain anatomy: this information can be used to analyze and describe the shape, size and integrity of gray and white matter structures in the brain. In particular, by means of morphometric techniques of analysis (such as, Voxel Based Morphometry, VBM), we can measure the volume of the gray matter structures, both at the cortical and subcortical level (Ashburner and Friston, 2000). The identification of structural changes in the brain is important in the study of neurological and psychiatric disorders. In this context, indeed, MRI can be used in the differential diagnosis of disease, in tracking disease progression, and for research purposes (Whitwell, 2009).

Both functional and structural approaches have been adopted in many studies to better understand how the healthy brain works and how the normal function or structures can be altered in disease, and this has led to a new wave of insights into the pathophysiology and treatment of psychiatric disorders (Sharma, 2003). Generally, combining structural and functional MRI may broadly characterize brain structure and function, helping disentangle the neural substrates of normal

behaviors (i.e., motor and cognitive processes) or clinical conditions (i.e., neurodegenerative or psychiatric disorders).

1.3.2 Task-based fMRI investigations

Unlike the diversity of approaches in the psychological literature, the neuroimaging literature related to inhibition has used a fairly narrow set of task paradigms, of which the two most commonly used are the GNG and SST (Bari and Robbins, 2013). By means of these tasks, investigations into the neural underpinnings of response inhibition have been conducted in a range of samples and different clinical and non-clinical conditions (Bari and Robbins, 2013). Despite the use of different types of analysis, samples and variations of the paradigms, the bulk of such data has consistently suggested an involvement of the right lateralized fronto-striatal pathway in response inhibition (for a meta-analysis see Buchsbaum et al., 2005). Converging evidence suggests indeed that the right Inferior Frontal Gyrus (IFG) coordinates response inhibition together with the pre-supplementary motor area (pre-SMA), via a connection with the sub-thalamic nucleus of the basal ganglia (see Figure 1.4; Aron et al., 2007; Chambers et al., 2006).

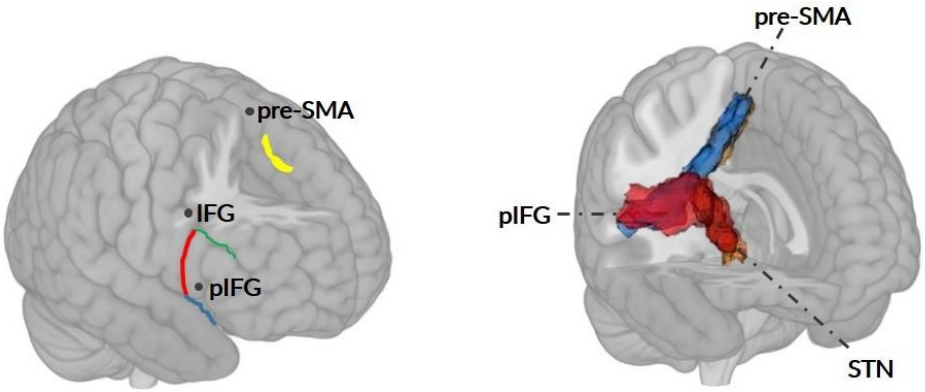


Figure 1.4. The brain network for stopping. **A**. Regions that are critical for stopping in the standard stop signal paradigm. Two regions within the inferior frontal cortex and the presupplementary motor area (preSMA) in the medial surface. **B**. White-matter tractography using diffusion tensor imaging reveals a three-way network in the right hemisphere between nodes that are critical for stopping action (Aron et al., 2007). Abbreviations: IFG= Inferior frontal gyrus; SMA= supplementary motor area; STN= subthalamic nucleus. Image adapted from Aron et al., 2007.

Thus, response inhibition and motor suppression may be sub-served by a neural network that encompasses the right IFG, the pre-SMA and sub-cortical (including subthalamic) regions (Rubia et al., 2001; Aron and Poldrack, 2005; Figure 1.4). Interestingly, circumscribed lesions of the right IFG and the basal ganglia seem to negatively influence SSRT, a measure of the latency of the stop process (Aron et al., 2003; Rieger et al., 2003).

Given that alike impulsivity also response inhibition is not a unitary construct (Everitt, 1999), one question of interest in the context of the present thesis is whether the same models and circuits underline different stages of response inhibition, such as *action restraint* and *action cancellation* (Eagle et al., 2008).

Action restraint and cancellation

From Aron's work on (2007; Figure 1.4), preliminary evidence of a non-unitary module for response inhibition derived from neuroimaging studies investigating the neural correlates of inhibition processes at the roots of GNG and SST (Swick et al., 2011). Overall, results showed that these two tasks differed both in terms of inhibitory mechanisms required and in terms of recruitment of brain regions (Rubia et al., 2011; Swick et al., 2011). More precisely, while early studies argued a right-lateralization of the motor response inhibition-related activity during GNG task (Garavan et al., 1999; Kawashima et al., 1996; Konishi et al., 1998), subsequent investigations (Liddle et al., 2001; Rubia et al., 2001) observed activations in several bilateral regions, such as dorsolateral and ventrolateral prefrontal cortex (DLPFC and VLPFC, respectively), anterior cingulate cortex (ACC), pre-SMA, medial PFC, Inferior Parietal Lobe (IPL) and basal ganglia. On the other hand, studies that used SST reported predominant bilateral activation of the IFG (Aron et al., 2007; Li et al., 2006), the pre-SMA (Chao et al., 2009), the striatum (Vink et al., 2006) and the sub-thalamic nucleus (Aron and Poldrack, 2006).

To solve these inconsistencies, a meta-analysis of Swick et al (2011) directly compared the evidence from studies that use the GNG and the SST (Swick et al., 2011). Results showed that these tasks involved some common neural circuits, but they also have been associated with distinct brain regions. The differences between the tasks were mainly located in two cognitive control networks, namely the fronto-parietal and the cingulo-opercular networks. The first mediates adaptive online control, whereas the second is implicated in maintaining task set and responding to salient stimuli (Dosenbach et al., 2007; Seeley et al., 2007). In general, the GNG engaged the fronto-parietal control network to a greater extent than SST, with a strong right lateralization in the middle frontal gyrus (MFG) and IPL. On the other hand, the SST engaged the cingulo-opercular network, with prominent foci in the left anterior insula and bilateral thalamus (see Figure 1.5). The maximal overlaps between the tasks were observed in the insular cortex and medial PFC (including SMA/pre-SMA).

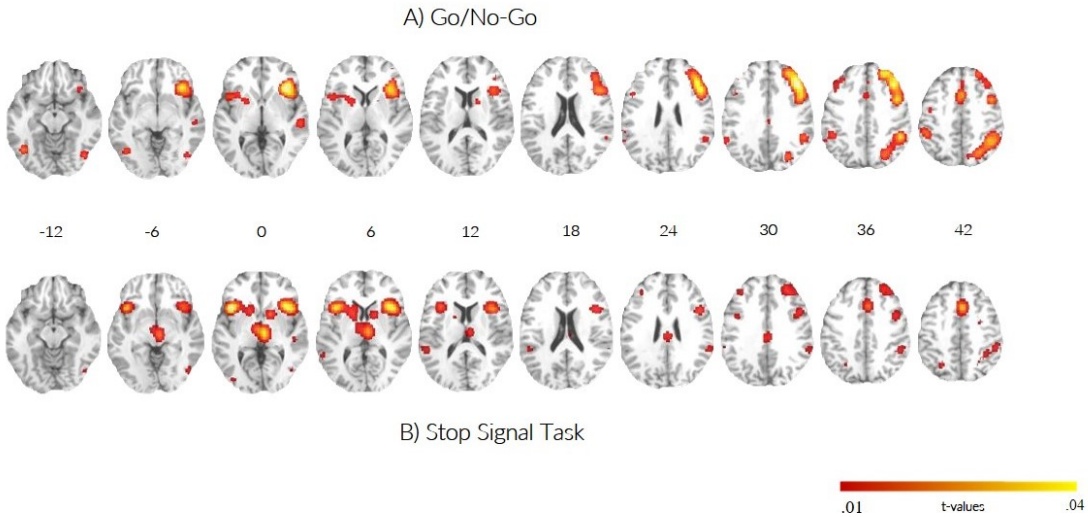


Figure 1.5. Swick et al (2011): Activation likelihood estimation (ALE) map showing significant inhibition-related activation clusters. (A) Studies using the Go/No-Go (GNG) task; (B) Studies using the Stop-Signal Task (SST). Image adapted from: Swick et al. (2011).

Thus, this meta-analysis revealed that right-lateralized clusters are present to a greater extent in the GNG than in the SST and showed anterior insula's importance in response inhibition tasks. According to Swick et al (2011) the highlighted differences between the two tasks might indicate that they reflect different aspects of response inhibition, consistently with the notion of action restraint and cancellation (Eagle et al., 2008). In line with this conclusion, Zhang and Li (2012) showed a distinct involvement of the two hemispheres in GNG and SST. According to the authors, while the right-hemispheric fronto-parietal network is more involved in attention to the stop signal, hence in the restraining of the action, the left-hemispheric network is involved in response inhibition itself, thus the canceling of the action (Aron and Poldrack, 2006; Schachar et al., 2007; Swick et al., 2008). Thus, the authors proposed contrasting roles for the right and left fronto-parietal networks with the left-hemispheric network more directly involved in motor inhibitory control during stop signal inhibition (Zhang and Li, 2012). Although the precise nature of those contributions remains to be established, dissociable neural systems seem to contribute to different components of inhibitory control over actions, which in turn are differentially engaged by the GNG and the SST (Swick et al., 2011).

Despite the consistency of this evidence, however, for some authors the distinct patterns of activation are related to the fact that the use GNG and SST do not allow to control for potentially confounding non-inhibitory cognitive demands (Erika-Florence et al., 2014). In more detail, it has been suggested that, although both GNG and SST incontrovertibly engage behavioral inhibitory processes, fMRI studies of their underlying circuitries may nonetheless be confounded with attentional or other cognitive requirements of the task (Erika-Florence et al., 2014; Robbins and Dalley, 2017). Thus,

notwithstanding the compelling hypothesis of specific modules for response inhibition, there is growing evidence to support the alternative view that response inhibition is just an example of the many top-down cognitive control processes that are supported by dynamic interactions within the same set of 'domain general' functional networks (Hampshire et al., 2015).

In light of the still open debate on the neural basis of response inhibition, the description of the neural basis of impulsivity and behavioral inhibition may benefit from the evidence of functional connectivity at rest and brain morphometry in relation to trait and state impulsivity indexes (paragraphs 1.3.3 and 1.3.4)

1.3.3 Resting-state fMRI investigations

A fair assumption while describing the neural basis of impulsivity would be that individual differences in this complex trait are associated with broader patterns of information processing that extend beyond the circumscribed alterations in cortico and striatal regions (Davis et al., 2013). Within this context, rsfMRI analysis has proven to be a useful tool for probing global brain organization (Fox and Greicius, 2010). By investigating the spontaneous fluctuations of BOLD signal when participants are at rest, rsfMRI allows to infer the relationship between the brain activity of anatomically separated – but functionally connected – brain regions, providing insights into how and when certain brain areas work together (Van den Heuvel and Hulshoff Pol, 2010).

Concerning impulsivity investigations, recent neuroscience research indicates that this trait is associated with individual differences in several interconnected neural circuits, including the mesocorticostriatal and corticolimbic networks (Jentsch and Taylor, 1999; Volkow and Fowler, 2000; McClure et al., 2004; Brown et al., 2006; Dalley et al., 2011; Forbes et al., 2009; Figure 1.6).

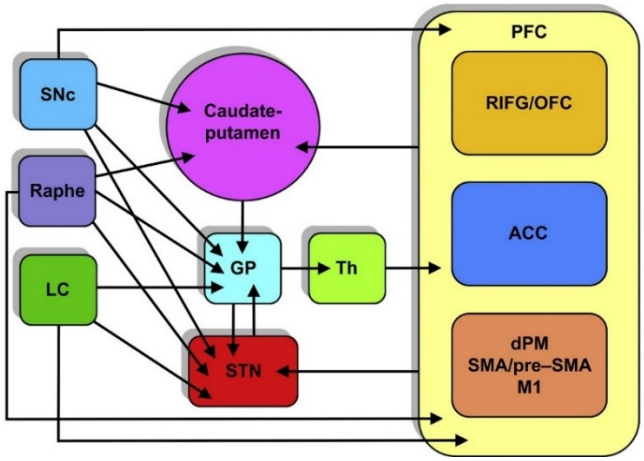


Figure 1.6. Representation of the circuitry mediating impulsivity (Dalley et al., 2011). Abbreviations: M1: primary motor cortex; SMA: supplementary motor area; dPM: dorsal premotor area; LC: locus coeruleus; GP: globus pallidus; STN: subthalamic nucleus; Th: thalamus; RIFG: right inferior frontal gyrus; SN: substantia nigra; ACC: anterior cingulate cortex. Image taken from Dalley et al. (2011).

Among others, a support for this evidence derives from a recent investigation (Angelides et al., 2017) that aimed at assessing resting-state brain activity and its correlations with individual differences in personality measures linked to impulsivity, reward responsiveness, drive and inhibition in healthy individuals. In this work, results supported a network of corticostriatal connections integrating reward, attention and executive processes. Interestingly, the authors observed a significant positive correlation between mid-orbitofrontal cortex (OFC)/putamen connectivity and trait impulsivity (Angelides et al., 2017). Increased resting-state correlation between the mid-OFC (involved in inhibition of impulsive behaviors) and regions of the basal ganglia (associated with 'wanting' of rewards) indicated that the role of mid-OFC in suppressing impulsive behavior was probably moderated by an increased communication with regions responsible for assessing desirable outcomes (Angelides et al., 2017).

Additional evidence derives from a study conducted by Davis et al (2013). The authors intended to study the functional connectivity of the whole brain networks as they related to self-reported impulsivity in healthy individuals. The analyses revealed striking differences in the organization of whole-brain neural networks as a function of impulsivity (Davis et al., 2013). In more detail, one of the main finding in this study was the modulation of functional connectivity between cortical and subcortical regions, as a function of impulsivity. Decreased functional connectivity between cortical (*control*) and subcortical (*drive*) regions modeled as a function of increasing impulsivity. In particular, the relation between the cortical and subcortical regions became more fragile as impulsivity increased, driving their separation into distinct modules (Davis et al., 2013).

Overall, these findings show some consistency with the task-based evidence – confirming a role of cortico-striatal regions at the roots of different aspects of impulsivity – and with the notion that impulsive behavior may result from increased approach tendency (subserved by subcortical regions) couple with a reduced cognitive control (subserved by cortical regions; Steinberg 2010). In addition, they extend previous task-based evidence by detecting distributed functional networks whose connectivity is modeled as a function of impulsivity, thus confirming that different neural systems may subserve diverse impulsivity aspects (Angelides et al., 2017; Davis et al., 2013).

1.3.4 Structural MRI investigations

Lastly, a further support to functional evidence derives from structural MRI (sMRI) investigations. Using a VBM approach (Ashburner and Friston, 2000) recent studies have assessed local and global grey matter volumes (GMV) in relation to trait impulsivity (Boes et al., 2009; Cho et al., 2013; Matsuo et al., 2009). In general, results showed that structural changes at cortical and subcortical levels (i.e., prefrontal regions, basal ganglia, insula, precuneus) might be responsible for different degrees of impulsive behavior and associated with different clinical conditions, such as ADHD or internet-gaming disorder (Du et al., 2016; McAlonan et al., 2007).

However, only few studies have correlated regional GMV with self-reported or behavioral measures of impulsivity in healthy individuals (Boes et al., 2009; Cho et al., 2013; Matsuo et al., 2009). These studies revealed that different regions of the PFC and, in particular, the ventromedial PFC – including ACC, medial PFC and OFC – played an important role in the modulation of impulsivity (Weiger and Bear, 1998). Importantly, the ventromedial PFC (vmPFC) is known to have anatomically intrinsic cortico-cortical connections and extrinsic connections with striatum, thalamus and limbic structures (Ridderinkhof et al., 2004). Therefore, it may be not just the vmPFC but also all these connections together to represent the hypothetical substrates of impulsivity (Mega and Cummings, 1994). An additional validation of a role of vmPFC at the roots of impulsivity derives from a study of Matsuo et al (2009) in which authors reported that individuals with higher impulsivity trait showed lower GMV of this region, and particularly the bilateral OFC, compared to individuals with low impulsivity (Matsuo et al., 2009). In addition, a more recent study reported positive correlations between the BIS-11 scores (i.e., a self-reported measure of trait impulsivity) and the GMV of the left MFG, medial frontal gyrus and ACC, with the left MFG having positive correlations with all the three subscales and the total score of the BIS-11 questionnaire (Cho et al., 2013).

These findings reinforce the evidence of a role of PFC regions (especially, ventromedial and dorsolateral regions) and cingulate cortex as plausible candidates for the neural substrates of self-reported (trait) impulsivity in healthy individuals and most importantly, they suggest regional specificity in the relationship between different aspects of self-reported impulsivity and GMV.

1.4 TAKE-HOME MESSAGE

While theories of the neurobiological substrates of impulsivity have focused on specific brain regions, a new line of evidence – especially involving the studies that used functional connectivity analyses – raises the possibility that more global network features may underlie different aspects of impulsivity (Davis et al., 2013). Taken together, the presented results confirm that impulsivity's different forms of expression are mediated by distinct, occasionally overlapping, neural systems, involving prefrontal and subcortical regions. In more detail, impulsivity might be subserved by cortical brain regions (such as PFC regions), involved in self-control and self-regulation, and their interactions with subcortical brain regions, involved in basic urges and motivations such as hunger or reward (Reeve, 2015). Thus, a fair assumption would be that the impulsive circuit involves two components: the *subcortical* circuit (including ventral striatum and nucleus accumbens) that drives the impulsive actions and the *cortical* circuit (ACC, vmPFC, DLPFC) that exerts inhibitory control (Figure 1.7; Fineberg et al., 2014). A hyperactivity of the striatal components together with an alteration (presumably a hypoactivity) of the PFC regions may result in a heightened automatic tendency to act, and thus for executing impulsive behavior (Fineberg et al., 2014). Within these circuits, the different regions subserve various facets of impulsivity and, via functional connections, elaborate information to plan the appropriate responses and guide behavior (Figure 1.7; Purves et al., 2008).

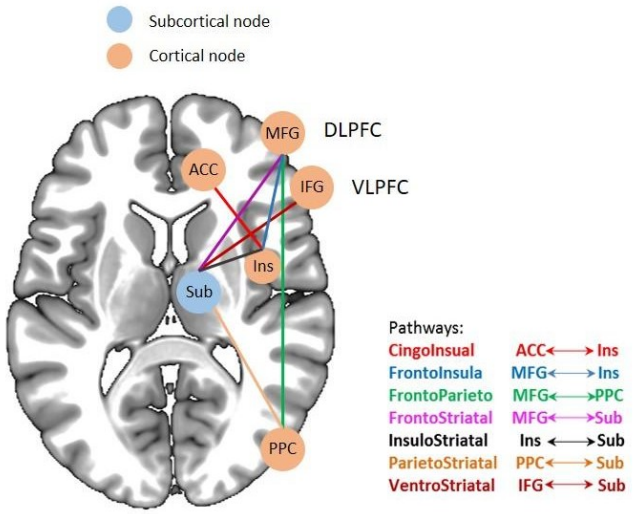


Figure 1.7. Visual representation of the brain regions mostly implicated in behavior regulation. Image adapted from Purves et al., 2008.

In sum, as opposed to arbitrarily focusing on one task, connection or module, a sensible future direction would be to combine different approaches to investigate frontal and subcortical functional architecture (Davis et al., 2013). Indeed, the use of different measures and approaches will not only inform our understanding of impulsivity mechanisms, but also sharpen the focus on which aspects of impulsivity provide the most predictive endophenotypes for impulsive disorders.

Chapter 2
IMPULSIVITY & EATING BEHAVIOR

In everyday life situations we are subjected to different choices for which we have to exert some sort of control, for example when buying or eating food, or just when stopping and chatting to a friend unexpectedly met in the street. The ability of self-control or self-regulation is one of the most remarkable aspects of the human condition: a good self-regulation is indeed implicated in various personal positive outcomes, concerning health (Griffin et al., 2012) or personal success (Tangney et al., 2004). Sometimes, however, when automatic impulses are not adequately handled, we may engage in acts that are characterized as impulsive and unwanted (Hofmann et al., 2012). One example of unwanted behavior is represented by uncontrolled or binge eating.

Binge eating[1] – defined as the consumption of large amounts of food in a discrete period of time – is usually described as a symptom of eating and weight disorders (e.g., Anorexia Nervosa Bingeing and Purging type (AN/BP), Bulimia Nervosa (BN), Binge Eating Disorder (BED) and obesity). Nonetheless, over the past 15 years, it has also gained recognition as being problematic in its own right (Fichter et al., 1992; McManus and Waller, 1995). Indeed, although binge eating can occur in individuals affected by obesity or eating disorder (Villarejo et al., 2013), sub-thresholded binge eating is found to be common in the healthy population and it has been associated with an increased risk of developing eating disorders (Davis, 2013).

Given the negative consequences and the chronicity of binge eating behavior (e.g., weight gain, overweight and overeating disorders; Davis, 2013), an important question that remains largely unexplored is what makes someone more vulnerable than other to engage in such behavior, often despite a desire not to do so (Corbit, 2017).

One possible answer to this question lies on the role played by impulsivity. It is likely indeed that more impulsive individuals, within the general population, may be more prone to have unplanned reactions to food, leading them to overeat and eventually gain weight. Thus, the investigation of the role of impulsivity at the roots of overeating behavior may help identify the

[1] Throughout this dissertation, the term binge eating will be used to refer to a sub-clinical behavior of loss of control eating episodes.

behavioral and neural markers of vulnerability for eating and weight disorders in the general population.

Toward the exploration of this topic, in the present chapter I will discuss the evidence on the relation between impulsivity and eating behavior, in clinical and non-clinical populations, covering both behavioral and neuroimaging recent investigations. Particular attention will be placed on trait impulsivity, general and food-related response inhibition, as these aspects are the main focus of the thesis and the experimental work (Chapters 3-7).

2.1 FROM HOMEOSTATIC TO DISORDERED EATING

A growing number of studies suggests that general impulsivity may be associated with eating disorders leading to overweight conditions, especially when binge eating is prominent (Fernández-Aranda et al., 2008; Waxman, 2009). The term binge eating refers to episodes of uncontrolled eating of considerable amount of food, within discrete periods of time (American Psychiatric Association, APA, 2000). As already outline in the introduction, although they are usually described as symptoms of BED, these episodes can also occur in those who do not meet the criteria for this eating disorder (Davis, 2013). BED is a relatively newly defined eating disorder in the Diagnostic Statistic Manual 5 (APA, 2013; see Table 2.1). The cardinal features of this disorder are the compulsive binge eating episodes, at least once a week for three months, without attempted compensatory weight behaviors (e.g., self-induced vomiting, diuretic use, and excessive levels of physical activity; APA, 2013). When binge eating episodes happen in the general population, the loss of control eating is not accompanied by one or more of the criteria defining full-blown BED (Table 2.1), such as the objective large size of the binge, frequency of bingeing, or the accompanying distress (Cotrufo et al., 1998).

A Recurrent episodes of BE. An episode of BE is characterized by both of the following:
1) eating, in a discrete period of time (for example, within any 2-hour period), an amount of food that is definitely larger than most people would eat in a similar period of time under similar circumstances;
2) a sense of lack of control over eating during the episode (for example, a feeling that one cannot stop eating or control what or how much one is eating).
B The BE episodes are associated with three (or more) of the following:
1) eating much more rapidly than normal;
2) eating until feeling uncomfortably full;
3) eating large amounts of food when not feeling physically hungry;
4) eating alone because of feeling embarrassed by how much one is eating;
5) feeling disgusted with oneself, depressed, or very guilty afterward.
C Marked distress regarding BE is present.
D The BE occurs, on average, at least once a week for 3 months.
E The BE is not associated with the recurrent use of inappropriate compensatory behavior (for example, purging) and does not occur exclusively during the course of anorexia nervosa, bulimia nervosa, or avoidant/restrictive food intake disorder.
Mild: 1–3 BE episodes per week
Moderate: 4–7 BE episodes per week
Severe: 8–13 BE episodes per week
Extreme: 14 or more BE episodes per week

Table 2.1 DSM 5 criteria for binge eating disorder (BED). Abbreviations: DSM 5= Diagnostic and Statistical Manual of Mental Disorders, Fifth Editions (APA, 2013); BE= binge eating.

A good exemplification of how overeating behavior occurs in the general population and gradually collects severity derives from Davis' model (2013). In her *Dimensional view of overeating*, Davis describes this behavior as a "*downward escalating dimension*" (Davis, 2013; Figure 2.1).

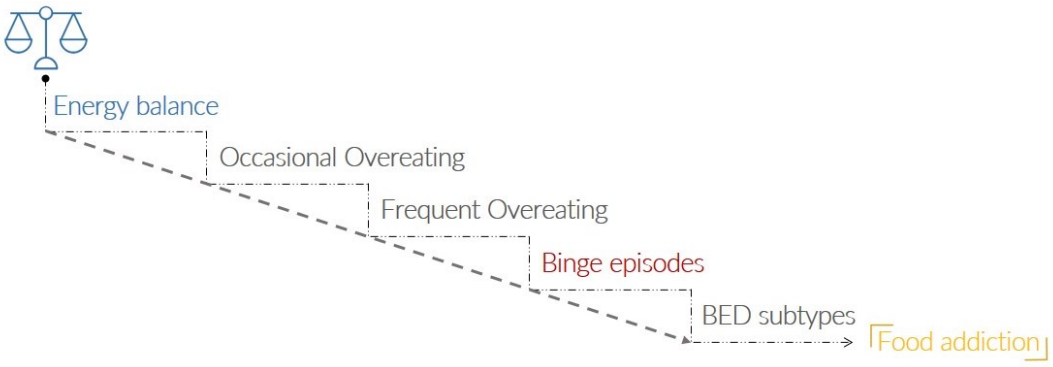


Figure 2.1: Downwardly escalating dimension of (over) eating and behaviors reflecting increased severity and compulsiveness (Adapted from: Davis, 2013).

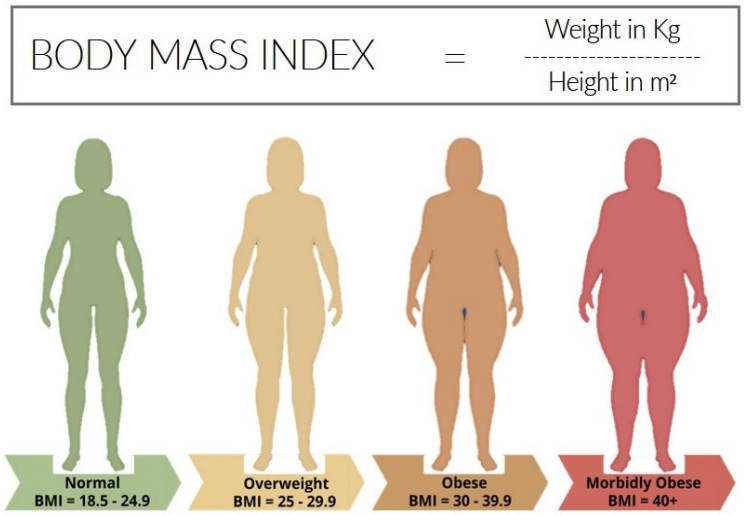
At the beginning of this continuum is the '*homeostatic eating*', which is mainly reflected by regular eating behavior (without loss of control episodes) and a stable body weight falling within the normal-weight range (Body Mass Index, BMI between 18.5 and 24.9; World Health Organization, 2000; see Box 2.1). Further along the continuum we find occasional and frequent overeating (i.e., snacking and grazing), which manifest themselves as episodic binges that can become more compulsive and frequent over time. When this happens, binge eating may turn into

a risk and prodrome factor for the development of BED, as reflected by the downward staircase (Figure 2.1).

Given the potential escalation mechanisms throughout which episodic bingeing may become severe, uncontrollable and intractable to change, it is fundamental to identify its underlying mechanisms to understand why some people are more vulnerable that others to engage in such behaviors and how these behaviors maintain over time.

Box 2.1. Graphical representation of Body Mass Index (BMI).

BMI is a value derived from the mass (weight) and height of an individual. The BMI is defined as the body mass divided by the square of the body height, and is universally expressed in units of kg/m^2, resulting from mass in kilograms and height in meters. The BMI is an attempt to categorize the person as underweight, normal weight, overweight, or obese. The guidelines of the United States National Institutes of Health (NIH) classified these categories as follows: BMI < 18.5 kg/m^2, underweight; BMI 18.5 to 24.9 kg/m^2, normal weight; BMI 25.0 to 29.9 kg/m^2, overweight; BMI 30.0 to 34.9 kg/m^2, obesity class I; BMI 35.0 to 39.9 kg/m^2, obesity class II; and BMI > 40.0 kg/m^2, obesity class III.



2.2 THEORETICAL MODELS OF OVEREATING BEHAVIOR

A preliminary insight toward a better understanding of the mechanisms underlying binge eating behavior derives from a recent line of evidence according to which there would be overlapping behavioral and neural mechanisms between overeating and substance use disorders (Gearhardt et al., 2011). As outlined in Davis' model (Davis, 2013), frequent overeating may increase the risk for more severe forms of disordered eating, so-called '*food addiction'* (Figure 2.1). In the past decade, growing attention has been placed in this new concept and an important catalyst for this interest has been the accumulating neurobiological and behavioral evidence that highly palatable foods (i.e., those rich in sugar, fat, and salt) may have an abuse potential similar to addictive drugs, like cocaine and alcohol (Gearhardt et al., 2011). In line with this evidence, many authors have subscribed to the view that binge eating behavior could share several similarities with both behavioral addictions and compulsive drug taking (Gearhardt et al., 2011; Davis and Carter, 2009; Meule, 2011). Their perspective is that addiction could be conceptualized as an excessive appetite for a particular behavior or substance, without the need to focus on psychoactive substances (Frascella et al., 2010). Although a complete account of this construct is beyond the aim of this Chapter, the increasing scientific attention to food addiction has led to new valuable insights for the understanding of the mechanisms underlying overeating behavior.

As an example, Moore et al (2017) proposed a model of compulsive eating behavior, by applying the evidence deriving from the context of drug addiction. They postulated that overeating behavior could be distinct in three different elements: (1) overeating despite negative consequences; (2) overeating to relieve an emotional state; and (3) habitual overeating. All of these elements are part of a unitary construct and are not mutually exclusive, nevertheless each of them emerges from dysfunctions in diverse processes: namely, (1) inhibitory control, (2) emotional processing and (3) reward learning. In this context, the loss of control over food (or drugs) is thought to result from deficits in inhibitory control mechanisms responsible for the (lack of) suppression of inappropriate actions (Moore et al., 2017). These deficits are extremely crucial because they are likely to confer vulnerability to addictive behavior and prolonged food overconsumption (Moore et al., 2017). Thus, it is the failure of inhibitory control (impulsiveness), which appears to play a central role in the initial stages of overeating and to underlie the tendency to overeat despite negative consequences (Moore et al., 2017).

An additional specification of the early stages of overeating has been offered by the theoretical model of Dawe and Loxton (2004) who drew upon the investigations on drug and

alcohol abuse to disentangle the shared and unique mechanisms of overeating and addictive disorders. Similarly to Moore et al (2017), the authors claimed that inhibitory control and rash impulsivity play a central role in the development of disordered eating (Dawe and Loxton, 2004). In addition, they stated that the acquisition of whichever substance (or food) requires a goal-directed planning, which in turn cannot be independent from the sensitivity and reactivity to the substance itself (Dawe and Loxton, 2004). Accordingly, when studying the role of impulsivity and inhibition in the development of overeating, at least two impulsivity-related components should be considered: rash spontaneous impulsiveness (i.e., inhibitory responses) and reward sensitivity (i.e., approach behavior). An impulsive act may indeed derive from the combination of (1) the lack of inhibitory control, thus the inability to stop a planned or ongoing action coupled with (2) an enhanced approach/motivation that draws the individual toward choices to gain the reward (often despite the negative consequences). These two components may operate in tandem and be responsible for the development and maintenance of the unhealthy eating behaviors.

In a recent paper on the role of these two components in overeating, Loxton (2018) followed up on this model and clarified that reward sensitivity might be more associated with a learning appetitive-cue associations and expectancies of reward; whereas, rash impulsiveness appears to pose additional risk for dysfunctional approach behaviors. Thus, while reward sensitivity is more associated with the initial approach 'drive' toward food (i.e., initial urges), in accordance with Moore et al (2017), the inability to inhibit may be the crucial responsible for the behavioral outcomes, namely the loss of control or the inability to inhibit (Loxton, 2018).

Based on these models, it becomes clear that in overeating, similarly to addictions, impulsivity and inhibitory control deficits may be at the roots of the lack of ability to stop overconsumption (Schag et al., 2013). Accordingly, to date several pieces of evidence have underlined the association between high trait impulsivity, dysfunctional inhibitory control and obesity (Verdejo-Garcia, 2014). However, the study of non-clinical populations is still in its infancy, therefore, it is not clear whether impulsivity represents a risk factor for the onset, symptomatic expression and maintenance of overeating or if the enhanced impulsivity traits are consequences of having developed and maintained unhealthy eating habits and weight gain (Lowe et al., 2009).

In order to give a preliminary answer to these open issues, in the following paragraphs, I will cover studies that used self-reported measures, behavioral tasks (2.3) and neuroimaging approaches (2.4) to investigate the relationship between impulsivity and eating behavior, in both

clinical conditions (i.e., BED and obesity) and non-clinical populations (i.e., normal-weight individuals).

2.3 BEHAVIORAL EVIDENCE OF THE ROLE OF IMPULSIVITY IN OVEREATING

As already outlined in Chapter 1, two of the most widely used methods for the study of impulsivity in healthy and clinical populations are self-report measures (i.e., questionnaires) and behavioral tasks (i.e., Go/No-Go, GNG or Stop Signal Task, SST). Even though self-reported impulsivity is usually positively correlated with impulsive reactions in behavioral measures, yet correlations are not often consistent (Cyders and Coskunpinar, 2011). Nonetheless, both self-report and behavioral measures indicate that high impulsivity may be a characteristic feature of a range of maladaptive behaviors, including behavioral addictions, substance use, or over- and binge eating (Dissabandara et al., 2014; Guerrieri et al., 2009; Waxman, 2009). In this context, high rash-spontaneous impulsiveness and the inability to inhibit responses might facilitate overeating in tempting situations, making it difficult to avoid unhealthy choices (Dawe and Loxton, 2004; Jasinska et al., 2012).

In the following paragraph, I will examine the evidence on the relationship between overeating and the three aspects of impulsivity described in Chapter 1 (i.e., trait impulsivity, response inhibition and food-related impulsivity).

2.3.1 Trait Impulsivity and eating behavior

Trait impulsivity is a characteristic personality aspect that refers to the individual's inability to inhibit actions and the tendency to act without foresight (Bari and Robbins, 2013). A growing amount of researches investigating this trait has revealed that it is associated with risky behaviors related to substance use and binge eating (Dissabandara et al., 2014; Schag et al., 2013). In particular, an enhanced rash impulsiveness may be at the roots of dysfunctional approach tendencies and addictive behaviors (Loxton, 2018). Within the eating behavior context, both the Barratt Impulsiveness Scale (BIS-11) and the Behavioral Inhibition Activation System (BIS/BAS) questionnaires (see Chapter 1, paragraph 1.2.1) have been commonly used to assess different aspects of trait impulsivity related to overweight and overeating disorders.

Many studies have used the BIS-11 total and subscales' scores (motor, attentional and non-planning) to examine the correlations between impulsivity and eating behavior in different clinical and non-clinical conditions (e.g., Nasser et al., 2004; Meule, 2013; Rosval et al., 2006). The evidence

on clinical populations consistently revealed higher impulsivity in obese BED compared to obese non-BED (Claes et al., 2006) or compared to normal-weight individuals (Nasser et al., 2004), suggesting a role of impulsivity at the roots of binge eating behavior in obesity.

Interestingly, the evidence on healthy individuals confirmed this assumption. For example, individuals with higher self-reported impulsivity have been reported to have a greater disinhibition in eating behavior, as assessed by the Eating Inventory (Stunkard and Messick, 1985; Lyke and Spinella, 2004) and a stronger tendency to overeat in response to external food cues and to negative emotional states (assessed with the External Eating and Emotional Eating subscales of the Dutch Eating Behavior Questionnaire; DEBQ - Van Strein et al., 1986; Jasinska et al., 2012). Moreover, in the latter study (Jasinska et al., 2012), the authors also demonstrated that heightened impulsivity was associated with a stronger tendency to prefer tasty-unhealthy food in a Food Choice Task[2]. In sum, they found support for an association between unhealthy eating and all three aspects of impulsive behavior (attentional, motor, and non-planning impulsiveness), with higher measures of impulsivity being associated with a greater tendency to choose unhealthy over healthy foods (Jasinska et al., 2012).

Very germane to our study, a recent investigation aimed at assessing impulsivity trait in normal-weight individuals with sub-clinical binge eating (Lyu et al., 2017). Findings revealed higher self-reported impulsivity in individuals who reported to have binge eating episodes compared to normal-weight non-binge eaters (Lyu et al., 2017). Thus they further confirmed a role of impulsivity in binge eating in the general population and implied that trait impulsivity may be a general hallmark of binge eating, regardless of weigh status or the presence of a full-blown eating disorder.

Even though rash impulsiveness seems to have a primary role in the characterization of loss of control eating, in the last decade, many authors examined the possible role of reward and approach tendencies in overeating by means of self-reported measures, such as the BIS/BAS questionnaire (Davis and Woodside, 2002; Loxton and Dawe, 2006). As food can be a positive reinforce, responsiveness to this stimulus potentially plays a substantial role in eating/self-regulation (Dietrich et al., 2014). In fact, these studies confirmed that scores in the BAS reward responsiveness subscale were positively correlated to body weight status and eating habits

[2] The Food Choice Task (Hare et al., 2009) is used to assess decision making about food. In Jasinska et al (2012) paradigm, participants were asked to rates some foods presented in the middle of the screen. The food items includes both healthy snacks (e.g., apple, banana, carrots) and "junk foods" (e.g., potato chips, nachos, candy bars). The subjective ratings were then used to classify all food items into four categories at the individual-subject level: Tasty–Healthy, Tasty–Unhealthy, Untasty–Healthy, and Untasty–Unhealthy.

contributing to weight gain in a sample of healthy women (Davis and Woodside, 2002; Davis et al., 2004; Loxton and Dawe, 2006). On the other hand, higher BIS scores (implicated in avoidance and inhibition) have been described in women as a function of restraint (Yeomans et al., 2015), indicating that the higher the restriction in eating behavior, the greater was the tendency to generally avoid stimuli. Overall, these results might indicate that, in the development of overeating, in addition to the pivotal role of inhibitory control and rash spontaneous impulsiveness, a key aspect is also represented by one's own approach tendency and responsiveness to food (Dawe and Loxton, 2004). Unfortunately, the majority of this evidence focused on samples of women, thus limiting the generalizability to healthy men (Dietrich et al., 2014). Nevertheless, this body of evidence suggests an involvement of impulsivity at the roots of loss of control eating within the general population, opening interesting scenarios on its possible role as a vulnerability and risk for overeating disorders.

2.3.2 State impulsivity and eating behavior

Generally, rash spontaneous impulsiveness is reported to be closely linked to inhibitory control, understood as the ability to inhibit responses and behavior. Within the context of eating behavior, loss of control overeating is thought to be the result of deficits in inhibitory control mechanisms, responsible for the suppression of inappropriate actions (Moore et al., 2017).

In order to investigate this assumption, many researches have used response inhibition paradigms to compare obese samples or individuals with overeating disorders (such as, BED or BN) to healthy controls (for a review see: Guerrieri et al., 2008; Lavagnino et al., 2016). In general, some of these studies showed that diminished inhibitory performance was associated with overeating (Guerrieri et al., 2008), and they underscored the importance of efficient inhibitory control for healthy eating and weight management (Appelhans, 2009). However, clear-cut results on the relationship between inhibitory control performance and binge eating have yet to be established (Bartholdy et al., 2016). As an example, Lavagnino et al (2016) conducted a meta-analysis to investigate the relationship between inhibitory control, obesity and BED, by reviewing studies in which obese with and without BED were compared to healthy controls. They confirmed the presence of inhibitory control deficits in the SST in obese individuals compared to controls, consistently with other findings (Kulendran et al., 2017; Nederkoorn et al., 2006; Weygandt et al., 2015). However, all the studies considered in the meta-analysis did not reveal differences in inhibitory performance between obese individuals with and without BED. Thus, they seemed to

point toward a role of inhibitory control deficits as a critical feature associated with obesity, but regardless of the presence of BED.

One possible reason for the large inconsistencies in literature may lie on the fact that studying individuals already affected by obesity or eating disorders may add weight- or eating disorders-related confounding variables (e.g., weigh-related metabolic changes, history of psychotherapy or pharmacological treatments) on the interpretation of the results.

Unfortunately, the number of studies on preclinical and non-clinical populations is still scarce. One of the few evidence derives from a recent study in which authors aimed at investigating the relationship between inhibitory control and the tendency to overeat (Jasinska et al., 2012). Interestingly, they revealed that greater deficits in inhibitory control, as indexed by higher rates of false alarm in the GNG task, were associated with a greater tendency toward overeating in response to negative emotional states (assessed with the DEBQ subscale) in healthy individuals (Jasinska et al., 2012). In addition, they revealed that inhibitory control deficits in the GNG were negatively associated with the proportion of healthy food items chosen in a Food Choice Task (see paragraph 2.3.1), meaning that higher inhibitory deficits were associated with fewer healthy choices with respect to food. They thus concluded that inefficient inhibitory control might contribute to unhealthy diet, not only by undermining the person's ability to resist the temptation of tasty food, but lowering the proportion of healthy choices made (Jasinska et al., 2012). Even if this is just one of the very few studies on non-obese individuals, it provides important hints, suggesting a possible relation between inhibitory dysfunctions and overeating episodes in the general population.

To date, however, the majority of the evidence on the relationship between eating, weight and inhibitory control remains inconclusive (Bartholdy et al., 2016). It is worth noticing that all the results presented derived from studies that used the term 'response inhibition' broadly, and response inhibition paradigms interchangeably, thus without distinguish between the processes of action restraint and action cancellation. This might have led to mixed findings due to the well-established evidence of the different cognitive and neural mechanisms underlying these two phases of response inhibition (Swick et al., 2011; Simmonds et al., 2008). In addition, some authors hypothesized that, since overeating reflects a lack of inhibitory control toward food, focusing on food-related inhibition, with tasks including not only neutral but also food stimuli, might be more informative in the context of BED (Bartholdy et al., 2016).

In line with this premise, in the following paragraph, some of the studies that used modified version of GNG and SST paradigms using food and neutral stimuli will be presented.

Food-related response inhibition

In order to assess the impact of rewarding stimuli on inhibitory control abilities, some studies have used modified versions of the GNG and SST, including not only neutral cues (i.e., geometric shapes or objects) but also food-related stimuli (e.g., high and low calorie foods). In their recent review, Giel et al (2017) provided an update on the evidence on food-related impulsivity in obese BED. In four to five of the studies reviewed (Schag et al., 2013; Leehr et al., 2016; Manasse et al., 2016; Svaldi et al., 2014), BED patients showed difficulties in inhibitory control, as compared to normal-weight participants and also to obese individuals without BED, however these deficits were mainly irrespective of the stimulus category (food or non-food stimuli; Giel et al., 2017). According to the authors, this might have indicated that, at least in the early stages of stimuli processing, participants were not enhanced when confronted with food and thus the type of stimulus did not impact on inhibitory performance.

Evidence from non-clinical samples derived from a recent study on normal-weight individuals in which authors aimed at exploring inhibitory control abilities in a food-related GNG task, comparing individuals with and without subclinical binge eating episodes (Lyu et al., 2017). In sum, the study showed an increase responsiveness to food cues in binge eaters, indicated by faster reaction times in food trials when compared to non-binge eaters, but no between-group differences in inhibitory control abilities. Nevertheless, when considering the entire sample, faster reaction times to go images and higher false alarm rates on no-go trials (regardless of the stimuli involved) were associated with greater post-task calorie consumption levels[3]. Hence, authors concluded that a greater general tendency to respond rapidly and impulsively may be a marker of subsequent calorie intake and may predict susceptibility to snacking among healthy normal-weight individuals.

Taken together these findings appear to speak in favor of an association between general (rather than food specific) impulsivity and binge eating, regardless of weight-status. Given that in clinical populations (i.e., obese BED) the general inhibitory problem increased as the severity of BED increased (Giel et al., 2017) and in the general population, more impulsive tendency (faster reaction times and higher commission errors) were associated with increased post-task snacking (Lyu et al., 2017), a possible speculation would be that inhibitory control impairments might contribute to problematic eating behaviour (Mobbs et al., 2011).

[3] Post calorie intake: after the GNG task participants were told by the experimenter that they could take as many snacks from the buffet and were left alone for 20 minutes. Total available snacks were weighted with a digital scale before and after this phase, with the difference reflecting the snacks consumed.

Despite the great number of researches on the topic, behavioral results are still often mixed and conflicting (Lowe et al., 2009). On the contrary, neuroimaging investigations have reached much more consistent conclusions (Tataranni and DelParigi, 2003; see paragraph 2.4). Hence, the investigation of the reasons for this difference may yield valuable insights into the underlying mechanisms of binge eating behaviour (Lowe et al., 2009). In the next paragraph, a summary of the major evidence deriving from neuroimaging studies on the topic will be provided.

2.4 NEUROBIOLOGICAL CORRELATES OF OVEREATING

A corroboration of the assumption that impulsivity is a central feature of addictive behaviors, eating and weight disorders, such as BED, obesity and the recently proposed construct of food addiction (Moore et al., 2017; Davis, 2013; Volkow et al., 2013) derives from the investigations of the neurobiological substrates of BED. Despite behavioral results in BED are still often mixed and conflicting (see paragraph 2.3; Lowe et al., 2009), neuroimaging research has shown much more consistency across studies (Tataranni and DelParigi, 2003). Using both functional and structural approaches, neuroimaging studies have identified a variety of brain regions associated with obesity and overeating. Overall, the evidence speaks in favor of the involvement of corticostriatal alterations in BED, similar to those observed in addiction (Kessler et al., 2016). Interestingly, the evidence on BED population are in line with Moore's model of compulsive overeating (Moore et al., 2017) where PFC, extended amygdala and basal ganglia are described as key systems in the neurobiology of overeating.

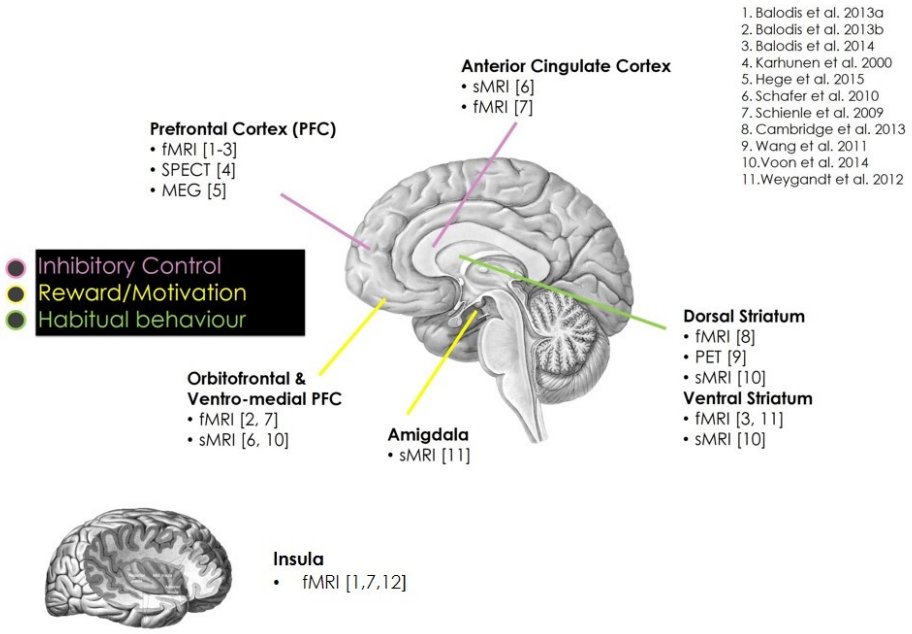


Figure 2.2. Schematic representations of brain circuitry implicated in BED and a neurobiological model proposed by Kessler et al (2016) with respect to reward, inhibitory control and habitual behavior. sMRI: structural Magnetic Resonance Imaging; fMRI: functional Magnetic Resonance Imaging; SPECT: Single Photon Emission Computed Tomography; MEG: Magnetoencephalography; PFC: Prefrontal Cortex. Image adapted from: Kessler et al (2016).

In more detail, Figure 2.2 provides a schematic representation of the neural basis of full-blown BED, which appears to be subserved mainly by the following regions: the PFC (including the vmPFC, DLPFC, ACC and OFC); the dorsal and ventral striatum; amygdala; insula. All these regions have distinct but central roles in some aspects of self- and eating regulation (Berridge and Kringelbach, 2008; Everitt et al., 2008; Small, 2010). The PFC – whose role in response inhibition has been elucidated in the Chapter 1 – is considered to be a crucial region for self-regulation and it allows the modulation of our responses to environmental stimuli by exercising top-down inhibitory control (Miller and Cohen, 2001). The dorsal and ventral striatum underlies habitual behaviors, motivation and reward sensitivity. More specifically, networks encompassing the ventral striatum are critical for the coding of outcome value and regulation of behavior in response to changes in reward value; whereas, networks including the putamen are more involved in habitual performance (Balleine and O'Doherty, 2010; Corbit et al., 2017). The amygdala is involved in overeating to relieve negative emotional states (Moore et al., 2017). And lastly, another critical structure that has been consistently found to be involved in disordered eating mechanisms is the insula (Gaudio et al., 2016). This region is classically known to be involved in interoception and feeding regulation (Everitt et al., 2008; Small, 2010). Nevertheless, the right anterior insula appears to have a pivotal role also in inhibitory control processes (Swick et al., 2011; Ghahremani et al., 2012). Taking into account its

well-established role in interoceptive awareness and processing of salient events, according to some authors, this region identifies salient events and it is responsible for the coordination of other brain networks (i.e., central-executive circuits) to guide behavior (Craig, 2002).

Overall, despite the evidence on BED individuals derives from studies that used different types of approaches (e.g., Single Photon Emission Computed Tomography, SPECT, functional and structural MRI), findings suggest that BED may be associated with dysfunctions in the cortico-striatal circuitry, which regulates behavior, motivation and impulse control (Kessler et al., 2016). According to Kessler et al. (2016), although the clinical relevance of these findings remains to be established, it seems reasonable to hypothesize that altered frontal and striatal function contributes significantly to the altered impulsivity observed in BED individuals.

In the following paragraphs I will briefly cover the evidence deriving from studies that used three different neuroimaging approaches, namely: task-based fMRI, resting-state fMRI and structural MRI. This evidence will be better discussed in the context of the four experiments of the present thesis (**Chapters 4-7**).

2.4.1 Task-based fMRI investigations

The use of behavioral paradigms is by itself fundamental in the study of any condition associated with functional brain changes, given that task-based acquisitions may capture specific dynamic responses in regions with a key role in task processing (Buckner et al. 2009; Mennes et al. 2013). As such, a number of studies have addressed the investigation of functional brain patterns in obesity and overeating by designing task-related fMRI experiments to assess inhibitory control substrates (see Lavagnino et al., 2016). In a meta-analysis of the studies investigating inhibitory control in obese BED and non-BED, Lavagnino et al. (2016) reported that obese individuals with BED compared to non-BED showed reduced activation of PFC regions, such as inferior frontal gyrus (IFG), vmPFC, and DLPFC, in the absence of inhibitory control differences (Balodis et al., 2013; Hege et al., 2014). In addition, some other studies outlined negative correlations between activity in inhibitory control-related brain areas, such as the PFC (superior frontal gyrus, SFG; MFG; and OFC) and current and future Body Mass Index (BMI; Batterink et al., 2010; Weygandt et al., 2013). These results appeared to be consistent with results of lesion studies that indicated an association between impairments of PFC activity, disinhibited eating behavior and subsequent weight gain (Freeman and Watts, 1950, Ikeda et al., 2002, Landtblom et al., 2002, Piguet, 2011, Regard and Landis, 1997, Whitwell et al., 2007). Conversely, successful dieting has been positively associated with PFC

activation (Weygandt et al., 2013). Hence, a fair assumption would be that dysfunctional inhibitory control, subserved by lower activation of PFC regions, may be at the roots of overeating behavior, that eventually lead to weight gain (Lavagnino et al., 2016).

Among the studies investigating the neural basis of inhibitory control, a small number used food-specific GNG or SST in combination with neuroimaging measures. Hege et al. (2015) used a modified version of the GNG with food stimuli to assess brain activity during response inhibition in obese and BED individuals. The authors did not find differences in behavioral performance and brain activity between obese and BED individuals. However, they revealed a strong negative correlation between self-reported impulsivity and recruitment of right PFC regions during response inhibition, especially in BED patients: those with higher trait impulsivity recruited these brain circuits less during response inhibition. Thus, impulsive individuals who tended to have rash spontaneous behaviors showed decreased activity in the right PFC regions, involved in response control. This impulsivity-related attenuation might have been related to limited resources to activate PFC regions during inhibitory control performance (Hege et al., 2015).

Another study used a food-specific GNG task to compare women with bulimia nervosa (BN)[4] to a control group (Skunde et al., 2016) and revealed that the latter performed better than women with BN in inhibiting motor responses toward neutral no-go stimuli. For the food-specific no-go trials, on the other hand, no group differences in accuracy were observed. In accordance with behavioral results, they showed lower frontostriatal activity in BN with a high symptom severity compared with healthy controls, in the neutral no-go trials (and not specifically in food no-go trials), suggesting a more generalized impairment of behavioral inhibition, sustained by cortico-striatal functional alterations, rather than a disorder-specific impairment (Skunde et al., 2016).

Overall, the findings from both food-specific and general response inhibition tasks confirm an involvement of cortico-striatal circuit in the characterization of inhibitory control in BED. But, results are still mixed concerning the specificity of these results for food inhibition. Nevertheless, studies that used food-specific tasks in BED and BN individuals, highlighted diminished activity in cortical and cortico-striatal circuit as impulsivity and symptom severity (i.e., binge eating) increased (Hege et al., 2015; Skunde et al., 2016). Given that all these clinical conditions are characterized by the presence of binge eating episodes (in different sizes and frequencies), results of these studies substantiate the importance of the investigation of brain-related markers, especially in specific

[4] Bulimia Nervosa (BN) is an eating disorder defined by repeated episodes of binge eating followed by compensatory behaviors (i.e., fasting, vomiting, excessive physical activity, or misuse of laxatives/diuretics; APA, 2013)

subgroups of individuals at the risk for overeating and overweight (such as, binge eaters; Hege et al., 2015).

2.4.2 Resting-state fMRI investigations

Even though in the last decade researchers focused on identifying regions specialized in specific cognitive and behavioral tasks, more recently the interest has shifted toward a wider prospective aiming at investigating how multiple brain regions interact and how this may relate to behavioral phenomena or personality traits (Rosazza and Minati, 2011). Similarly to the majority of fMRI studies, also rsfMRI investigations focused mainly on excessive-weight populations, without focusing on BED individuals. Still, the evidence on overweight people seems to consistently highlight impairments within impulsivity-related networks (Chodkowski et al., 2016; Garçia-Garçia et al., 2015; Moreno-Lopez et al., 2016; Park et al., 2016). For example, a recent rsfMRI study aimed at exploring the associations between unhealthy eating, impulsivity and functional connectivity at rest in obese children (Chodkowski et al., 2016). Using seed-based analysis, they assessed functional connectivity between regions associated with response inhibition (inferior parietal lobe [IPL]), impulsivity (frontal pole [fPole]), and reward (nucleus accumbens [NAc]). Results highlighted that as impulsivity-associated functional connectivity increased (i.e., stronger frontal pole:NAc connectivity), food approach behaviors and adiposity also increased (Chodkowski et al., 2016). These results confirmed a relationship between impulsivity and food approach, but more importantly they provided new insights into the relationship between functional connectivity patterns (in frontal, parietal and striatal regions) and unhealthy eating behavior and weight gain.

As another example, it has been revealed a lower functional connectivity (i.e., functional centrality) in the right MFG, a region involved in inhibitory control and monitoring processes, in obese compared to NW individuals (Garçia-Garçia et al., 2015). This lower functional centrality most likely indicated a lower total number of connections (perhaps a diminished communication) between this region and the whole network. Interestingly, this study revealed lower functional centrality in the right MFG both at rest and during a visual task. Hence, the authors concluded that this aspect might be considered a trait characteristic of obesity and thus, a potential risk factor for the development and maintenance of this condition (Garçia-Garçia et al., 2015).

A further investigation of frontal and parietal functional connectivity derives from a recent study on overweight individuals (Contreras-Rodriguez et al., 2017). In their work, authors showed increased functional connectivity between the ventral caudate and medial PFC as well as between

the ventral striatum and parietal cortex in overweight individuals compared to normal-weight. In addition, food craving[5] (i.e., generally referred to as an intense desire to consume a specific food) was correlated with connectivity between the dorsal striatum and the somatosensory cortex, with greater associations for those with high BMI. These results confirmed the involvement of regions of the dorsal and ventral striatum at the roots of overweight conditions: based on the well-known role of these structures in behavioral control (see Figure 1.7), increased connectivity in these regions might cause food stimuli to be more salient, which in turn could increase the probability of food cravings and loss of control overeating (Contreras-Rodriguez et al., 2017; Corbit, 2017).

Lastly, a bulk of data reported functional alterations within the insular region in eating-related disorders, linking them to a disrupted tuning towards interoceptive inputs (Avery et al., 2017; Mata et al., 2015; Moreno-Lopez et al., 2016) and altered reward-related processes (Brooks et al., 2013; Gaudio et al., 2016; Kullmann et al., 2012; Wijngaarden et al., 2015). It may be possible that insula altered connectivity underlies an approach toward food dominated by a reward-seeking behavior, rather than by interoceptive information from the body (Mata et al., 2015). If so, eating behavior would not be guided by our signals of hunger and satiety (i.e., interoceptive signals), but by our sensitivity to the rewarding effect of a certain foods.

All these rsfMRI studies, in accordance with the task-based, support a role of impulsivity in overeating (in overweight populations), by highlighting functional alterations in impulsivity-related regions and networks, such as prefrontal and subcortical regions (Park et al., 2016; Moreno-Lopez et al., 2016; Garçia-Garçia et al., 2015). Crucially, the overlapping evidence from task-based and resting-state fMRI investigations provides additional valuable information to the study of functional brain processes, allowing the identification of more fundamental brain activity and connectivity patterns (Fox and Greicius, 2010). Moreover, they underline the importance of considering the brain as a whole, with the different patterns of functional connectivity giving important insights on the substrates of the diverse facets of impulsivity over eating behavior (Davis et al., 2013).

2.4.3 Structural MRI investigations

As already outlined in Chapter 1 (paragraph 1.3.4), structural MRI provides information about brain anatomy. The analysis of structural data, by means of morphometric techniques of analysis

[5] **Food craving** was assessed asking participants to rate their level of craving while viewing six photographs of highly appetizing foods (e.g., cheesecake, chocolate). Ratings were made using a Visual Analog Scale (VAS; range 0–10).

(such as, VBM), provides measures of the volume of the gray matter structures, both at the cortical and subcortical level. The identification of structural changes in the brain is central in the investigation of diverse pathologies (e.g., neurological and psychiatric disorders; Whitwell, 2009).

To date, not many researchers have used VBM to investigate brain volumes in BED individuals. One of the first study exploring GMV abnormalities in patients suffering from binge-eating syndromes (i.e., BED and BN) was conducted by Schäfer et al. (2010). They highlighted the both eating-disordered groups – compared to healthy controls – were characterized by increased medial OFC volumes, a region that represents the hedonic value of food stimuli (Kringelbach and Rolls, 2003), whose greater activity has been reported during anticipation of reward in fMRI studies (O'Doherty et al., 2002). Thus, these data might implicate a crucial role of the medial OFC in bulimic-type eating disorders, namely those characterized by the presence of binge eating episodes. The structural abnormality might be associated with dysfunctions in food reward processing and/or self-regulation (Schäfer et al., 2010).

More recently, a couple of studies sought to examine the relationship between eating behavior traits and brain structural changes in the general population (Yao et al., 2015; Maayan et al., 2011). Maayan and colleagues (2011) employed a region of interest (ROI) method to analyze the relationship between disinhibition and PFC volumes. They showed that higher disinhibition scores in the Three Factor Eating Questionnaire (TFEQ; Stunkard and Messick, 1985), indicating enhanced dysregulation toward food, were negatively correlated with the OFC volume (Maayan et al., 2011). Thus, greater disinhibition toward food was associated with lower GMV within the OFC. On the other hand, Yao et al (2016) considered a large sample of normal-weight, overweight and obese individuals and investigated GMV at a whole brain level, correlating these variables with the scores of the TFEQ subscales: restraint (i.e., the purpose of restraining intake assumption) and disinhibition (i.e., dysregulation over food). They showed that (i) restraint was positively correlated with the GMV in the DLPFC and negatively correlated with the GMV in the putamen; and (ii) disinhibition scores were negatively associated with the GMV in the left MFG. Irrespective of the directionality of these correlations, they revealed that different aspects of eating behavior were tightly correlated with the GMV of brain regions involved in homeostatic keeping, cognitive control and habitual learning (Yao et al., 2016).

Thus, overall results indicated a close connection between eating behavior, weight status and structural changes in specific brain regions, mainly associated with the behavioral control, habitual learning and reward (Pannaciulli et al., 2006). Despite the paucity of studies on the topic,

the consistency of these results among different clinical and non-clinical populations may confirm the evidence of a fronto-striatal involvement at the roots of overeating behavior. Nevertheless, further studies are needed to clarify if these alterations might play a role as vulnerability and risk factors for developing an eating disorder or whether they are the results of disorder-specific behaviors (e.g., bingeing) and/or altered nutritional status (Schäfer et al., 2010).

2.5 TAKE HOME MESSAGE

This Chapter aimed at reviewing the current theoretical models of overeating, and the behavioral and neural evidence on the relationship between impulsivity and eating behavior. While the evidence on self-reported impulsivity shows an association between overeating behavior and higher trait impulsivity, in both clinical and non-clinical populations of binge eaters (e.g., Lyu et al., 2017), findings on behavioral inhibition are still contradictory. The impact of BED on response inhibition abilities, indeed, is not clear: the majority of the evidence on the topic focused on obese and overweight individuals and besides, used different behavioral paradigms interchangeably, thus relying on a unitary definition of 'response inhibition' (Giel et al., 2017; Lavagnino et al., 2016). On the contrary, neuroimaging studies are more consistent in indicating the involvement of fronto-parietal and fronto-striatal regions in the characterization of overweight and overeating conditions. Interestingly, these regions, generally implicated in eating disorder symptomatology (Figure 2.3) are overlapping with those involved in behavioural regulation (Figure 1.7; Chapter 1).

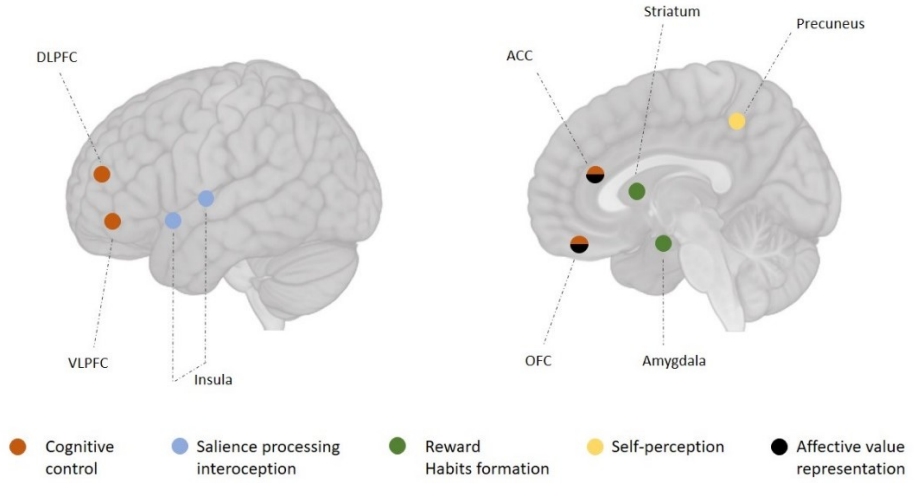


Figure 2.3. Visual representation of the brain regions mostly implicated in eating disorder symptomatology according to Steward et al., 2018. Image adapted from: Steward et al. (2018). Abbreviations: DLPFC: Dorsolateral Prefrontal Cortex; VLPFC: Ventrolateral Prefrontal Cortex; OFC: Orbitofrontal Cortex; ACC: Anterior Cingulate Cortex.

This evidence provides additional support to the assumption that impulsivity may play a central role in the characterization of disordered eating, therefore, further investigation of these regions and mechanisms with different approaches may contribute to a better understanding of the role of these aspects as risk factors for binge eating (Atalayer et al., 2018). In this context, the

combined investigation of normal-weight individuals with binge eating episodes, presented in this thesis, may provide greater insights into the investigation of the behavioral and neurobiological basis of disinhibited eating behavior.

PART II

EXPERIMENTAL WORK

Aims and Outline of the Experimental Work

From the evidence thus far compiled, deficits in inhibitory control abilities and greater impulsivity seem to play a cardinal role in the characterization, and possibly, in the development of overeating (Davis et al., 2013; Dawe and Loxton, 2004; Schag et al., 2013). A recent hypothesis is indeed that impulsivity may contribute to the onset of overeating behavior and the progression toward weight gain (Atalayer et al., 2018). Unfortunately, to date the majority of behavioral and neuroimaging studies on impulsivity and overeating focused on the already-obese individuals or full-blown BED, limiting the generalizability of the results to individuals in the general population and telling little about the underlying mechanisms potentially leading to uncontrolled eating behavior (Lowe et al., 2009). In addition, although it is widely accepted that impulsivity is a multifaceted construct, this aspect is often not considered when it comes to its measurement (King et al., 2014). Indeed, most of the researches on the topic did not combine different measures and approaches to explore impulsivity in the same group of individuals, hence delivering only a partial and incomplete description of this complex construct (King et al., 2014).

Drawing upon these gaps in the current literature, this PhD thesis aims at providing a comprehensive account of impulsivity in normal-weight individuals with binge eating episodes, combining both behavioral and neuroimaging methods, and opening a new window onto the role of impulsivity at the roots of overeating behavior. The experimental work presented in the thesis involves four studies, all considering the same samples: two groups of normal-weight individuals with and without binge eating episodes. Participants were selected according to self-reported Body Mass Index (BMI) and to a complete assessment related to eating behavior (Eating Attitude Test, Garner et al., 1982; Binge Eating Scale; Gormally et al., 1982; see Chapter 3).

Overall, the whole project involved a combination of the following measures:

- Self-reported questionnaires to assess general *trait* impulsivity [Experiment I-IV]
- Response inhibition paradigms to measure *state* impulsivity [Experiment I-II]
- *Functional* MRI data to assess brain activity during the execution of a task [Experiment I-II]
- *Functional* MRI data to assess brain activity at rest [Experiment III]
- *Structural* MRI data to assess brain morphometry [Experiment IV]

A summary of the main aims and measures used in each experiment is provided below.

Task-based functional MRI investigation (Chapter 4 and 5)

Chapter 4 and 5 will describe the first two Experiments (I and II), whose aim was to assess response inhibition abilities toward food stimuli and their neural underpinnings. To this purpose, we designed two task-related fMRI experiments:

- A food-specific GNG paradigm, assessing action *restraint* toward food and non-food stimuli (Chapter 4);
- A food-specific SST, assessing action *cancellation* processes (Chapter 5).

Analysis of fMRI data collected during the execution of both focused on functional brain patterns associated with response inhibition toward food and non-food stimuli.

Resting state functional MRI investigation (Chapter 6)

Chapter 6 will explore resting-state brain activity. While task-based fMRI is useful to capture specific dynamic responses in regions with a key role in task processing, rsfMRI may allow for the identification of more fundamental brain activity patterns and traits underlying specific conditions, not task-related (Fox and Greicius, 2010; paragraph 1.3.3). In this experiment, we used different approaches to analyze global and local functional connectivity at rest, at a whole brain level.

Structural MRI investigation (Chapter 7)

Chapter 7 will focus on brain morphometry, exploiting VBM to examine regional and global grey matter volumes (GMV). In this experiment, we aimed at comparing the two groups in regional GMV, correlating these differences with measures of trait impulsivity.

The novelty of the whole project lies mainly on two aspects. *First*, as previously outlined, impulsivity and inhibition mechanism in eating behavior have been investigated mainly in clinical populations (e.g., obesity or BED). Investigating impulsivity in normal-weight healthy individuals, with subclinical binge eating, may provide new insights into the role of inhibitory control deficits and heightened impulsivity at the roots of the tendency to lose control over eating behavior, regardless of weight status. *Second*, the integration of multiple neuroimaging approaches (functional and structural) may offer complementary information on impulsivity underpinnings in this population (Davis et al., 2013).

Overall, this project delivers the opportunity to advance a broad neuro-behavioral understanding of the role of impulsivity at the roots of overeating behavior within the general population. Findings may hold promise in mapping the hallmarks and potential risk factors for overeating (Davis et al., 2013).

Chapter 3
GENERAL PROCEDURE OF THE EXPERIMENTAL WORK

The next section will provide an overview of those aspects of the general procedure that are shared among the four experiments of the thesis (Chapters 4-7).

3.1. PARTICIPANTS

We recruited normal-weight (NW) male and females ranging from 20 to 35 years old and divided them in two groups according to the declared occurrence of BE episodes. The BE status was certified by means of the behavioral questions of the Eating Attitude Test (EAT 26 – Garner et al., 1982), assessing the presence of BE episodes and the absence of compensatory behaviors (i.e., excessive physical activity, purging etc.). In more detail, these items were considered:

- *"I have gone on eating binges where I feel that I may not be able to stop"* which was scored on a six-point scale ranging from 1 (never) to 6 (once a day or more).

The following items assessed the absence of purging behavior in both groups:

- "*Ever made yourself sick (vomited) to control your weight or shape?"*
- *"Ever used laxatives, diet pills or diuretics to control your weight or shape?"*

Further, the absence of a history of eating disorders was assessed by one item:

- *"Have you ever been treated for an eating disorder?"*

Participants reporting at least one BE episode per month in the last three months (i.e., at least three episodes in the last three months) constituted the BE group, while participants declaring to have never had a BE within the same time window constituted the non-BE group. To further confirm the surmised BE status we used the Binge Eating Scale (BES – Gormally et al., 1982): participants who reported no episodes of overeating were expected to score lower than 8 in the BES to be included in the non-BE group (Filbey et al., 2012). Every participant of both groups scored as expected in the BES and was included in the group to which they belonged (Appendix A; Figure A1).

Participants of both groups had a Body Mass Index (BMI; kg/m^2) ranging from 18.5 to 24.9 and were right-handed according to the Edinburgh Handedness Inventory (EHI – Oldfield, 1971). In addition, for both groups specific exclusion criteria had to be fulfilled, such as: no history of psychiatric,

neurological disorders or head injuries, absence of other relevant medical issues, absence of psychoactive medication or psychotherapy. Further, all participants had to be checked with safety criteria for MRI examination (e.g., metal implants, pacemaker, claustrophobia, etc.). 10 participants were excluded after the screening (rejection was mainly due to MR exclusion criteria, treatment with psychoactive medication, history of eating disorder, psychotherapy and high degree myopia). The finale sample involved 21 participants for the BE group (17 females; age: M= 23.9, SD= 3.19) and 21 participants for the non-BE group (16 females; age: M= 25.23, SD= 3.08). The study was conducted according to the guidelines provided by the Declaration of Helsinki and the ethical requirements of the University of Padua.

3.2 PROCEDURE

Participants were recruited through local advertisements at the University of Padua. The screening for exclusion criteria (see paragraph 3.1) and a complete description of study procedures was carried out during the first appointment. During the same appointment they were asked to fill out the written informed consent, to complete self-report assessment related to eating behavior and impulsivity, and to report their height and weight (in order to compute BMI). If they meet all inclusions criteria (NW range, BE status as assessed by the BES and EAT-26, MRI criteria), the MR measurement was scheduled for a subsequent appointment (approximately one week after the screening). Before the fMRI measurement, participants were asked to refrain from drinking caffeinated beverages and from smoking for 3 hours preceding their imaging session. Since hunger might be an additional factor to consider in the assessment of response inhibition toward food, we ensured comparable hunger states of participants by instructing them not to come hungry to the imaging session and to consume a small meal right before their appointment (Loeber et al., 2013; Price et al, 2016). All fMRI-scanning sessions occurred between 2 pm and 6 pm. All participants underwent: task-based fMRI (Chapter 4 and 5); resting-state fMRI (Chapter 6); structural MRI (Chapter 7) acquisition.

3.3 MATERIALS AND METHODS

3.3.1 Questionnaires

During the screening, all participants completed the self-reported assessment related to impulsivity, eating behavior and the feelings and thoughts associated with such behavior (a copy of the questionnaires adopted included in Appendix A).

Impulsivity measurements included:

a. Barratt Impulsiveness Scale (BIS-11 – Patton et al., 1995): in line with the definition of impulsivity as a multidimensional construct, the BIS-11 investigates distinct forms of impulsivity: attentional impulsivity (the inability to concentrate or focus attention), motor impulsivity (the tendency to act without thinking), and non-planning impulsivity (lack of future orientation or forethought).
b. Behavioral Inhibition/Behavioral Activation Scale (BIS/BAS – Carver and White, 1994): it refers to two complementary motivational systems controlling behavior. The BIS represents the aversive motivational system, sensitive to cues of punishment/non-reward and supposed to inhibit behavior that may lead to negative outcomes (e.g., "*I worry about making mistakes*"; the BAS represents the appetitive motivational system which is sensitive to cues of reward and instrumental in activating goal directed behavior (e.g., "*When I see an opportunity for something I like I get excited right away*"; Gray, 1991). Responsiveness of both systems (BIS and BAS) is thought to play a substantial role in body weight regulation (Dietrich et al., 2014).

Eating behavior assessment included:

c. EAT-26 (Garner et al., 1982): it is a screening questionnaire that allows to assess the possible presence of an eating disorder, by measuring the symptoms and concerns that are characteristic of eating disorders (e.g., "*I give too much time and thought to food*"). In the present research, we were interested in assessing the presence of BE episodes and the absence of a history of eating disorders or compensative behaviors; therefore we specifically focused on the behavioral questions of the questionnaires (see paragraph 3.1).
d. BES (Gormally et al., 1982): it is a 16-item questionnaire used to assess the presence of binge eating behavior with questions based upon both behavioral characteristics (e.g., amount of food consumed; "*I eat 3 meals a day, but I also normally snack between meals*") and the emotional, cognitive response (e.g., guilt/shame, preoccupation with food and eating; e.g., "*I feel like I have failed to control my eating more than the average person*"). Given that an increasing number of

perspectives conceptualizes overeating as a 'food addiction', involving changes in brain regions implicated in executive functions, reward and interoceptive processes (Barry et al., 2009; Volkow et al., 2013), we decided to further investigate the potential differences between the two groups in their eating behavior with the YFAS.

e. Yale Food Addiction Scale (YFAS – Gearhardt et al., 2009): it is a 25-item self-reported measure used to identify those who are most likely to be exhibiting markers of substance dependence with the consumption of high fat/high sugar foods. The answers to the items (both dichotomous and Likert-type format) are used to obtain food-addiction symptoms count (e.g., loss of control, tolerance) based on the criteria for substance dependence of the DSM IV-TR (American Psychiatric Association, 2000). The questionnaires' items refers to the person's eating habits of the past year (e.g., "*I find that when I start eating certain foods, I end up eating much more than planned*").

3.4 ANALYSIS: SELF-REPORTED MEASURES

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS; IBM Corp. 2015). In order to assess between-group differences in total and subscales questionnaires' scores we performed two-sample t-test analysis. The statistical significance level for these analyses was set at $p < .05$.

3.5 DESCRIPTIVE CHARACTERISTICS OF THE SAMPLES

Descriptive characteristics and scores of the self-reported questionnaires are shown in Table 3.1. The two groups did not differ for age, sex (~ 30% males) and BMI parameters. The groups differed in most of the total and subscales' scores of the questionnaires. The BE group was characterized by higher scores in the BES (BE: M= 17.7 ± 3.8; non-BE: M= 3.8 ± 2.6), YFAS (BE: M= 3.05 ± 1.43: non-BE: 0.29 ± 0.56) and BIS 11 (BE: M= 63.4 ± 8.8; non-BE: M= 56 ± 7.5), whereas, non-BE had higher scores for the BIS (BE: M=13.3 ± 2.3; non-BE: M=16.2 ± 3.6) and the BAS drive (BE: M= 7.8 ± 1.7; non-BE: M= 9.3 ± 1.9) subscales of the BIS/BAS questionnaire. No significant differences between the groups were revealed in the reward responsiveness subscale (BE: M= 7.3 ± 1.8; non-BE: M= 7.6 ± 2.1) of the BIS/BAS questionnaire. Hence, the BE group, compared to non-BE, showed an enhanced *general trait* and *food-related* impulsivity (as assessed by the BES, YFAS and BIS-11), but did not show

a greater responsiveness to general rewards (as indicated by the lack of differences in the 'reward responsiveness' subscale of the BAS questionnaire).

Characteristics	BE (n=21)	Non-BE (n=21)	Two-sample t-test	
	M ± SD	M ± SD	t	p
AGE	23.9 ± 3.19	25.23 ± 3.08	2.05	.191
BMI (kg/m^2)	22.3 ± 2.1	21.29 ± 2.02	1.73	.074
BES	17.7 ± 3.8	3.8 ± 2.6	17.1	.000*
YFAS	3.05 ± 1.43	0.29 ± 0.56	8.23	.000*
BIS-11				
- Attentional subscale	17.05 ± 3.7	15 ± 3.3	1.8	.075
- Motor subscale	20.73 ± 4.2	17.75 ± 3.3	2.5	.015*
- Non-planning subscale	26.32 ± 5.1	22.25 ± 4.1	2.8	.007*
- Total score	63.4 ± 8.8	56 ± 7.5	2.7	.011*
BIS/BAS				
- BAS Reward responsiveness	7.3 ± 1.8	7.6 ± 2.1	0.43	.075
- BAS Drive	7.8 ± 1.7	9.3 ± 1.9	2.51	.017*
- BAS Fun seeking	8.7 ± 2.1	9.4 ± 2.4	1.03	.13
- BIS	13.3 ± 2.3	16.2 ± 3.6	2.88	.007*

Table 3.1 Descriptive characteristics of the samples. The following details are reported: M= mean; SD= Standard Deviation; t score and p-value. BMI: Body Mass Index; BES: Binge Eating Scale; YFAS: Yale Food Addiction Scale; BIS-11: Barratt Impulsiveness Scale; BAS: Behavioral Activation System; BIS: Behavioral Inhibition System; Non-BE: non-binge eaters; BE: Binge Eaters.

Chapter 4
EXPERIMENT I

The Neural Correlates Of Action Restraint toward Food in Normal-Weight Binge Eaters: A Task-Based fMRI Study

This experiment forms part of a manuscript, recently submitted to: *NeuroImage Journal*.

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4.1 BACKGROUND

Converging evidence suggests that dysfunctional inhibitory control and heightened impulsivity might be at the roots of overeating behavior (Stice et al., 2013; Chapter 2). The theoretical dual-process model of overeating posits that this behavior may arise from the combination of two different aspects within the impulsivity framework: a decreased ability to inhibit responses coupled with heightened approach/sensitivity toward reward (Dawe et al., 2004; Houben et al., 2014; Moore et al., 2017; Nederkoorn et al., 2006). In support of these models, mounting evidence has reported higher impulsivity trait (Micanti et al., 2017; Schag et al., 2013) and dysfunctional inhibitory control, during food-specific response inhibition paradigms (Giel et al., 2017), in overweight individuals with Binge Eating Disorder (BED). In addition, converging fMRI investigations of the neural basis of BED have highlighted an involvement of fronto-striatal regions, implicated in impulsivity-related aspects, in the characterization of this condition (for review see: Kessler et al., 2016; Lavagnino et al., 2016; or Chapter 2, paragraph 2.4).

Unfortunately, most of these findings linking inhibitory control deficits to overeating stems from studies on obese populations (Lavagnino et al., 2016; Giel et al., 2017), therefore, given the well-established effects of weight gain on cognitive processes (Horstmann et al., 2015; Smith et al., 2011; van den Akker et al., 2014), it may be possible that defective inhibitory abilities are consequences of having developed a weight disorder. On the contrary, we hypothesized that heightened impulsivity or dysfunctional inhibitory control might act as potential prodromes and that can be evident also in a non-clinical condition, when binge eating episodes are present (without a diagnosis of BED) and a normal Body Mass Index (BMI) is preserved.

In order to address these issues, the experiment described in this chapter aimed to examine the behavioral and neural correlates of response inhibition, in normal-weight individuals with binge eating episodes.

Given the multi-dimensional nature of the impulsivity construct (Bari and Robbins, 2013), we combined different measures:

- *Self-reported* measures to assess general-trait impulsivity;
- *Reaction times* and *accuracy* in performing a food-specific Go/No-Go (GNG) task to examine response inhibition abilities;
- *Task-related brain activity* measured by fMRI during the execution of the GNG.

The GNG – used to examine one aspects of response inhibition (namely, *action restraint* see Chapter 1, paragraph 1.2.2) – has been modified to measure the ability to manage impulses towards a specific category of stimuli, which is food. To this end, images depicting both common use objects (non-food; e.g., household items) and palatable food (e.g., ice-cream, pizza, etc.) have been included to disentangle possible differences in the ability to inhibit pre-potent responses according to the nature of the stimulus and to assess the effect of a possible bias for food on inhibitory control.

In conclusion, our study meant to explore whether:

(i) BE and non-BE differed in response inhibition abilities;

(ii) BE and non-BE showed differential patterns of brain activation during the execution of the task;

(iii) Differences were generalized across food and non-food conditions or specific for response inhibition toward food stimuli.

4.2 METHODS

4.2.1 Procedure

See Chapter 3 for the 'GENERAL PROCEDURE OF THE EXPERIMENTAL WORK'.

In this experiment, participants underwent an fMRI measurement during the execution of a food-specific GNG task (see paragraph 4.2.2 for details). Before the imaging session, participants were familiarized with the behavioral paradigms through a practice session with additional stimulus material (stimuli that were not used in the paradigms during the fMRI acquisition).

4.2.2 Go/No-Go Task

The GNG is a measure of response inhibition that requires participants to perform speeded responses on go trials and to inhibit responding on no-go trials - *action restraint* (Schachar et al., 2007; paragraph 1.2.2, Chapter 1). It involves a high load on response selection since the participant has *a priori* knowledge about whether or not to respond to a certain stimulus. In this context, the food-specific GNG paradigm was designed to examine inhibition of prepotent responses to food stimuli compared to non-food stimuli. The task was programmed using E-Prime 2.0 presentation software (Psychology Software Tools, Inc. Pittsburgh, PA) and consisted of two runs, in which pictures of food (i.e. hamburger, ice-cream, sandwich etc.) or non-food (i.e. tools, books etc.) were presented. Participants had to either press a button with their right hand or inhibit their response to each

picture, according to the instructions at the beginning of each run (e.g., "*Press the key button as fast as you can with the right index finger whenever a food image appears on the screen. Do not press the key button when non-food images appear"*). The role of food and non-food images was different according to the run: in the "GO FOOD" run, food pictures served as target stimuli, therefore participants were told to press the button with the right index finger to food pictures (GO) and withhold their response to non-food pictures (NO-GO). Conversely, in the "GO NON-FOOD" run, non-food pictures served as target stimuli, therefore participants were told to press the button with non-food stimuli (GO) and to withhold their response to food stimuli (NO-GO). The order of the runs was counterbalanced across participants. In either case, participants were instructed to respond as quickly and accurately as possible. In order to develop a prepotent response pattern, the GO stimuli appeared in 75% of the trials of each run (n=75 trials/run) and NOGO stimuli appeared 25% of the time (n=25 trials/run; Réveillon et al., 2013; Shultz et al., 2007).

At the beginning of each run, an instruction slide was presented as a reminder. In each run, the trials began with a fixation cross (1000 milliseconds), followed by a non-food or a food stimulus presented for 500 milliseconds. The time window to respond lasted 1000 milliseconds. Within a given run, trials were separated by a random inter-trial interval (ITI) ranging from 2000 to 5000 milliseconds, in order to better capture the hemodynamic response (Figure 4.1). The order of the stimuli was randomized across participants and the order of the runs was counter-balanced across the groups to further optimize the efficiency of the design. Each run lasted 9 minutes and 15 seconds (18 minutes and 30 seconds scanning in total).

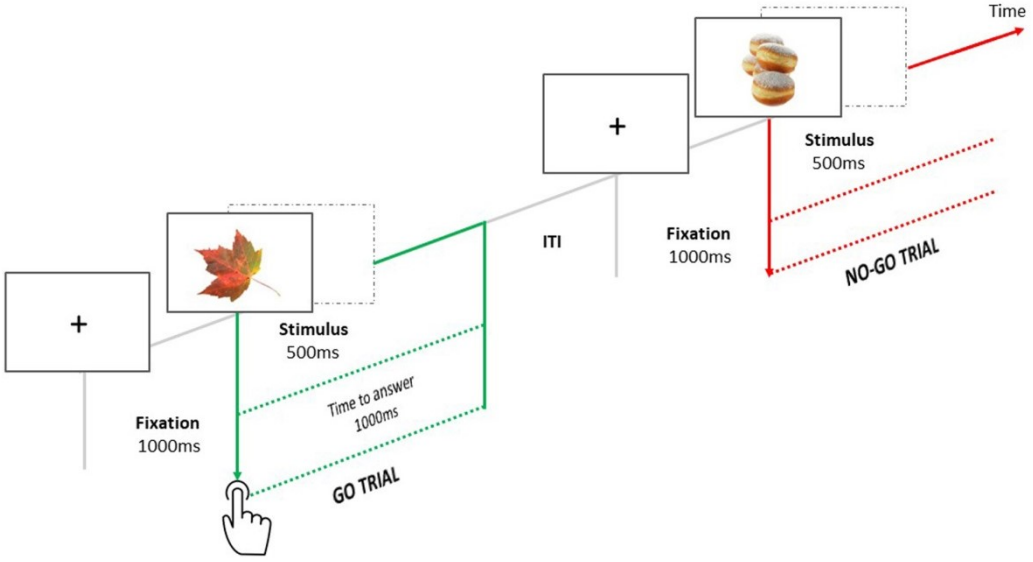

Figure 4.1 GNG task. Example of 'go non-food run': participants had to respond to non-food stimuli (75%) and withhold the response to food stimuli (25%). Stimuli appeared (for 500ms) after a random Inter-Trial interval, ITI (2000-5000ms) followed by the appearance of a fixation cross (1000ms). The instructional set of the other run ('go food') was the opposite. ITI: Inter-Trial Interval.

4.2.2.1 Stimuli

Stimuli were either food (sweet and savory foods/meals) or non-food images (objects that had no association with eating, such as books, cars or household items - Figure 4.2). Both food and non-food images were items with simple figure-ground composition in the center of the visual field and were presented only once in the whole task. Food pictures were selected from the *food.pics database-extended* (www.food-pics.sbg.ac.at) which contains information on calorie content, subjectively rated palatability and physical features of the food pictures (Blechert et al., 2014). Non-food images were selected as to match as close as possible for size, colors and visual complexity.

Figure 4.2. Examples of food and non-food stimuli used for both paradigms, included in the *food.pics database-extended* (Blechert et al., 2014).

4.2.3 Acquisition

4.2.3.1 Behavioral data

The GNG task was administered using E-Prime 2.0 presentation software (Psychology Software Tools, Inc. Pittsburgh, PA). Participants executed the task during the fMRI measurement: during stimuli presentation, they were lying down in the scanner, wearing MR-compatible LCD video goggles (VisuaStim XGA, Resonance Technology Inc.) with a resolution of 800x600 and 60 Hz refresh rate. Responses to the task (see section 4.2.2.1) were given with the index finger of the right (dominant) hand using an MR-compatible response box (Evoke Response Pad, Resonance Technology Inc.).

4.2.3.2 Magnetic Resonance Imaging (MRI) data

Whole-brain functional Magnetic Resonance Imaging (fMRI) data were obtained using a 1.5 T Siemens Avanto MRI scanner (Siemens Medical Systems, Erlangen, Germany) equipped with a standard Siemens eight-channel coils. Functional images were acquired with a gradient-echo, echo-planar (EPI) T2*-weighted sequence in order to measure blood oxygenation level-dependent (BOLD) contrast throughout the whole brain (37 contiguous axial slices acquired with ascending interleaved sequence, 56 × 64 voxels, 3.5 mm × 3.5 mm × 4.0 mm resolution, Field of View, FOV = 196 mm × 224 mm, flip angle = 90°, TE = 49 ms). Volumes were acquired continuously for each run with a repetition time (TR) of 3 seconds. Functional data were collected in two runs of 188 volumes each (9 min and 15 seconds each; 18 minutes and 30 seconds total scanning time). A high-resolution structural MRI image was also acquired with a T1-weighted sequence (176 axial slices with no interslice gap, data matrix = 256 × 256, 1 mm isotropic voxels, TR = 1900 ms, TE = 2.91 ms)

4.2.4 Analyses

4.2.4.1 Behavioral data

Analyses of behavioral data were conducted with R (R Core Team, 2017), lme4 (Bates et al., 2015), and lmerTest (Kuznetsova et al., 2014). Statistical analyses were carried out by means of linear mixed-effect model (LME) for reaction times (RTs) and generalized mixed-effect model (GLME) with binomial link function for commission errors (Pinheiro and Bates, 2000). These models provide greater statistical power compared to traditional repeated measures ANOVA, and a robust method for the analyses of repeated and unbalanced measures, such as RTs (Baayen et al., 2008). LME and

GLME allow taking into consideration both the standard and the random-effect factors. In this study, fixed effects consisted of group (BE and non-BE) and condition (food and non-food); whereas, random effects consisted of experimental blocks and participants. Models were fitted using the Restricted Maximum Likelihood (REML) and p-values were estimated by likelihood ratio tests (LRT) of the full model with the effect in question against the model without the effect in question. LRT tests the difference in two nested models using the Chi square distribution.

The two groups were compared for (1) RTs in milliseconds for correct GO trials and (2) percentage of commission errors (a 'GO' response for NO-GO trials). The main effect of condition and group and the interaction group-by-condition were considered in the analysis.

4.2.4.1 Magnetic Resonance Imaging (MRI) data

Data were preprocessed and analyzed using SPM12 (www.fil.ion.ucl.ac.uk/spm) working in Matlab environment (MathWorks, Natick, MA, USA). The ArtRepair (AR) toolbox was used to detect slices corrupted by motion artifacts and/or signal spikes at both slice and entire volume levels (Mazaika et al., 2007). Then standard preprocessing including realignment, coregistration to the anatomical T1-weighted image, normalization into Montreal Neurological Institute (MNI) space and smoothing with a 7 × 7 × 8 mm full-width-at half-maximum (FWHM) Gaussian Kernel (twice the native voxel size) was performed. Statistical analysis of fMRI data was performed using a General Linear Model (GLM; Friston et al., 1994) approach. Analysis was conducted on the whole brain and statistical inference was performed by using a cluster-wise control of Family-Wise Error (FWE). Statistical images were first assessed for cluster-wise significance with a primary cluster-defining threshold of p= 0.001, then the thresholded cluster was considered significant at a FWE rate of .05.

At the first-level, a GLM was applied to identify activations in relation to separate event types: correct GO FOOD trials; correct GO NON-FOOD trials; correct NO-GO FOOD trials; correct NO-GO NON-FOOD trials; unsuccessful no-go trials. This resulted in five task-related regressors (one for each condition) for each participant. The onset of each event was set according to the onset of the appearance of the stimuli and it was modeled using a stick function (duration=0) convolved with the canonical hemodynamic response function (HRF, Henson and Friston, 2006). RTs for GO conditions were included in the model as parametric modulators (Grinband et al., 2008). To account for head movement, the six movement parameters of the rigid body transformation applied by the

realignment procedure were also introduced as regressors in the first-level analysis. We used a 128-second high-pass filter (SPM12 convention) to remove low-frequency noise and slow drifts in the signal.

At the **second level**, between-group differences were examined only for successful trials (i.e., both go and no-go trials where participants did not make any errors): the four individual contrast images (GO FOOD trials, GO NON-FOOD trials, NO-GO FOOD trials, NO-GO NON-FOOD) were entered into a full factorial design, with Group (BE; non-BE); Type of stimulus (Food; Non-Food) and Response (Go; No-Go) as factors. Further, the BES score was added as covariate to control for their possible effect on the results. Given that BES score was the criterion used to confirm the assignment to one of the two groups (BE and non-BE), the inclusion of this regressor in the model and the interaction with the factor 'Group' allowed us to maintain the differences between the groups in this variable but to control for within-group differences in the interpretation of the results.

4.3 RESULTS

One participant of the non-BE group had to be excluded from the analysis due to artifacts in the fMRI acquisition; therefore the resulting number for total sample was 41 (BE=21; non-BE=20).

4.3.1 Descriptive characteristics

See Table 3.1 (Chapter 3; paragraph 3.5).

4.3.2 Behavioral Results

4.3.2.1 Reaction Times

Figure 4.3 shows that the analysis on RTs yielded a significant main effect of condition ($\chi^2(1) = 120.61$, $p < .001$) but neither main effect of group ($\chi^2(1) = 0.34$, $p = 0.56$) or interaction (Group X Condition) ($\chi^2(1) = 3.69$, $p = 0.06$). Overall, these results suggest that reactions were faster towards food compared to non-food stimuli, with no distinction of group (BE or non-BE). For a summary of mean RTs see Appendix B, Table B1.

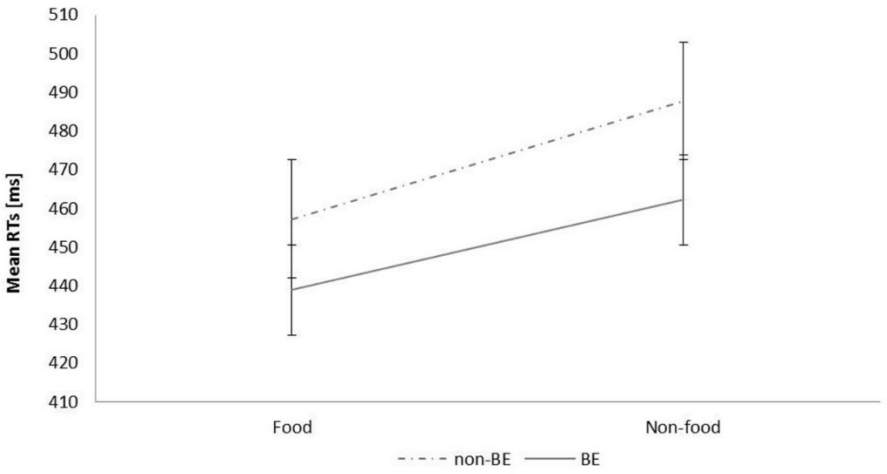

Figure 4.3. Go/No-Go Task: Mean reaction times (RTs) for correct GO trials (food and non-food).
BE: Binge eaters, non-BE: non-binge eaters; RTs: Reaction Times. Error bars are representative of Standard Errors (SE).

4.3.2.2 Commission Errors

Figure 4.4 summarizes the percentage of commission errors for each condition and for both groups. In line with the RTs results the main effect of Condition was significant ($\chi^2(1) = 26.116$, $p < .001$), indicating that all participants tended to be less accurate when asked to inhibit their responses to food compared to non-food stimuli. No differences between the groups across all conditions (main effect of Group, $\chi^2(1) = 0.3381$, $p = 0.561$) and for specific conditions (interaction Group X Condition, $\chi^2(1) = 1.3949$, $p = 0.24$) were observed. For a summary of the percentage of commission errors see Appendix B, Table B2.

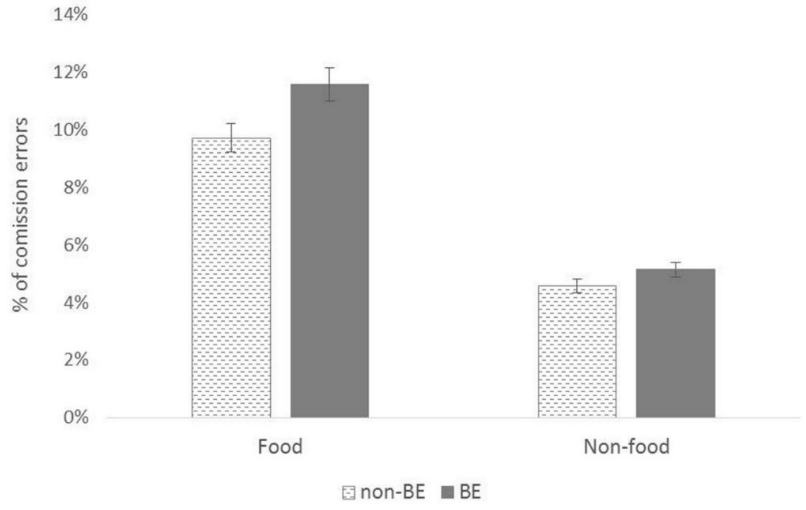

Figure 4.4. Go/No-Go Task: Percentage of commission errors.
BE: Binge eaters, non-BE: non-binge eaters. Error bars are representative of Standard Errors (SE).

4.3.3 fMRI Results

The objective of this experiment was to investigate the differences in brain activity, between BE and non-BE, during the execution of the GNG task. As a first step, we revealed significant differences between the groups when all conditions of the task were pulled together (For a summary of main effects for both tasks see Appendix B, Tables B3, B4 and B5. Consequently, we decided to perform between-group comparisons within each conditions, to investigate whether the differences were specific for condition or generalize to the overall task.

In order to do so, we first focused on the between-group comparison regarding GO and NO-GO conditions. Subsequently, we focused on the NO-GO conditions (food and non-food) to highlight possible differences in brain activity during response inhibition toward food and non-food stimuli. In this paragraph the between group comparisons within each condition are reported.

4.3.3.1 Between-group comparisons within NO-GO and GO trials

NO-GO trials: The contrast *BE > non-BE* revealed two clusters in the right Superior and Inferior Occipital Gyrus, while for the contrast *Non-BE > BE* differences were located in the right MFG, left Cerebellum, right Precuneus and right Caudate/Putamen (Figure 4.5; Table 4.2).

GO trials: The contrast *BE > non-BE* revealed significant differences in one cluster in the right Inferior Occipital Gyrus. For the contrast *Non-BE > BE* differences between the groups were located in the right MFG, left Cerebellum, right Precuneus and right Angular Gyrus (Figure 4.5; Table 4.2).

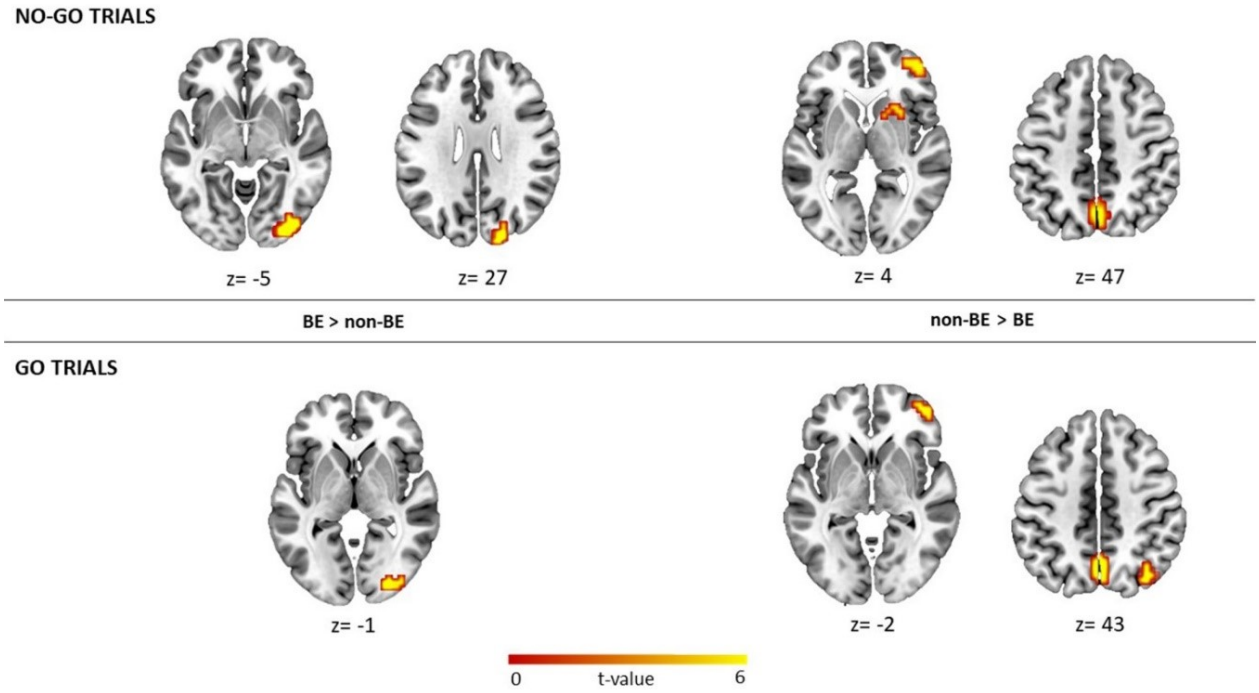

Figure 4.5. Between-group comparisons for successful no-go trials (top) and go trials (down). Figures on the left part show results for the contrast BE > non-BE; on the right results for non-BE > BE. Statistical parametric maps were overlaid onto a T1-weighted canonical image, provided by the MRIcroGL software. Color bar is representative of the t-scores given in the table below (4.2). Images are shown in neurological convention and with Z-axial slice coordinates (z) as defined in Montreal Neurological Institute (MNI) 152 space. BE: binge eaters

cluster		peak		MNI			Side	Region
k	p(FWE)	t	z	x	y	z		
NO-GO TRIALS								
BE > non-BE								
41	0.004	5.45	5.21	36	-88	-6	R	Inferior Occipital Gyrus
24	0.048	5.27	5.04	19	-91	30	R	Superior Occipital Gyrus
non-BE > BE								
67	0.0003	5.45	5.21	-45	-67	-22	L	Cerebellum
59	0.001	4.83	4.65	1	-70	50	R	Precuneus
30	0.020	4.61	4.45	43	53	-2	R	Middle Frontal Gyrus
24	0.048	4.19	4.07	12	7	-2	R	Caudate
		4.13	4.02	26	14	-2	R	Putamen
GO TRIALS								
BE > non-BE								
40	0.005	5.50	5.24	36	-88	-6	R	Inferior Occipital Gyrus
non-BE > BE								
66	0.000	5.46	5.22	-45	-67	-22	L	Cerebellum
29	0.023	4.78	4.61	36	-74	46	R	Angular Gyrus
45	0.003	4.67	4.51	1	-63	42	R	Precuneus
		4.61	4.46	5	-70	50	R	Precuneus
26	0.035	4.45	4.31	43	53	-2	R	Middle Frontal Gyrus
32	0.015	4.23	4.11	-13	-70	-46	L	Cerebellum

Table 4.2. Between-group comparisons for successful no-go trials and go trials. The following details are reported: k=number of voxels; t and z scores; stereotaxic coordinates according to the Montréal Neurological Institute (MNI); brain side and region. Results were considered significant at p< .001 that additionally met a FWE correction at cluster level (p< .05). Non-BE: non-binge eaters; BE: binge eaters; FWE= Family Wise Error; L= left; R= right.

4.3.3.2 Between-group comparisons within NO-GO food and NO-GO non-food trials

NO-GO food: The contrast *BE > non-BE* revealed differences in the right Inferior Occipital Gyrus; while for the contrast *Non-BE > BE* differences were located in the right Putamen, Precuneus, left Cerebellum and Precentral gyrus (Figure 4.6; Table 4.3).

NO-GO non-food: The contrast *BE > non-BE* showed differences in the right Inferior Occipital Gyrus, whereas the contrast *Non-BE > BE* revealed differences located in Precuneus, Middle Frontal gyrus, left Cerebellum (Figure 4.6; Table 4.3).

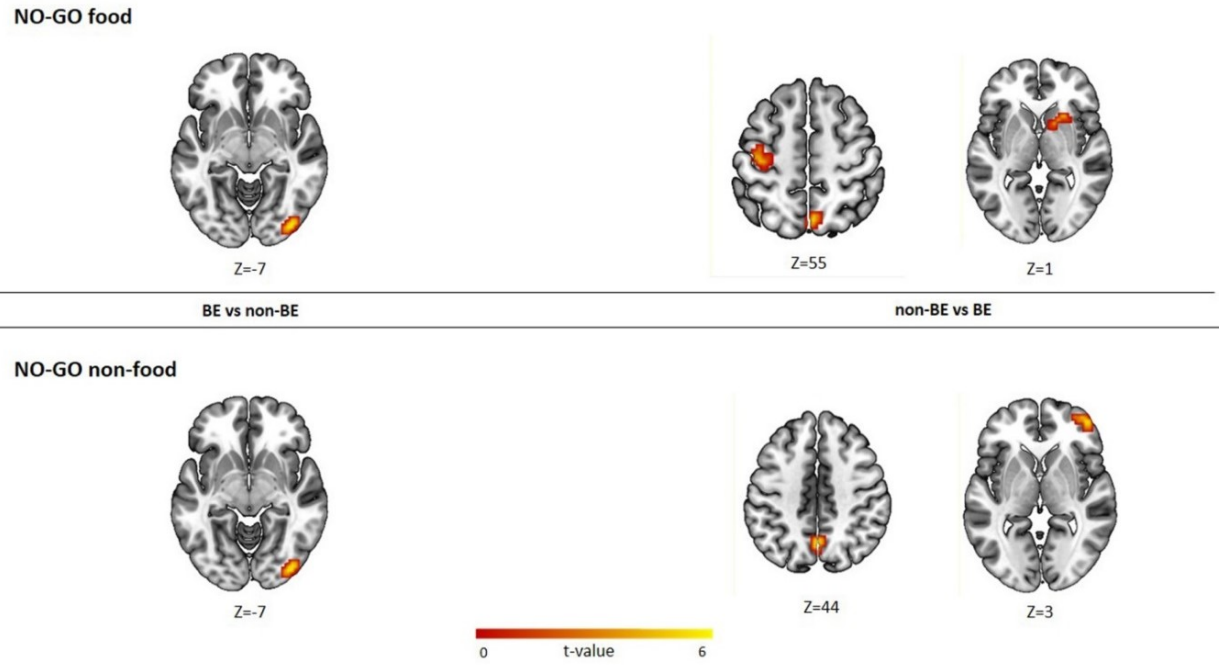

Figure 4.6. Between-group comparisons in no-go food trials (top) and no-go non-food trials (down). Figures on the left part show results for the contrast BE > non-BE. Figures on the right show results for contrast non-BE > BE. Statistical parametric maps were overlaid onto a T1-weighted canonical image, provided by the MRIcroGL software. The color bar is representative of the *t*-scores given in the table below (4.3). Images are shown in neurological convention and with Z-axial slice coordinates (z) as defined in Montreal Neurological Institute (MNI) 152 space. Non-BE: non-binge eaters; BE: binge eaters; FWE= Family Wise Error; L= left; R= right.

cluster		peak		MNI			Side	Region
k	p(FWE-corr)	t	z	x	y	z		
NO-GO FOOD								
BE > non-BE								
25	0.041	4.90	4.71	36	-88	-6	R	Inferior Occipital Gyrus
non-BE > BE								
56	0.0007	5.29	5.07	-45	-67	-22	L	Cerebellum
63	0.0003	4.95	4.76	5	-70	50	R	Precuneus
56	0.0007	4.70	4.53	-13	-70	-46	L	Cerebellum
25	0.0410	3.89	3.79	26	14	-2	R	Putamen
24	0.0477	3.78	3.69	-38	-21	58	L	Precentral Gyrus
NO-GO NON-FOOD								
BE > non-BE								
38	0.0070	5.04	4.84	36	-88	-6	R	Inferior Occipital Gyrus
non-BE > BE								
45	0.003	4.67	4.51	-34	-84	-38	L	Cerebellum
24	0.048	4.40	4.26	43	53	2	R	Middle Frontal Gyrus
28	0.026	4.17	4.05	1	-63	42	R	Precuneus

Table 4.3. Between-group comparisons in no-go food trials and no-go non-food trials. The following details are reported: k=number of voxels; t and z scores; stereotaxic coordinates according to the Montréal Neurological Institute (MNI); brain side and region. Statistic threshold: Results were considered significant at p< .001 that additionally met a FWE correction at cluster level (p< .05). Non-BE: non-binge eaters; BE: binge eaters; FWE= Family Wise Error; L= left; R= right.

4.4 DISCUSSION

In the present experiment we aimed at characterizing the neural correlates of action restraint toward food in a non-clinical population of normal-weight (NW) individuals with binge eating episodes (BE), using self-report, behavioral and brain imaging approaches. Overall, results showed that, despite comparable inhibitory efficiency in behavioral terms, BE and non-BE individuals differed in self-reported general impulsivity measures and in brain activity engagement during Go/No-Go (GNG) task, requiring the ability to restrain an action.

4.4.1 Trait impulsivity: self-reported questionnaires results

As reported in Table 3.1 (Chapter 3; paragraph 3.5), in line with previous studies (Guerrieri et al., 2009; Meule and Platte, 2015; Waxman, 2009), the BE group scored higher on self-reported measures of impulsivity compared to non-BE. In particular, the BIS-11 motor, non-planning subscales and total scores were higher in BE, indicating a greater degree of impulsivity in this group. The greater impulsivity trait in individuals with binge eating episodes may support the association between self-reported impulsivity and loss of control eating behavior, as already reported both in clinical (Nasser et al., 2004) and non-clinical samples (Lyke and Spinella, 2004). In addition, BE showed lower scores compared to non-BE on the BIS subscale of the BIS/BAS questionnaire. This subscale investigates the regulation of aversive motives (in which the goal is to move away from something unpleasant) and higher scores usually indicate a tendency to avoid aversive or new stimuli (Carver and White, 1994; Avila, 2001). Since there is evidence of BIS score increasing as a function of restraint (Nederkoorn et al., 2004; Yeomans and Brace, 2015), lower scores in the BE group might indicate a lower tendency in these individuals to avoid or inhibit behavior with a greater propensity to respond. Contrary to expectations, the BE group did not score higher than the non-BE in the '*reward responsiveness*' subscale of the BIS/BAS questionnaire. Since the small number of questions of the subscale refers to general rewards (either internal, such as expectancies of goal attainment, or external, such as presence of a desired goal) but not specifically to food, our results could indicate that the BE group is not characterized by a generalized heightened sensitivity toward any type of reward-relevant stimuli. This result is in accordance with the assumption that the impulsivity trait (rush spontaneous impulsiveness) plays a clearer role in the characterization of BE behavior compared to reward sensitivity and that the inability to inhibit it is the crucial responsible for the behavioral outcome (i.e., binge episodes, loss of control, inability to cut down; Loxton, 2018). In line

with this view, Meule (2013) stated that the BIS subscale, rather than BAS subscales, should be used to disentangle individual differences in impulsivity components (Meule, 2013).

Overall, our findings support the relationship between disinhibited eating behavior and impulsivity facets, already revealed in obesity and BED (Giel et al., 2017; Meule et al., 2013) and further extend this concept showing that higher scores in measures of impulsivity characterize also NW individuals with BE, without a diagnosis of eating or weight disorder. This evidence together with the assumption that self-reported measures of impulsivity investigate stable personality traits (Meule et al., 2013) underscores the relevance of trait impulsivity as a possible general hallmark of BE, evident even in the absence of obesity or clinically significant eating disturbances (Lyu et al., 2017).

4.4.2 State impulsivity: food-related Action Restraint

The GNG task was used to assess differences in action restraint abilities and to highlight possible differences in inhibitory control performance accordingly to the type of stimuli used (food or non-food). Contrary to expectations, the two groups were characterized by comparable performances in terms of RTs and commission errors. A general main effect of condition (food/non-food) indicated that both groups tended to respond faster and less accurately to food stimuli. This result, already reported in the literature (Loeber et al., 2012; Mobbs et al., 2008), is consistent with the assumption that food-cues – probably due to the high relevance of food for survival – elicit automatic actions and approach tendencies regardless of dieting success, self-reported impulsivity, or hunger levels (Meule et al., 2013).

Even if not in line with our hypotheses, this result is consistent with those of Lyu et al (2017), who assessed response inhibition toward food in normal-weight individuals with binge eating episodes compared to non-binge eaters. The authors adopted a visual GNG task, comprising images of foods (e.g., high and low calorie foods) and non-food stimuli (e.g., household objects), and results showed that the two groups did differ in self-reported impulsivity but did not in the rate of false alarm or commission errors. According to the Authors, the lack of between-group differences in the GNG task might have been linked to the fact that binge eaters may be susceptible to impulse control problems, only under particular conditions (i.e., stressful situations; Lyu et al., 2017). Hence, it may be possible that deficits in inhibitory control toward food in healthy participants emerge in certain situations, for example when increased negative affect arises, and are less likely to be capture during experimental conditions, in the absence of stressor or negative affect (Lyu et al., 2017).

Another possible explanation derives from the tasks' design and difficulty. In fact, the GNG should elicit prepotent responses to make response inhibition toward no-go stimuli difficult to achieve. However, to better capture the hemodynamic response at the basis of the fMRI signal, for methodological reasons single events had to be separated by long inter-trial interval (ITI). This might have made the task easier than usual (i.e., outside the scanner; Zamorano et al., 2014) and not suitable to highlight differences in response inhibition performance between groups of non-clinical samples of healthy individuals.

Lastly, as already outlined in Chapter 1 (paragraph 1.2), self-reported measures of impulsivity are usually weakly correlated with behavioral measures (Cyders and Coskunpinar, 2012). The reasons for this lie on the assumption that, compared to self-reported questionnaires, behavioral tasks are more subject to state-dependent variations (Cyders and Coskunpinar, 2012; Meule et al., 2013). Thus, it is likely that some of the above-mentioned aspects, such as characteristics of the paradigms (e.g., length of the ITI) or the conditions during which the task was performed (e.g., MRI acquisition), might have played a role in the lack of clear behavioral differences between the groups.

4.4.3 Neural correlates of Action Restraint

In contrast to behavioral data, the fMRI results showed differences between BE and non-BE in brain activity during the execution of the GNG task. The co-occurrence of comparable behavioral performances on one side and differences in brain activity on the other side has already been reported in the literature. Several task-based fMRI studies on substance users (Roberts and Garavan, 2010), gambling addicted (Ding et al., 2014) and obese individuals (Hendrick et al., 2012) have revealed that, compared to healthy controls, participants' brain activity differed when completing response inhibition tasks (such as GNG and SST), despite similar behavioral performances. In the light of this evidence, our results might thus indicate that the two groups differed in the neural recruitment of specific brain regions to adequately perform the task. In more detail, the between-group comparisons revealed that in conditions requiring the inhibition of responses (NO-GO trials), BE showed significantly lower activity in the right Middle Frontal Gyrus (MFG), Precuneus, Caudate/Putamen and bilateral Cerebellum, in comparison with non-BE. On the other hand, in the same condition BE appeared to be characterized by higher involvement in occipital regions. When looking at the same contrasts (BE > non-BE; non-BE > BE) in GO trials, a similar picture of results was identified, except for the significantly higher activity in right Angular Gyrus and Caudate/Putamen for the BE group.

Overall, in GO and NO-GO trials, the BE – when compared to non-BE – appeared to be characterized by lower activity in regions that are typically involved in the inhibition mechanisms such as those required by GNG tasks, namely prefrontal, parietal, temporal and striatal areas (Simmonds et al., 2008). These regions are associated with stimulus recognition, maintenance, manipulation of stimulus-response (SR) associations and response selection (Braver et al., 2001; Grafton et al., 1992; Liddle et al, 2001; Rubia et al., 2001), all of which are relevant aspects to perform the GNG task. In particular, the MFG together with temporo-parietal regions seem to be specifically involved in '*complex*' GNG, namely those tasks with multiple GO cues (i.e., different types of objects within the same category) and thus requiring a frequent updating of SR association (Corbetta and Shulman, 2002; Simmonds et al., 2008). The common activation of these regions in the GO and NO-GO conditions is consistent with the assumption that both conditions involve response selection processes and should not be considered as opposite and independent events (Simmonds et al., 2008). Nonetheless, the right fronto-parietal network is thought to play a role specifically in the restraining of the action (Stevens et al., 2007; Aron and Poldrack, 2006; Schachar et al., 2007; Swick et al., 2008; Zhang et al., 2012). In particular, Zhang et al (2012) assumed that, as opposed to the left fronto-parietal network, the right network would be especially implicated in the attention to the no-go signal, a crucial event in the GNG where inhibition needs to begin before the response has been started (i.e., *action restraint*; Zhang et al., 2012). A hypoactivation of this regions during the GNG task in BE groups might indicate an altered functionality of frontal and parietal regions during the execution of the task in this group, compared to non-BE. However, the between-group difference in the MFG was revealed only in response inhibition trials toward non-food stimuli (See Figure 4.6; Table 4.3). Considering the investigated population (i.e., participants reporting episodes of loss of control overeating), we expected to find a lower activity in prefrontal regions especially in those trials involving food stimuli. Surprisingly, the BE group showed a diminished involvement of the right MFG both in GO and NO-GO trials; besides, this difference was not revealed in NO-GO trials only when food was involved. This result could be attributed to the effect of food cues, as reward-related stimuli, in BE individuals. It is now well established that individuals with addiction (e.g., substance dependence) usually show enhanced BOLD responses in PFC regions when confronted with drug-related cues (Goldstein and Volkow, 2011). Hence, it could be possible that the presentation of food-related stimuli – during no-go trials – might have had an impact on BOLD responses within the MFG regions in the BE group, as compared to the non-BE. Nevertheless, given that findings revealed lower activity in BE individuals in the right MFG also during GO trials, we could assume that differences

within this region may not be linked to a specific task-condition, but to a more general functional alteration during the execution of the task. In light of this consideration, this result deserves further investigation in order to better elucidate the role of the right MFG in the GNG, both when food and non-food stimuli are involved. A reasonable approach to tackle this issue, would be investigating the task-related functional connectivity of this region within the entire brain network, by means of functional centrality measures (Bullmore and Sporns, 2009) or with regions involved in inhibitory control (e.g., prefrontal regions) and reward sensitivity processes (e.g., subcortical regions) by means of Seed-based Connectivity analysis (Biswal et al., 1995).

One remarkable finding was the between-group difference in the right dorsal striatum (Caudate/Putamen): this result was distinctive of NO-GO trials (and not GO trials) only when food stimuli were presented. The basal ganglia structures (especially the dorsal striatum consisting of putamen and caudate nuclei) are known to be involved in response inhibition and thus commonly recruited during stopping (Aron and Poldrack, 2005; Everitt and Robbins 2016; Hampshire and Sharp 2015). More importantly, the dorsal striatum together with PFC is part of the mesocortical pathway, which is implicated in motor control (Toni and Passingham, 1999) and in the modulation of stimulus-response-reward associations (Ghahremani, 2012). Therefore, the lower activity in BE in these regions might indicate a different modulation of inhibitory control processes toward reward in this group.

Interestingly, a recent emphasis has been placed on the role of the fronto-striatal network in behavioral inhibition and more specifically, of the right striatum and PFC as core regions of impaired inhibitory control in individuals with bulimia nervosa, BN (Berner and Marsh, 2014; Donnelly et al., 2018; Skunde et al., 2016). Given that BN is an eating disorder characterized by recurrent episodes of binge eating (APA, 2013), a fair assumption would be that differences located in regions within the prefrontal and striatal areas might be at the roots of binge eating behavior, regardless of the (clinical or non-clinical) conditions to which they are associated. In support of this assumption, the fronto-striatal network was reported to have a prominent role in inhibitory control of impulsive responses (Jentsch and Taylor 1999). Dysfunction of this network had indeed been associated with different pathological conditions, characterized by excessive impulsive behavior, such as attention deficit hyperactivity disorder, ADHD (Rubia et al., 2005) and Tourette's syndrome (Marsh et al. 2007). In addition, a hypoactivation within the fronto-striatal regions have been reported in individuals with pathological gambling and alcohol addiction (Balodis et al., 2012; Courtney et al., 2012). Drawing upon the hypothesized common substrates and features of

substance addiction and overeating (Gearhardt et al., 2011), we might speculate that, alterations within the fronto-striatal pathway may be at the roots of an increased impulsivity that in turn may lead to the development of impulsive and compulsive behavior (such as, overeating behavior or addiction). Overall, the compelling hypothesis of a hypo-activity in fronto-striatal regions as a possible hallmark and susceptibility factor for multiple losses of control behaviors merits further exploration.

Lastly, both between-groups comparison in GO and NO-GO trials revealed higher activation in BE compared to non-BE in occipital regions. Although not strictly related to response inhibition, this result has been previously observed in BN patients engaged in both a visual task that involved emotional and food stimuli (Uher et al., 2004) and an attentional task (Seitz et al., 2016). According to Seitz et al (2016), the hyperactivation of these regions, implicated in alerting functions (Fan et al., 2005), might indicate a possible compensatory mechanism for the attentional network during the completion of the tasks. Moreover, a hypoactivation in fronto-striatal circuits paralleled by a hyperactivation in occipital areas might be linked to inattention and impulsivity features (Seitz et al., 2016).

In sum, general trait impulsivity, as measured by self-reported questionnaires, characterized our BE group. Even with similar behavioral performances, the fMRI results showed between-group differences mainly located in the fronto-striatal and parietal areas, encompassing regions that are known to be involved in impulsive behavior. Crucially, recent studies highlighted a role of the right fronto-parietal regions not only in impulsive behavior, but also more specifically in response inhibition and selection during the GNG task (Corbetta and Shulman, 2002; Stevens et al., 2007; Zhang et al., 2012). This combination of findings provides support for the captivating hypothesis that regions involved in response inhibition and selection might be the substrate of conditions characterized by impulsive behaviors, such as BE (Lubman et al., 2004). Further investigations are warrant to shed light on the nature of these differences. Nevertheless, albeit preliminary, our findings yield valuable insights on the role of impulsivity in BE conditions, with impulsivity being a possible stable characteristic linked to BE behavior even in the absence of a weight disorder. In addition, they provide new hints on the role of frontal and striatal regions in food-related action restraint in BE individuals and thus, on their potential role as vulnerability factors for loss of control and impulsive eating behavior.

In this context, the investigation of the neural correlates of action cancellation (**Chapter 5**) may help creating a more complete account of the neural substrates of response inhibition between the groups.

Chapter 5
EXPERIMENT II

The Neural Correlates of Action Cancellation Toward Food in Normal-Weight Binge Eaters: A Task-Based fMRI Study

This experiment forms part of a manuscript, recently submitted to: *NeuroImage Journal*.

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5.1 BACKGROUND

Drawing about the theoretical background of Chapter 4 (see paragraph 4.1), in the present experiment we aimed to investigate the behavioral and neural correlates of response inhibition with a stop signal task (SST) in normal-weight binge eaters.

In more detail, given the multidimensional nature of the 'response inhibition' constructs, we decided two adopt both the GNG (described in Chapter 4) and the SST to assess both action restraint (with the GNG) and action cancellation (with the SST). As already outlined in Chapter 1, the two tasks are thought to tap into different aspects of response inhibition and also to be subserved by different neurocognitive mechanisms (Simmonds et al., 2008). The main behavioral difference between the two lies in the temporal location of the stop signal: while in the GNG the no-go stimulus is presented instead or with the go stimulus; in the SST the stop signal appears after the go stimulus. Hence, in the SST the process of response inhibition involves the cancellation of an already initiated action.

Similarly to the previous experiment, we modified the SST using images of both food and non-food objects (see paragraph 4.2.2.1; Figure 4.2; Chapter 4), in order to assess possible between group difference in the ability to inhibit responses specifically toward food stimuli.

Overall, the present experiment aimed to assess whether:

(i) BE and non-BE differed in response inhibition abilities, in a SST;

(ii) BE and non-BE showed differential patterns of brain activation during the execution of the SST;

(iii) Differences were generalized across food and non-food conditions or specific for response inhibition toward food stimuli.

5.2 METHODS

5.2.1 Procedure

See Chapter 3 for the 'GENERAL PROCEDURE OF THE EXPERIMENTAL WORK'.

In this experiment, participants underwent an fMRI measurement during the execution of a food-specific SST (see paragraph 5.2.2 of this Experiment).

5.2.2 Stop Signal Task

The SST requires withholding an already initiated response - *action cancellation* (Logan, 1994; Schachar et al., 2007), triggered by a stop signal shortly following the go signal. In comparison to GNG, SST has a high load on response inhibition processes rather than response selection. Like for GNG, the SST adopted in the present study included food and non-food stimuli and consisted of two functional runs of 112 trials each.

At the beginning of each run, an instruction slide was presented as a reminder. During the go trials (75%; n=84 trials/run), a 1000 milliseconds fixation point preceded the stimuli, and participants were instructed to respond as fast and accurate as possible to both food and non-food stimuli using the left or the right button of the response pad (e.g., press the left button for food with the index finger and right button for non-food stimuli with the middle finger). During the stop trials (25%; n=28 trials/run), participants were instructed to inhibit their response if after a fixed delay of 200 milliseconds (Stop Signal Delay, SSD) from the presentation of either a food or non-food stimulus a visual stop signal would appear (Figure 5.1). The two runs were counterbalanced across subjects and differed only for the instructions regarding which button to press to which stimulus (left for food and right for non-food in one run; left for non-food and right for food in the other run). Within a given run, trials were separated by a jittered inter-trial interval (ITI) ranging from 2000 to 5000 milliseconds. Each run last approximately 11 minutes. The order of the trials was randomized to optimize the efficiency of the design. Within each experimental set, SSD remained fixed at 200 ms to yield a low inhibitory rate (Logan et al., 1995) and make the task more demanding, compared to the GNG.

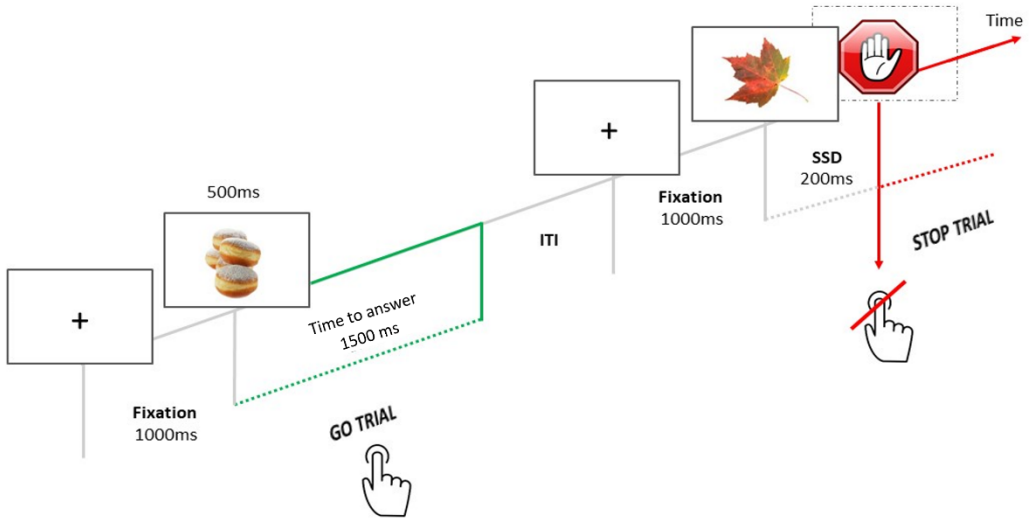

Figure 5.1. SST paradigm. Participants had to respond to both food and non-food stimuli (go trials: 75%) and withhold the response if they saw a stop signal (25%). Stimuli appeared after a random Inter-Trial interval, ITI (2000-5000ms) following by the appearance of a fixation cross (1000ms). The stop signal appeared after a fixed delay (stop signal delay, SSD) of 200 milliseconds, following either food or non-food stimuli.

5.2.2.1 Stimuli[6]

See paragraph 4.2.2.1 (Chapter 4).

Each image was presented four times within a run (three times (75%) it served as a GO stimulus and for one time (25%) it was followed by a STOP signal). We decided to have the same GO/STOP ratio for each stimulus so that we could control for a possible effect of the stimulus type on response inhibition.

5.2.3 Acquisition

5.2.3.1 Behavioral data

See paragraph 4.2.3.1 (Chapter 4).

5.2.3.2 Magnetic Resonance Imaging (MRI) data

See paragraph 4.2.3.2 (Chapter 4).

For the SST, data were collected in two functional runs of 229 volumes each (11 minutes each; 22 minutes total scanning time).

[6] Different images were used for the GNG and the SST.

5.2.4 Analyses

5.2.4.1 Behavioral data

See paragraph 4.2.4.1 (Chapter 4).

The two groups were compared for (1) RTs in milliseconds for correct GO trials and (2) percentage of commission errors (a 'GO' response for STOP trials). The main effect of condition and group and the interaction group-by-condition were considered in the analysis. Trials in which participants failed to stop their response were excluded from the behavioral analysis.

5.2.4.1 Magnetic Resonance Imaging (MRI) data

At the **first-level**, a GLM was applied to identify activations in relation to separate event types: correct GO FOOD trials; correct STOP FOOD trials; correct GO NON-FOOD trials; correct STOP NON-FOOD trials; unsuccessful STOP trials. This resulted in five task-related regressors (one for each condition) for each participant. The onset of each event was set according to the onset of the appearance of the stimuli and it was modeled using a stick function (duration=0) convolved with the canonical hemodynamic response function (HRF, Henson and Friston, 2006). RTs for GO conditions were included in the model as parametric modulators (Grinband et al., 2008). To account for head movement, the six movement parameters of the rigid body transformation applied by the realignment procedure were also introduced as regressors in the first-level analysis. We used a 128-second high-pass filter (SPM12 convention) to remove low-frequency noise and slow drifts in the signal.

At the **second level**, between-group differences were examined for successful trials: the four individual contrast images (GO FOOD trials, GO NON-FOOD trials, STOP FOOD trials, STOP NON-FOOD) were entered into a full factorial design, with Group (BE; non-BE); Type of stimulus (Food; Non-Food) and Response (Go; No-Go) as factors. Further, the BES score was added as covariate to control for their possible effect on the results. Given that BES score was the criterion used to confirm the assignment to one of the two groups (BE and non-BE), the inclusion of this regressor in the model and the interaction with the factor 'Group' allowed us to maintain the differences between the groups in this variable but to control for within-group differences in the interpretation of the results. Trials in which participants failed to stop their response were excluded from the fMRI analysis.

5.3 RESULTS

Three participants of the BE group and three participants from the non-BE group were excluded from both the behavioral and the fMRI analysis because no correct responses were provided in one or more 'Stop' conditions (either to food or non-food stimuli) per run. Thus, the resulting sample of 36 participants in total: 18 for the BE group and 18 for the non-BE group.

5.3.1 Descriptive characteristics

See Table 3.1 (Chapter 3; paragraph 3.5).

5.3.2 Behavioral Results

5.3.2.1 Reaction Times

The analysis on RTs revealed significant results neither for main effect of Condition ($\chi^2(1) = 1.611$, p= 0.204) nor Group ($\chi^2(1) = 0.184$, p = 0.668). Whereas, the interaction Group X Condition was statistically significant ($\chi^2(1) = 4.57$, p = 0.032). For a summary of mean RTs see Appendix B, Table B6. The significant interaction indicates that the non-BE group tended to respond faster (lower RTs) with non-food stimuli compared to food stimuli. Regarding the BE group the type of stimuli used did not affect RTs (Figure 5.2).

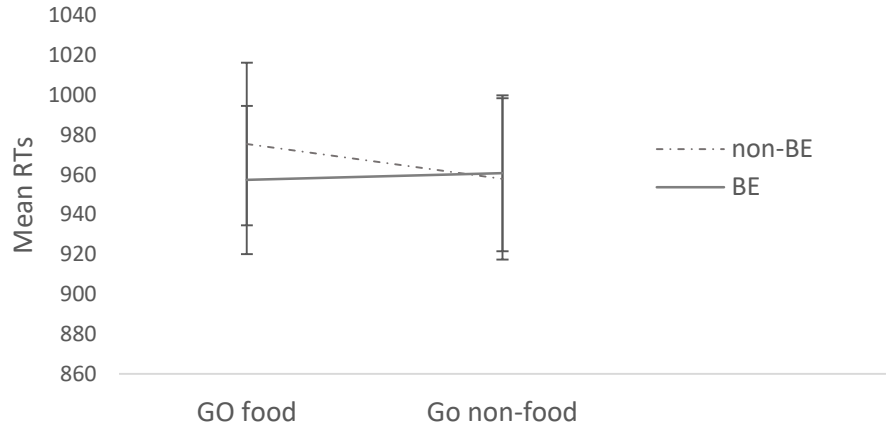

Figure 5.2. Stop Signal Task: Mean reaction times (RTs) for correct GO trials (food and non-food). BE: Binge eaters, non-BE: non-binge eaters; RTs: Reaction Times. Error bars are representative of Standard Errors (SE).

5.3.2.2 Commission Errors

Figure 5.3 shows the percentage of commission errors for each condition and for both groups. This analysis revealed no significant results for any of the factors considered: main effect of Condition ($\chi^2(1) = 1.1214$, p= 0.29); main effect of Group ($\chi^2(1) = 0.472$, p= 0.49); interaction Group X Condition ($\chi^2(1) = 0.3065$, p= 0.58). This indicates that there were no differences between the two groups neither in the overall percentage of commission errors nor within each specific condition. For a summary of the percentage of commission errors see Appendix B, Table B7.

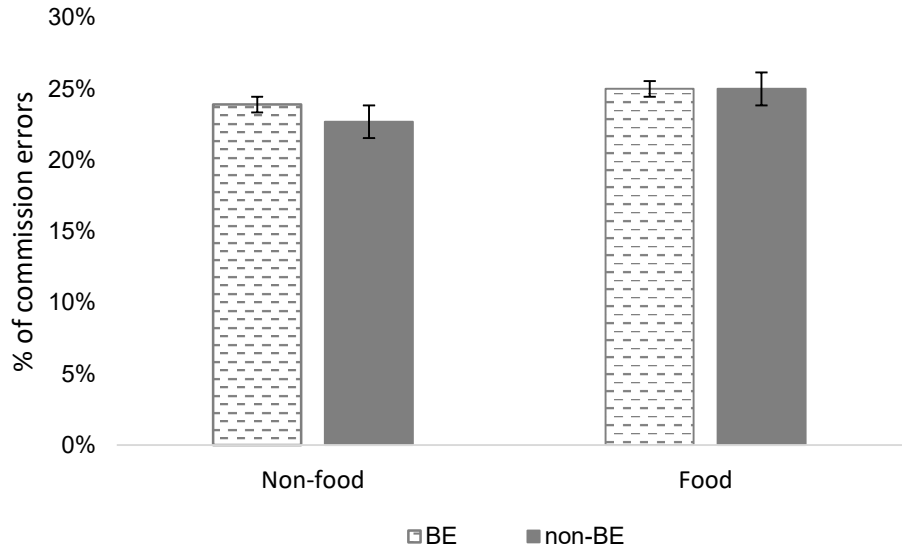

Figure 5.3. Stop Signal Task: Percentage of commission errors.
BE: Binge eaters, non-BE: non-binge eaters. Error bars are representative of Standard Errors (SE).

5.4.3 fMRI Results

In this section the between group comparisons within each condition are reported. First, we focused on the between-group comparison within GO and STOP conditions. Subsequently, we investigated the between-group differences with STOP conditions (food and non-food) to highlight possible differences in brain activity during response inhibition toward food and non-food stimuli. For a summary of main effects (group, response and stimulus) for both tasks see Appendix B, Tables B8, B9 and B10.

5.4.3.1 Between-group comparisons within STOP and GO trials

STOP trials: The contrast *BE > non-BE* revealed two clusters in the left MFG and left Cerebellum. For the contrast *non-BE > BE,* differences between the groups were located in one cluster in the right postcentral gyrus (Figure 5.4; Table 5.1).

GO trials: The contrast *BE > non-BE* revealed one cluster in the left Cerebellum, whereas the contrast *Non-BE > BE* highlighted differences between the groups in the right postcentral gyrus and the left precentral gyrus (Figure 5.4; Table 5.1).

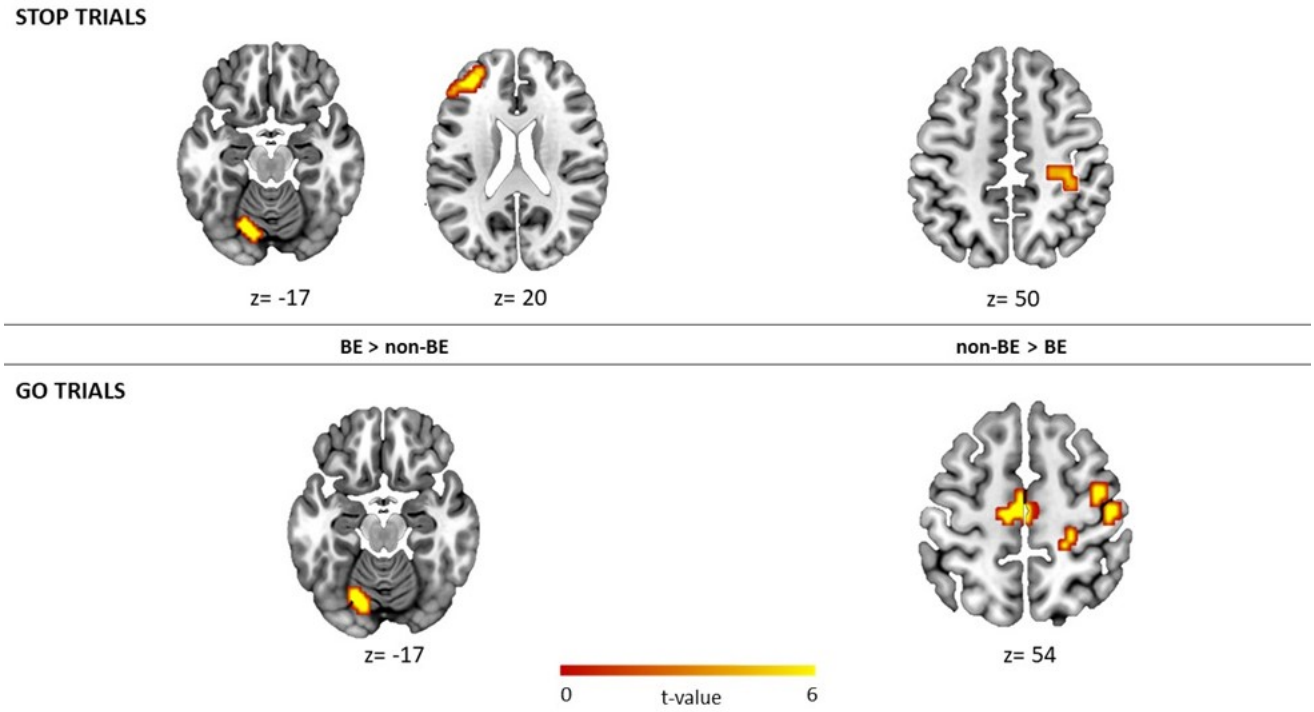

Figure 5.4. Between-group comparisons for successful stop (top) and go (down) trials. Figures on the left show results for the contrast BE > non-BE. Figures on the right show results for contrast non-BE > BE. Statistical parametric maps were overlaid onto a T1-weighted canonical image, provided by the MRIcroGL software. The color bar is representative of the *t*-scores given in the table below (5.1). Images are shown in neurological convention and with Z-axial slice coordinates (z) as defined in Montreal Neurological Institute (MNI) 152 space. BE= Binge Eaters; non-BE= non-binge eaters; FWE= Family Wise Error; L= left; R= right.

cluster		peak		MNI			Side	Region
k	p(FWE-corr)	t	z	x	y	z		
STOP TRIALS								
BE > non-BE								
37	0.004	5.18	4.94	-20	-70	-22	L	Cerebellum
42	0.002	4.87	4.66	-31	49	26	L	Middle Frontal Gyrus
non-BE > BE								
23	0.038	4.78	4.58	36	-28	46	R	Postcentral Gyrus
GO TRIALS								
BE > non-BE								
48	0.001	5.64	5.33	-17	-74	-18	L	Cerebellum
non-BE > BE								
95	0.000	5.31	5.05	36	-28	46	R	Postcentral Gyrus
46	0.001	4.32	4.18	-20	-21	70	L	Precentral Gyrus

Table 5.1. Between-group comparisons for successful stop and go trials. The following details are reported: k=number of voxels; t and z scores; stereotaxic coordinates according to the Montréal Neurological Institute (MNI); brain side and region. Statistic threshold: Results were considered significant at p< .001 that additionally met a FWE correction at cluster level (p< .05). BE= Binge Eaters; non-BE= non-binge eaters; FWE= Family Wise Error; L= left; R= right.

5.4.3.2 Between-group comparisons within STOP food and STOP non-food trials

STOP food: The contrast *BE > non-BE* revealed differences located in the left Middle Frontal Gyrus, while the contrast *non-BE > BE* did not yield any significant results (Figure 5.5; Table 5.2).

STOP non-food: In the contrast *BE > non-BE* differences were located in the left Cerebellum, while the contrast *non-BE > BE* revealed differences in the right Precentral Gyrus (Figure 5.5; Table 5.2).

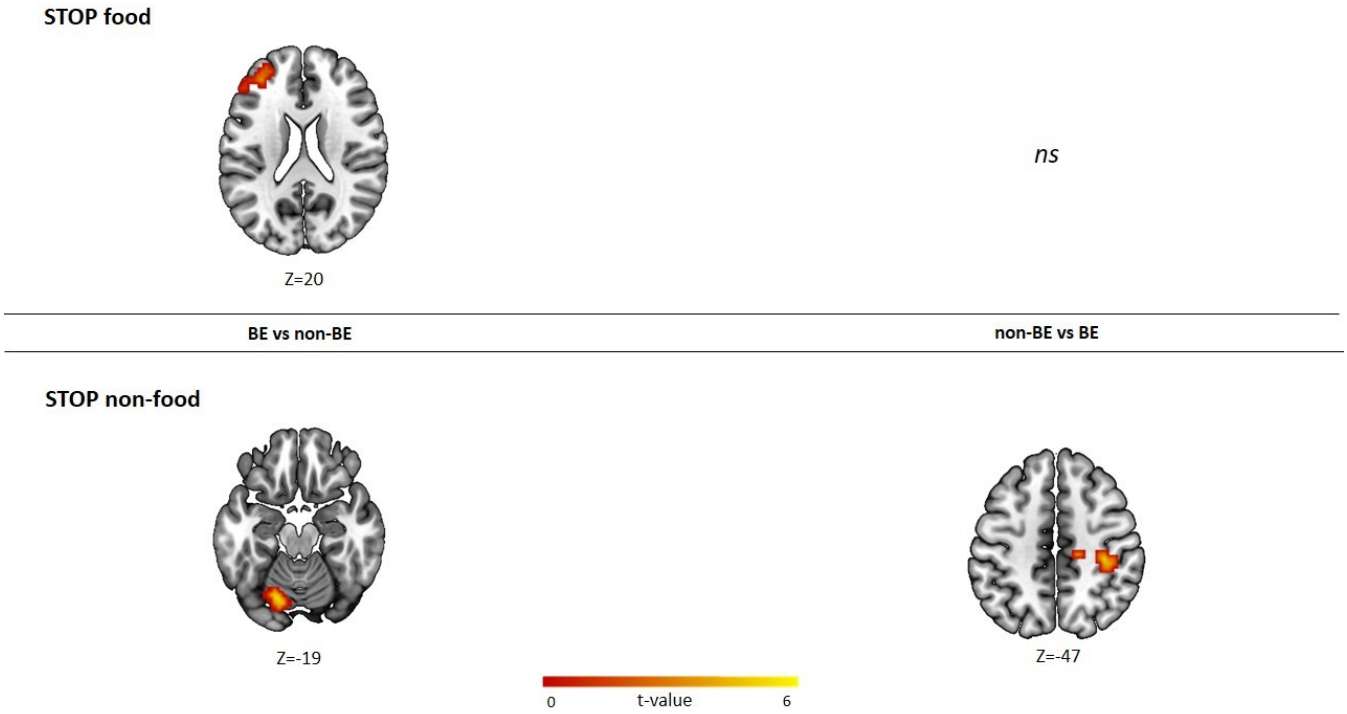

Figure 5.5. Between group comparison within stop food trials (top) and stop non-food trials (down). Figures on the left part show results for the contrast BE > non-BE. Figures on the right show results for contrast non-BE > BE. Statistical parametric maps were overlaid onto a T1-weighted canonical image, provided by the MRIcroGL software. The color bar is representative of the *t*-scores given in the table below (5.2). Images are shown in neurological convention and with Z-axial slice coordinates (z) as defined in Montreal Neurological Institute (MNI) 152 space. BE: binge eaters; FWE= Family Wise Error; L= left; R= right; ns: non-significant.

cluster		peak		MNI			Side	Region
k	p(FWE-corr)	t	z	x	y	z		
STOP FOOD								
BE > non-BE								
26	0.024	4.21	4.07	-31	49	26	L	Middle Frontal Gyrus
non-BE > BE								
ns								
STOP NON-FOOD								
BE > non-BE								
4	0.003	5.17	4.93	-17	-74	-22	L	Cerebellum
non-BE > BE								
39	0.003	5.44	5.17	36	-28	46	R	Precentral Gyrus

Table 5.2. Between group comparison within stop food trials (top) and stop non-food trials (down). The following details are reported: k=number of voxels; t and z scores; stereotaxic coordinates according to the Montréal Neurological Institute (MNI); brain side and region. Statistic threshold: Results were considered significant at p< .001 that additionally met a FWE correction at cluster level (p< .05). Non-BE: non-binge eaters; BE: binge eaters; FWE= Family Wise Error; L= left; R= right; ns: non-significant.

5.4 DISCUSSION

The present experiment aimed at investigating trait impulsivity and response inhibition in normal-weight individuals with binge eating episodes (BE). In order to give a more complete account of the behavioral and neural mechanisms of response inhibition in this population, we decided to assess inhibitory control abilities with the SST, in addition to the GNG task (see Chapter 4): in this way we were able to assess two different facets of inhibitory control abilities: namely, action restraint and cancellation. Results showed that BE and non-BE individuals differed in brain activity engagement during the SST, which required the ability to cancel an ongoing action. Results from self-reported questionnaires have been already discussed in Experiment I (paragraph 4.4.1)

5.4.1 State Impulsivity: food-related Action Cancellation

In the present experiment, the SST was used to assess between-group differences in action cancellation abilities and to highlight possible differences in inhibitory control accordingly to the type of stimuli used (food or non-food). Contrary to expectations, the two groups were characterized by comparable performances in terms of commission errors. The SST highlighted a significant Group x Condition interaction, indicating that non-BE tended to have slower RTs when asked to respond to food stimuli, compared to non-food stimuli, whereas, for the BE group, the nature of the stimuli (food and non-food) did not affect RTs. Even if unexpected, the lack of effects of stimulus' category on RTs in BE was consistent with previous results (Mühlberg et al., 2016). As an example, Mühlberg et al (2016) aimed to characterize inhibitory control abilities in relation to Body Mass Index (BMI) in lean and obese individuals. They used a food-specific SST to assess if obese individuals, whose heightened appetitive motivation and responsibility to food cues has been well documented (Garcia-Garcia et al., 2014; Pursey et al., 2014), would show an impaired ability to inhibit their responses to food, compared to lean individuals. In contrast with their hypothesis, they did not reveal obesity-related effects of response inhibition (i.e., commission errors) or RTs when confronted with food stimuli. One possible explanation proposed by the authors was that the palatability ratings of the food pictures used in their paradigm were comparable for all participants. Thus they claimed that this comparable hedonic value of the presented visual food cues in both groups might have had an impact in the absence of behavioral differences (Mühlberg et al., 2016). This conclusion argues for the importance of hedonic value of food stimuli when assessing response inhibition capacity. Hence, even if speculative, our hypothesis is that the interaction effect Group x Condition (see paragraph 5.3.2.1) could be motivated

by possible different hedonic values of the presented visual cues. However, since we did not rate them within the group, this result needs to be confirmed with further investigations.

The lack of between-group differences in false alarms or commission errors is consistent with some previous studies on obese population (Manasse et al., 2015; Muhlberg et al., 2016); however, it was inconsistent with our initial hypothesis. Indeed, we expected different performances between the groups and in more detail, that the BE group would have shown higher rate of commission errors in food conditions (i.e., when food stimuli were followed by a stop signal), compared to non-BE. Similarly to the GNG results in Experiment I (Chapter 4; paragraph 4.4.2), this unexpected result might be explained in light of task's design and difficulty. One plausible explanation would be that, since we decided to use a fixed SSD, the difficulty of the SST task has not been adjusted according to the performance of each participant, and this might have heightened the variability within the group.

Nevertheless, the sample-specifics must be considered very carefully for results' interpretation: most of the evidence linking inhibitory control to overeating derived studies that focused on obese populations (Giel et al., 2017; Lavagnino et al., 2016). However, it is now well established that obesity-related central effects, such as systematic inflammation or insulin resistance, might have an impact on cognitive performance (Smith et al., 2011; van den Akker et al., 2014). Thus, the association between obesity and executive functions is likely to be bi-directional (Smith et al., 2011), not solely linked to eating behavior (i.e., excessive food intake or overeating episodes) but more to the weight disorder itself. Future studies are needed to confirm our results in normal-weight populations with binge eating and to better elucidate the possible association between inhibitory control abilities and eating behavior.

5.4.2 Neural correlates of Action Cancellation

Contrary to behavioral data, the fMRI results showed between-group differences in brain activity during the SST. This result, together with the lack of differences in behavioral terms, might indicate that the two groups differed in the neural recruitment of specific brain regions to adequately perform the tasks.

The between-group comparisons in the STOP conditions (*action cancellation*) revealed greater activation in the left MFG and cerebellum in the BE, while the opposite comparison revealed greater activation in precentral regions for the non-BE group. In comparison to the GO trials, results in the STOP trials are similar, with the exception of the left MFG. Therefore, the greater activity in the left MFG in the BE group seemed to be specific in conditions in which participants were required to cancel

an ongoing action. Although a right prefrontal dominance for inhibitory control has become a commonly accepted view (Aron 2003; Aron, 2007), an increased attention for a role of the left hemisphere in self-regulation and impulsivity has been recently pointed out (Swick et al., 2008). In support of this notion, neuro-modulatory interventions, such as Transcranical magnetic stimulation (TMS), to increase self-regulation capacity have successfully targeted not only the right PFC but also the *left* side of the PFC (Val-Laillet et al., 2015). In addition, lesion studies have also indicated that the integrity of the left prefrontal regions is also critical for successful implementation of inhibitory control over motor responses (Swick et al., 2008).

In line with this evidence, the left MFG has been indicated as part of a network believed to process low-probability stimuli, with higher activity linked to the presence of infrequent no-go stimuli and failed inhibition trials (Stevens et al., 2009). Consistently, we showed higher activation during the presentation of stop signal (*action cancellation*), which appeared only the 25% of the trials (i.e., infrequent no-go stimulus). In addition, higher activation of the left MFG was also found to be linked to efficiency during a response inhibition task (Hirose et al., 2012). Hirose et al (2012) claimed that the neural substrate of response inhibition in the left hemisphere is a measure of efficiency and plays a supplementary role in inhibitory control when the right hemisphere is fully engaged or hypoactive (Hirose et al., 2012). Hence, a higher activation of the left hemisphere in the BE group might indicate the need to additionally engage this region to successfully perform the inhibition of the action (Hirose et al., 2012), whenever an infrequent stop signal appeared (Stevens et al., 2009). In support of this assumption, Zhang et al (2012) proposed a differential role for the right and the left fronto-parietal hemispheres. As already outlined in Chapter 4 (paragraph 4.4.3), the authors claimed that the right fronto-parietal network is involved in the process of action restraint, whereas the left lateralized network would be implicated in the process of motor inhibitory control during inhibition (Zang et al., 2012). More specifically, the left hemisphere would be involved in the process of response inhibition itself, the canceling of an ongoing action – *action cancellation* (Zhang et al., 2012). Crucially, our results pointed out a higher activity in the left MFG in the BE specifically during STOP trials, hence, during the process of cancellation of the action. Based on the assumption that the inhibitory load is higher in the cancellation of an ongoing action than in withholding (Schachar et al., 2007), an enhanced involvement of the left prefrontal regions might indicate that the task places a greater demand on the system responsible for inhibitory control and requires a supplementary engagement of the left module, in addition to the regular involvement of the attentional monitoring system, sustained by the right hemisphere (Zhang et al., 2012). In this context, a greater activity in the left MFG in the STOP

conditions in BE compared to non-BE might mean that a supplementary engagement of this region for BE participants was required to successfully cancel the ongoing action at the sight of the stop signal.

To further investigate this result, we separately looked at the STOP conditions toward food and non-food stimuli and the heightened activity observed in the left MFG in the BE – compared to non-BE – was specific for STOP food trials (Figure 5.5; Table 5.2). Therefore, the hypothesized additional engagement of this region during stopping might be linked not only to response inhibition in general, but particularly to inhibition when food is involved. Hence, this result further supports the possibility that BE group engaged the left MFG to a greater extent compared to non-BE to successfully inhibit their response toward food stimuli. The specificity of this finding might say something about the mechanisms underlying response inhibition (and particularly, action cancellation) toward food in normal-weight BE. In particular, this result might indicate that individuals prone to overeating (i.e., BE group) need to exert an enhanced control when required to inhibit their actions toward food and this results in an enhanced engagement of the left prefrontal regions. If so, this finding might provide fundamental hints to delineate the substrates of loss of control eating in healthy individuals and may provide insights for the exploration of possible risk factors for the maintenance of unhealthy eating habits, and eventually weight gain.

5.5 *AD INTERIM* CONCLUSIONS: Action Restraint and Cancellation

Taken together fMRI results from the GNG and SST investigations seem to speak in favor of an involvement of the MFG during both action restraint and cancellation in NW binge eaters (BE). The right MFG has shown a decreased activity during the execution of the GNG task in BE compared to non-BE (Experiment I; Figure 5.6); whereas, in the same group, an enhanced engagement of the left MFG has been revealed during action cancellation in the SST (Experiment II; Figure 5.6).

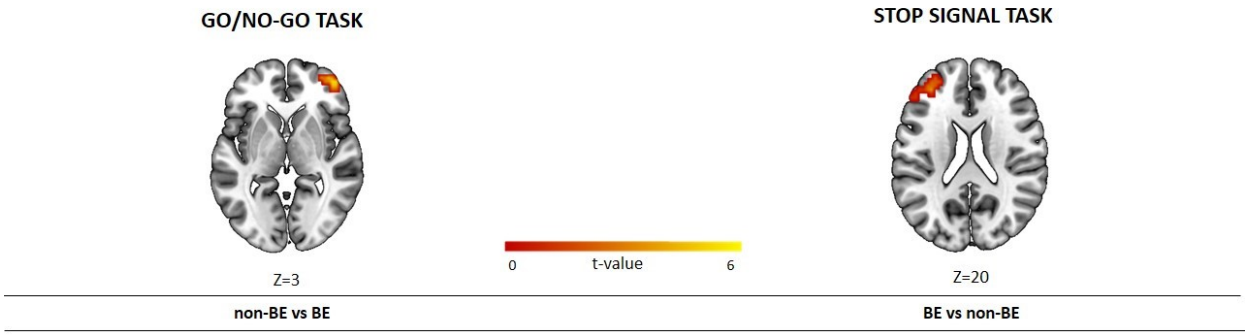

Figure 5.6. Representation of MFG clusters of activation in the GNG (non-BE vs BE) and in the SST (BE vs non-BE). On the left side of the figure the resulting cluster of the contrast non-BE vs BE, in the GNG [**RIGHT MFG**: MNI= 43; 53; -2]; on the right side of the figure the resulting cluster of the contrast BE vs non-BE, in the SST [**LEFT MFG**: MNI= -31; 49; 26]. Statistical parametric maps were overlaid onto a T1-weighted canonical image, provided by the MRIcroGL software. The color bar is representative of the *t*-scores given in the table 4.2 (Chapter 4) and 5.2 (Chapter 5). Images are shown in neurological convention and with Z-axial slice coordinates (z) as defined in Montreal Neurological Institute (MNI) 152 space. BE: binge eaters; non-BE: non binge eaters; MFG: Middle Frontal Gyrus.

The differential involvement of the right MFG in the GNG task and the left MFG in the SST can be read in light of the two distinct processes of inhibition involved in these tasks: action restraint and action cancellation (Logan et al., 1998). Recent evidence has indeed suggested the implication of the right-hemispheric fronto-parietal network in attention to the no-go signal (when the action needs to be restrained – *action restraint*) and the left fronto-parietal network in response inhibition itself (hence the canceling of the ongoing action – *action cancellation*; Zhang et al., 2012). Drawing upon the assumption that the inhibitory load is higher in the cancellation of an ongoing action than in withholding (Schachar et al., 2007), Hirose et al (2012) hypothesized that when the right hemisphere is hypoactive of fully engaged, the left hemisphere plays a supplementary role. Nevertheless, inhibitory processes are likely to involve a spread and large cerebral network, involving both right and left PFC regions. Thus, although asymmetries may be found during performance of these tasks, it is difficult to draw definitive conclusions of lateralized brain function of PFC regions with univariate analysis. Further investigation could be done using Multivoxel pattern analysis (MVPA; Norman et al.,

2006), a technique exploited to investigate the information contained in distributed patterns of neural activity to infer the functional role of brain areas and to capture the relationships between spatial pattern of fMRI activity and experimental conditions. Still, these results might give preliminary hints on the differential role of the left and right prefrontal regions and might provide useful insight on the substrates of inhibitory control in individuals with binge eating episodes.

Surprisingly, while between-group differences in the *right* MFG during GNG were observed only while inhibition response to non-food stimuli, those in the *left* MFG during the SST were specific for inhibition to food stimuli. There are several possible explanations for this result. One reason may lie on the food stimuli chosen for the paradigms. In more detail, given that we adopted different stimuli for the GNG and the SST but we did not rate their pleasantness for each individual, it is possible that food images in the SST elicited different responses compared to those used in the GNG. Another account for this result may be found in the different role of the right and left PFC regions. Between-group differences in the *left* MFG during food trials in the SST might be linked an additional engagement of this region in the BE group during action cancellation, particularly when food is involved. On the other hand, alterations within the *right* MFG in BE might be less linked to a specific task-condition (e.g., GO vs NO-GO trials; food vs non-food) and more to the execution of the whole task or the underlying condition itself (i.e., binge eating behavior). Indeed, while in the SST between-group differences in the left MFG were only found in STOP trials (Chapter 5; paragraph 5.4.3.1.), the differences located in the right MFG in the GNG are shown both during GO and NO-GO trials (Chapter 4; paragraph 4.3.3.1).

Nevertheless, regardless the lateralization of these clusters of activation, both tasks highlighted between-group differences in the MFG. The MFG has been defined as a key region involved in overeating and obesity (Alonso-Alonso and Pascal Leone, 2007; Garçia-Garçia et al., 2015): among others, Garçia-Garçia et al. (2015) observed an involvement of the MFG during both a resting-state condition and a visual task paradigm in obese participants compared to healthy controls. According to the authors, the consistency of this result, both at rest and during the task, indicated that functional alterations in this region could reflect a stable (across conditions) feature of obesity. Thus, since from both task-based investigations (Chapter 4 and 5) the MFG resulted to have a different activation in the two groups, we might hypothesize that a different modulation within the MFG regions may be implicated in the characterization of overeating conditions, regardless of weight status.

Overall, these findings encourage further investigation not only of a possible functional lateralization of the MFG linked to differential aspects of response inhibition (action restraint and cancellation), but also of the role for the MFG in BE as a possible pre-morbid or pre-existing risk factor for overeating. Recently a growing interest has been place on the role of the prefrontal regions in impulsivity and inhibitory control (e.g., Aron, 2003; 2007; Swick et al., 2008) and a number of different psychopathology that involves increases in impulsive behavior (e.g., substance addiction, gambling, eating disorders etc.) has been described as dysfunctions of "frontal" inhibitory processes (Swick et al., 2008). Hence, the exploration of which frontal brain regions is implicated in these different conditions, and especially, in which impulsivity-related aspects (e.g., action restraint, action cancellation, and trait impulsivity) might provide important hints to deepen our understanding of the substrates of impulsive behavior and to delineate suitable neuromodulatory interventions.

Chapter 6
EXPERIMENT III

Characterizing Functional Connectivity in Normal-Weight Binge Eaters: A Resting State fMRI Study

This experiment forms part of a manuscript, recently submitted to: *NeuroImage Journal*.

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6.1 BACKGROUND

As underlined in the previous Chapters, several lines of evidence point toward the involvement of impulsivity at the roots of overeating (Davis et al., 2013; Dawe and Loxton, 2004; Schag et al., 2013). In support of this assumption, a number of task-based fMRI investigations has consistently reported lower activation in inhibitory-control related regions (such as the PFC) when inhibitory control was challenged (e.g., response inhibition task), and heightened activation in reward-related regions (e.g., striatum) in response to food cues in individuals with Binge Eating Disorder (BED) compared to normal-weight controls (for a review see: Kessler et al., 2016). This evidence supports the dual-process model of overeating, according to which both a dysfunctional inhibitory control coupled by an enhanced sensitivity to reward might be at the roots of overeating behavior in eating and weight disorders (such as, obesity and BED; Dawe and Loxton, 2004). Further, it supports the assumption that these conditions might be subserved by functional alterations in impulsivity-related brain regions (i.e., prefrontal, striatal and parietal regions; Kessler et al., 2016). Due to the large amount of evidence of altered brain activity in a these distributed pattern of brain regions (i.e., prefrontal, striatal and parietal) in overeating conditions (Kessler et al., 2016), recently authors have begun to investigating the possible alterations in the functional connectivity among these regions, by means of resting-state fMRI (rsfMRI).

As described in Chapter 1 (paragraph 1.3.1), the measurement of spontaneous fluctuations of Blood Oxygen Level Dependent (BOLD) during a resting condition (e.g., fixation of a cross in the middle of a screen, or keeping eyes closed and relaxing) provides information useful to infer the relationship between brain activity of anatomically separated – but functionally connected – regions (e.g., Baek et al., 2017; Garcia-Garcia et al., 2015; Gaudio et al., 2016; Lohmann et al., 2013). This approach allows for the detection of subtle and fundamental changes in brain activity underlying different conditions or disorders, potentially neglected by canonical task-based investigations (Fox and Greicius, 2010). RsfMRI is indeed a promising method for uncovering the neural correlates of psychopathology and possible biomarkers underlying psychopathology (Woodward and Cascio, 2014). As an example, Xia et al (2018), investigated patterns of functional connectivity and some psychiatric symptoms (such as, mood, psychosis, fear, and externalizing behavior). They revealed that each dimension was subserved by unique features of functional connectivity, but that all dimensions were characterized by diminished functional connectivity between the default mode network and executive network regions. According to the authors, the identification of characteristic patterns of functional connectivity for each dimension together with common patterns between dimensions may provide

the potential to clarify the high co-morbidity between psychiatric diagnoses and, at the same time, explain the heterogeneity within each diagnostic category (Xia et al., 2018). Hence, there is growing interest in the use of rsfMRI as a potential foundation for developing network-based biomarkers in psychiatry (Xia et al., 2018; Barch, 2017; Woodward and Cascio, 2014).

With regard to overeating behavior, preliminary evidence obtained with rsfMRI converged in identifying functional connectivity alterations in association with disinhibited eating, in regions implicated in impulsivity-related aspects (such as, prefrontal, subcortical and parietal regions; see Chapter 2 paragraph 2.4.2 for a more complete description of the studies; Chodkowski et al., 2016; Moreno-Lopez et al., 2016; Park et al., 2016). For instance, a recent study revealed an association between unhealthy eating, impulsivity and functional connectivity at rest in obese children (Chodkowski et al., 2016). Using seed-based analysis (Biswal et al., 1995), the authors showed that the connectivity between frontal and subcortical (nucleus accumbens, NAc) regions – involved in impulsive behavior – was stronger as food approach and adiposity increased. These results highlighted a relationship between impulsivity and food approach, but more importantly provided support to the hypothesized association between functional connectivity patterns, unhealthy eating behavior and weight gain in children (Chodkowski et al., 2016). In line with these conclusions, a link between the fronto-parietal connectivity, disinhibition over eating behavior and Body Mass Index (BMI) was revealed in both normal-weight and overweight individuals, using Independent Component Analysis (ICA; Park et al., 2016). In particular, fronto-parietal network showed significant positive correlations with disinhibition scores of the Three Factor Eating Questionnaire (TFEQ, assessing eating behavior; Stunkard et al., 1985) and BMI (Park et al., 2016).

Overall, these findings provided valuable insights into the association between functional connectivity alterations in impulsivity-related regions and unhealthy- or over-eating (Park et al., 2016; Moreno-Lopez et al., 2016; Chodkowski et al., 2016). However, to date, few studies have focused only on normal-weight individuals, thus it remains difficult to infer whether the functional changes are reconfigurations of the brain connectivity as a result of weight gain, or if they are specifically associated with unhealthy eating behavior, regardless of weight status. In fact, the impact of chronic consumption of high-calorie foods and consequent weight gain may have an impact on both reward/cognitive processes and brain functional connectivity (Horstmann et al., 2015; Smith et al., 2011; van den Akker et al., 2014).

For this reason, the present study investigated resting-state brain connectivity in individuals with binge eating episodes, but with a BMI falling within the normal weight range (See Box 2.1;

Chapter 2). In order to provide a detailed account of resting-state functional connectivity we decided to use two different measures: degree and eigenvector centrality (Bullmore and Sporn, 2009). Degree centrality (DC) – the simplest centrality measure – identifies the most connected nodes by counting the number of direct connections (edges) to all other nodes. The higher the degree, the stronger the connections to other nodes in the network (Zuo et al., 2012). On the other hand, eigenvector centrality measure (ECM) – a natural extension of degree centrality – reflects the number of direct connections a node has with other nodes that have high centrality. Thus, the ECM of a given node depends not only on its own centrality, but the centrality of the nodes it connects to. A node becomes relevant if it is connected to important nodes in the network (Zuo et al., 2012). Both measures are relevant in the assessment of network connectivity: indeed, a node having several connections does not automatically have a high eigenvector centrality and, at the same time, a node with high eigenvector centrality is not necessarily highly connected to other nodes (Lohmann et al., 2010).

In addition, centrality results have been further investigated with seed-based connectivity analysis (Biswal et al., 1995) choosing centrality results as seeds (i.e., regions of interest).

In line with the evidence previously described (Chodkowski et al., 2016; Park et al., 2016), we hypothesized to find between-group differences located in brain areas involved in impulsivity-related aspects, and especially prefrontal and subcortical (i.e., striatum, insula) regions. Based on the task-based results described in the previous Chapters (4 and 5), and the consistent involvement of the MFG in the characterization of the BE group during the execution of both the GNG and the SST (see Figure 5.6; Chapter 5), we might assume that the rsfMRI will highlight differences specifically located in this region. If so, these results would strengthen the assumption that MFG might be a plausible candidate as neural substrate of binge eating in normal-weight individuals.

In general, the investigation of the differences between normal-weight individuals with and without binge eating can be of extreme importance to provide a detailed account of the role of impulsivity in overeating and of the hallmarks of this behavior, without overweight and obesity-related confounding effects. Within this framework, the rsfMRI approach might be particularly helpful in identifying core abnormalities underlying binge eating independently of task-related factors, and thus inform on brain-based characteristics of this condition, regardless of weight status.

6.2 METHODS

6.2.1 Procedure

See Chapter 3 for the 'GENERAL PROCEDURE OF THE EXPERIMENTAL WORK'.

In this experiment, participants underwent an fMRI measurement while at rest (paragraph 6.2.2).

6.2.2 Functional MRI: acquisition

6.2.2.1 MRI Acquisition

Whole-brain functional Magnetic Resonance Imaging (fMRI) data were obtained using a 1.5 T Siemens Avanto MRI scanner (Siemens Medical Systems, Erlangen, Germany) equipped with a standard Siemens eight-channel coils. 240 volumes were collecting using a gradient-echo, echo-planar (EPI) T2*-weighted sequence in order to measure blood oxygenation level-dependent (BOLD) contrast throughout the whole brain (37 contiguous axial slices acquired with ascending interleaved sequence, 56 × 64 voxels, 3.5 mm × 3.5 mm × 4.0 mm resolution, Field of View, FOV = 196 mm × 224 mm, flip angle = 90°, TE = 49 ms). Volumes were acquired continuously for each run with a repetition time (TR) of 3 seconds. During the fMRI measurement, participants were lying down in the scanner and wore MR-compatible LCD video goggles (VisuaStim XGA, Resonance Technology Inc.) with a resolution of 800x600 and 60 Hz refresh rate. During the acquisition participants were instructed to look at a white fixation cross (overlaid onto a black background) at the center of the screen. Structural scans were collected using T1-weighted 3D magnetization prepared rapid acquisition gradient echo (MPRAGE) sequence in the same orientation as the functional sequences to provide detailed anatomic images aligned to the functional scans. High-resolution anatomical images were acquired (176 axial slices, FOV = 256 × 256 mm^2, 256 × 256 matrix, 1 mm isotropic voxels, TR = 1900 ms, TE = 2.91 ms).

6.2.3 Functional MRI: analysis

6.2.3.1 Preprocessing

Data were preprocessed and analyzed using SPM12 (www.fil.ion.ucl.ac.uk/spm) working in Matlab environment (MathWorks, Natick, MA, USA). The ArtRepair (AR) toolbox was used to detect slices corrupted by motion artifacts and/or signal spikes (Mazaika et al., 2007). Preprocessing steps included: (i) realignment, (ii) coregistration to the anatomical T1-weighted image, (iii) normalization into Montreal Neurological Institute (MNI) space, and (iv) smoothing with a 6mm FWHM Gaussian kernel. Global AR was applied to detect outlier volumes (Mazaika et al., 2007). The output of these

steps was a 4D residual functional volume in native functional space for each participant. The 4D native data were registered to the MNI152 template with 3-mm resolution using affine transformation.

6.2.3.2 Analysis: Functional Connectivity Measures

After preprocessing, we used graph theory approaches (Bullmore and Sporns, 2009) to assess between-group differences in local and global functional connectivity. In graph theory analysis the brain is considered as a complex network involving different nodes (from single voxels to extended brain regions) connected by edges (i.e., functional relationships among the nodes; Bullmore and Sporns et al., 2009). Graph theory methods enable the localization of relevant brain regions (i.e., central hubs) considering the connection patterns associated with them and it provides measures of functional centrality (Buckner et al., 2009; Zuo et al., 2012). In the context of this study, two centrality measures (degree and eigenvector centrality) were used to investigate the localization of functionally important brain regions based on the connection patterns associated with them (Buckner et al., 2009; Zuo et al., 2012). In more detail, DC attributes a greater value to a voxel on the basis of its connections to other voxels in the brain: the more the connections, the stronger the value. In other words, DC indexes the total number of connections for a given node (Buckner et al., 2009) and provides information on the integrity of the resting state networks (Fox and Raichle, 2007). Differences in DC can be considered 'local', given that this metric captures the amount of direct connections with a given node (Zuo et al., 2012). We computed individual DC correlation maps within gray matter using AFNI (3dDegreeCentrality; Cox, 1996) as implemented in the Nipype framework (Gorgolewski et al., 2011). According to Garçia-Garçia and colleagues (2015), we thresholded the maps at a value of r=0.5, where only values above this threshold were considered for the second level analysis.

ECM enables the identification of nodes connected to hubs of specific networks (Lohmann et al., 2010). The term hubs refers to nodes that are central within a given network (Rubinov and Sporns, 2010). Differences in ECM, compared to DC, can be generally regarded as 'global' in the sense that this metric captures 'indirect' functional connectivity (Zuo et al., 2012). Individual ECM maps were computed within gray matter using AFNI (3dECM; Cox, 1996) within the Nipype framework. Here, the sparsity was set to 1%, which means that only the strongest 1% of correlations was considered for the second level analysis.

6.2.3.3 Analysis: Seed Based Connectivity

To further examine the connectivity patterns of the main centrality changes, seed-based analyses (Biswal et al., 1995) were conducted, choosing as regions of interest those areas showing group differences in DC and ECM. We extracted mean time series for each of the seeds and correlated it with remaining voxels in the brain within an identical brain mask for each participant (Pearson's correlation). This analysis was done using a custom-made script within the Nipype framework. Resulting connectivity maps were then Fisher-z transformed and entered into the second level analysis.

6.2.3.4 Second-level analyses: Between-group comparisons

All second-level analyses were conducted with SPM12. General differences in functional centrality in resting-state conditions were assessed through a two-steps procedure: first, ECM and DC maps for BE and non-BE were compared, in order to assess differences in functional centrality. Second, brain regions revealed by the comparison of ECM and DC maps were entered into the seed-based analysis, comparing the individual correlational maps between the two groups. In all second-level analyses, BES individual scores were entered as covariate to control for the possible effect of this variable. In more detail, BES score was the criterion used to assign participants to one of the two groups (BE and non-BE): therefore the inclusion of this value in the model allowed us to both maintain the differences between the groups regarding this variable and to control for within-group differences in the interpretation of the results. Statistical images were first assessed for cluster-wise significance with a primary cluster-defining threshold of $p= 0.001$, then the thresholded cluster was considered significant at a FWE rate of $p < .05$.

6.3 RESULTS

After preprocessing, the images of two females participants of the binge eaters group (BE) and one female participant of the non-BE group and had to be excluded from the analysis due to artifacts in data acquisition. The resulting sample for rsfMRI analysis was 20 non-BE and 19 BE.

6.3.1 Descriptive characteristics

See Table 3.1 (Chapter 3; paragraph 3.5).

6.3.2 Centrality Measures: Degree Centrality (DC)

The comparison 'non-BE > BE' showed a lower degree centrality for BE in the right MFG, left inferior temporal cortex, superior parietal lobe, and insula. The opposite comparison ('BE > non-BE') did not yield any significant result (Figure 6.1; Table 6.1).

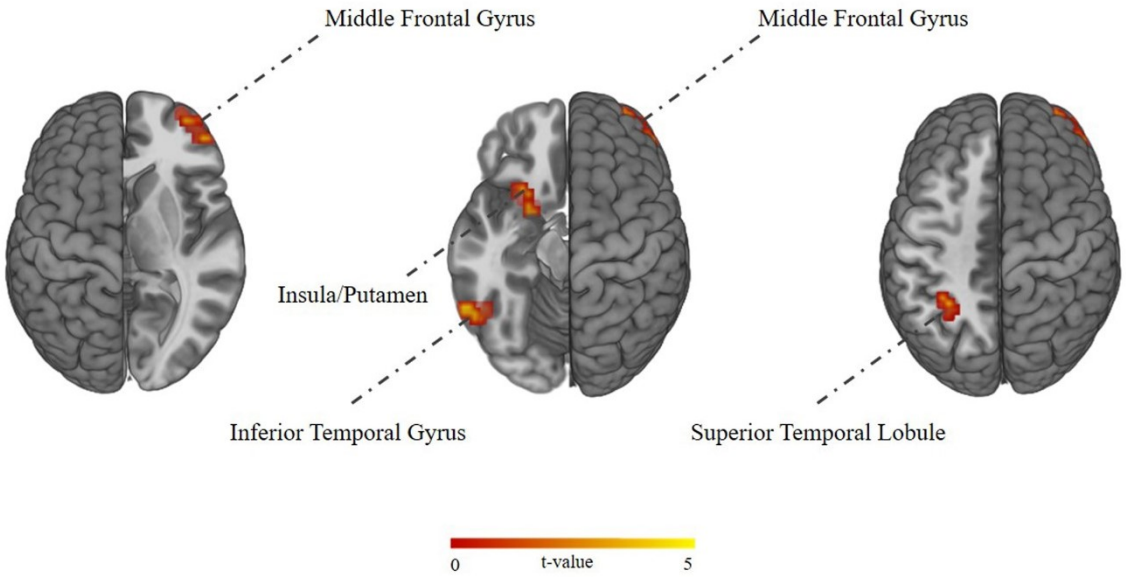

Figure 6.1. Degree Centrality: non-BE > BE. Figure shows results for the non-BE > BE comparison. Statistical parametric maps were overlaid onto a Montreal Neurological Institute (MNI) render provided by the MRIcroGL software. The color bar is representative of the *t*-scores given in Table 6.1. Images are shown in neurological convention.

Cluster		Peak		MNI			Side	Region
k	p(FWE-corr)	t	z	x	y	z		
20	0.0098	4.51	3.97	36	60	10	R	Superior Frontal Gyrus
		4.08	3.66	50	46	10	R	Middle Frontal Gyrus
16	0.0281	4.34	3.86	-24	11	-10	L	Putamen
		3.55	3.25	-27	14	-18	L	Anterior Insula
19	0.0126	4.18	3.74	-62	-53	-14	L	Inferior Temporal Gyrus
14	0.0489	4.16	3.72	-31	-56	50	L	Superior Parietal Lobe

Table 6.1. Degree Centrality: non-Binge Eaters (non-BE) vs Binge Eaters (BE). Abbreviations: k=number of voxels; t and z scores; stereotaxic coordinates according to the MNI space; brain side and region. Statistic threshold: Results were considered significant at p< .001 that additionally met a FWE correction at cluster level (p< .05). BE = Binge Eaters; non-BE = non-binge eaters; FWE = Family Wise Error; L = left; R = right.

6.3.3 Centrality Measures: Eigenvector Centrality (ECM)

No differences were observed in ECM. Thus, seed-based connectivity analysis (SCA) was run on the basis of DC results only.

6.3.4 Seed-based connectivity analysis (SCA)

Given the relevance in inhibitory, interoceptive and reward-related processes, we chose the clusters located in the right MFG and left Putamen/anterior Insula as seeds for the SCA.

(i) Seed: right Middle Frontal Gyrus

BE participants exhibited lower functional connectivity compared to non-BE between the seed located in the right MFG and the right anterior insula. The opposite comparison (non-BE > BE) did not reveal any significant results (Figure 6.2; Table 6.2).

(ii) Seed: left Putamen/anterior Insula

For both contrasts (BE > non-BE; non-BE > BE), SCA did not reveal any significant results when left anterior insula was used as a seed.

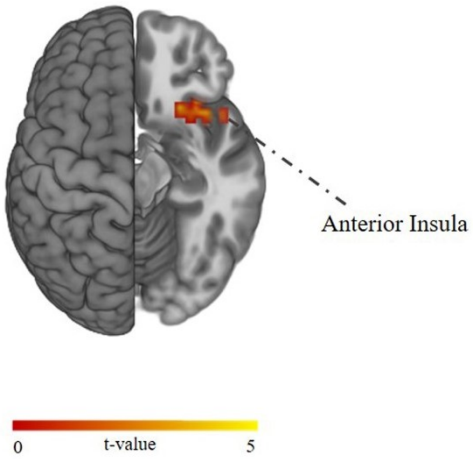

Figure 6.2. Seed-based connectivity: Middle Frontal Gyrus. Figure shows results for the non-BE > BE comparison, with right Middle Frontal Gyrus as seed. Statistical parametric maps were overlaid onto Montreal Neurological Institute (MNI) render, provided by the MRIcroGL software. The color bar is representative of the *t*-scores given in the table below (6.2). Images are shown in neurological convention.

Cluster		Peak		MNI			Side	Region
k	p(FWE-corr)	t	z	x	y	z		
32	0.037	4.48	3.94	39	15	-9	R	Anterior Insula

Table 6.2. Seed-based connectivity: Middle Frontal Gyrus. Abbreviations: k=number of voxels; t and z scores; stereotaxic coordinates according to the MNI space; brain side and region. Statistic threshold: Results were considered significant at p< .001 that additionally met a FWE correction at cluster level (p< .05). BE= Binge Eaters; non-BE= non-binge eaters; FWE= Family Wise Error; L= left; R= right.

6.4 DISCUSSION

In the present research we aimed at assessing resting-state brain activity in normal-weight (NW) individuals with loss of control eating but without a weight or eating disorder (BE), compared to NW individuals without BE (non-BE). Given the hypothesized role of impulsivity in overeating behavior (Moore et al., 2017; Dawe and Loxton, 2004), we assumed that BE would show different functional connectivity in impulsivity-related regions (e.g., prefrontal and subcortical regions).

As already reported in Chapter 4 (paragraph 4.4.1), the two groups showed different levels of impulsivity toward food – as measured by Binge Eating Scale (BES; Gormally et al., 1985) and Yale Food Addiction Scale (YFAS; Gearhardt et al., 2011) and of general trait impulsivity, assessed by the Barratt Impulsiveness Scale (BIS-11; Patton et al., 1995). In particular, BE individuals had higher scores in the motor and non-planning subscales, suggesting that for this group impulsivity was related not only to food but also expressed in general terms.

Consistently, functional connectivity measures revealed between-group differences in prefrontal, parietal and subcortical regions. In more detail, degree centrality (DC) analysis – which indexes the total number of connections for a given node (Buckner et al., 2009) – revealed that BE participants, compared to non-BE, had a lower functional centrality in the right MFG, left anterior insula/putamen, inferior temporal gyrus and superior parietal lobule. Overall, these findings indicate that the differences between the groups were located in regions involved in cognitive control (right MFG; Fuster, 2002), interoception (anterior insula; Craig, 2002) and multimodal sensory integration (temporal and parietal regions; Macaluso and Driver, 2005). These results mirror those described by some previous work (Moreno-Lopez et al., 2016) comparing functional connectivity measures in overweight and lean adolescents: the authors describe how regions such as the insula, the temporal and the dorsolateral prefrontal cortex (DLPFC) are characterized by lower functionality in overweight individuals. Our results further extend this result, showing how similar functional connectivity patterns do not characterize overweight individuals only (Moreno-Lopez et al., 2016; Verdejo-Garcia et al., 2010), but also NW with high level of impulsivity. This novel finding indicates that alterations in regions relevant for the coding of stimulus significance and exerting top-down executive control (i.e., prefrontal and insular regions) characterize BE individuals, even in the absence of a weight disorder and hence, they could be potential prodromes of overweight.

In line with our hypothesis, a lower DC was revealed in the right MFG, an important region belonging to the PFC. Like other prefrontal regions, MFG participates in different cognitive processes,

such as inhibitory control, working memory and monitoring of goal-directed behavior (Fuster, 2002). As previously reported in Chapter 4, the right MFG is known to be implicated in response inhibition processing and, in particular, the right PFC regions seems to play a pivotal role in the process of *action restraint* (Zhang et al., 2012).

Recently, rsfMRI studies have revealed an association between excessive weight and alterations in functional connectivity in PFC regions (Kullmann et al., 2012; 2013) and lower DC in the right MFG has been described in obese compared to NW adults (Garçia-Garçia et al., 2015). In the latter study, lower DC appeared to characterize both brain activity at rest and during a visual task. The authors concluded that the consistent alterations, across conditions, within the right MFG might constitute a stable trait characterizing obesity (Garçia-Garçia et al., 2015). Along this line, our result showing diminished DC in the right MFG suggests that the modulation of activity within this region might be a sort of brain 'fingerprint' of overeating already in NW, and not only in obese conditions. In other words, this difference could be more related to overeating behavior than to a proper overweight condition. Interestingly, the task-based fMRI investigation, described in Chapter 4 (paragraph 4.3.3.1), revealed a diminished activation of the right MFG during the execution of a GNG task, in the BE group compared to non-BE. Thus, both the task-based and the resting-state results seem to point toward an involvement of the right MFG in the characterization of the BE group, compared to the non-BE. Drawing upon Garçia-Garçia et al (2015) conclusions, the possible implications of the consistency of these results within the same study population will be examined in the "General Discussion" section (Chapter 8).

A further investigation of this result with seed-based connectivity analysis (SCA) revealed a lower functional connectivity between the right MFG and the right anterior insula. The insula is known to be a multimodal integration region, involved in the evaluation of emotional and motivational salience of stimuli and providing an interface between external information and internal motivational states (Craig, 2002; Seeley et al. 2007). In more detail, the anterior insula is well established as the primary gustatory cortex, integrating multiple bodily sensations to generate an interoceptive state (Maffei et al., 2012; Small, 2006). In addition, insula, as a part of the limbic sensory cortex, is involved in the generation of the hedonic states of the individual (Craig, 2009). Thus, altered connectivity of the anterior insula could suggest a dysregulation of hedonic-taste processing in disordered eating conditions and could underlie an approach toward food dominated by a reward-seeking behavior rather than by interoceptive information from the body (Mata et al., 2015). More specifically, eating behavior would not be guided by our signals of hunger and satiety (i.e., interoceptive signals), but

rather by our sensitivity to the rewarding effect of a certain food. Thus, the result of a diminished functional connectivity between the insula and the MFG in the BE group points toward a possible disequilibrium between inhibitory/cognitive control, reward sensitivity processes and gustatory processing in NW individuals with BE, as already reported in obese adolescents (Moreno-Lopez et al., 2016) and adults (Lips et al., 2014). This would practically lead to a dysregulation between our ability to exert control (e.g., not eat when feeling satiated) and our urges to obtain reward from the consumption a certain food. In addition, results confirm an involvement of networks associated with impulsivity (i.e., inhibitory control and reward processes) in BE conditions, independently of weight status.

Furthermore, the DC analysis revealed a lower functional centrality in the left anterior insula and the putamen, in BE compared to non-BE. Both the insula and the putamen have been identified as critical nodes in cravings and functional alterations in these regions have been associated with enhanced vulnerability for compulsive habits and addiction (Everitt et al., 2008; Gilman et al., 2018; Sjoerds et al., 2015). Given the role of the insula in the orexogenic network, responsible for food regulation (Tataranni et al., 1999), and the putamen in habits formations (Dolan and Dayan, 2013), alterations within these networks might be at the roots of eating dysregulation and maladaptive habitual behaviors (e.g., compulsive eating; Kullmann et al., 2012). However, no evidence of altered SCA was observed when the cluster in the left insula/putamen was used as seed. On these bases, we might speculate that the group differences could be more ascribable to a different number of total connections in these regions rather than to differences in their functional connections with specific areas (Garçia-Garçia et al., 2015). A lower total number of connections might denote a diminished exchange of information with the entire network, not directly linked to a specific region. Taking into account this body of evidence, lower DC in these regions in NW individuals with BE may point toward a possible role of these alterations as vulnerability factors for the development of compulsive habits and cravings (toward food), as already reported for addictive disorders (Gilman et al., 2018; Sjoerds et al., 2015).

In sum, our results indicate that the BE group is characterized by a diminished functional centrality of the right MFG, subcortical, temporal and parietal regions; and a diminished functional connectivity of the MFG with the right anterior insula. Thus, BE group appears to differ from non-BE, in the functional connectivity of regions involved in the detection and representation of motivationally significant signals and cognitive control (Moreno-Lopez et al., 2016). Taken together, DC and SCA results put forward the idea that binge eating behavior may be not only subserved by alterations in

regions that regulate metabolic needs but mostly by regions relevant for coding higher-level stimuli and top-down cognitive mechanisms (Verdejo-Garcia et al., 2010). The lack of significant differences in the ECM is hard to interpret and needs additional exploration; nonetheless, it is in line with the lack of ECM differences between obese and NW individuals showed in previous studies (Garçia-Garçia et al., 2015).

Although the directionality and causality of the changes remains to be established, we can conclude that the between-group differences were not dependent on the presence of an excessive weight condition. Therefore, our findings suggest the intriguing possibility that diminished functional connectivity at rest in the right MFG and insula might be considered a potential hallmark and mechanism at the roots of BE behavior.

Chapter 7
EXPERIMENT IV

Brain Volumes and Impulsivity in Normal-Weight Binge Eaters: A Voxel-Based Morphometry Study

This experiment forms part of a manuscript currently in preparation.

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7.1 BACKGROUND

As described in the previous Chapters, several studies have attempted to characterize the neural correlates of overeating, in Binge Eating Disorder (BED) and obesity, clinical conditions characterized by the presence of overeating episodes, in different sizes and frequencies (for a review see: Kessler et al., 2016; Van den Eynde et al., 2012). By means of neuroimaging techniques (e.g., fMRI) differences in regions mainly implicated in impulsivity (such as prefrontal and subcortical regions) have been highlighted in both task-related and resting-state investigations, suggesting an involvement of impulsivity-related aspects at the roots of these conditions (Kessler et al., 2016). Crucially, also our task-related and resting-state fMRI investigations confirmed the involvement of impulsivity-related regions (such as, prefrontal, parietal and subcortical regions) in the characterization of normal-weight individuals with binge eating (Chapters 4-6).

However, the body of evidence in the literature comes mainly from fMRI investigations, and less is known about a potential counterpart in terms of brain structure. Nevertheless, evidence from structural MRI investigations is needed to gain a more comprehensive understanding of the neurobiology of eating behavior. In this context, Voxel Based Morphometry (VBM), a computational morphometry automated technique, can be a useful tool to explore brain structure in terms of differences in regional and global brain volumes between different populations, in association with specific personality traits or clinical characteristics (Ashburner and Friston, 2000).

Concerning impulsivity as a potential hallmark for binge eating behavior, preliminary VBM studies on obese individuals reported alterations (in terms of regional grey matter volumes, GMV) in brain regions associated with behavioral control (i.e., prefrontal and cingulate regions; Brooks et al., 2013; Pannaciulli et al., 2006) and reward (orbitofrontal and subcortical regions; Pannaciulli et al., 2006) when obese were compared to normal-weight individuals. Some of these regions, especially prefrontal areas, have been assumed to interfere with obese persons' ability to predict future consequences of their eating behaviors, leading them to pursue overeating despite the negative outcomes (Del Parigi et al., 2002). However, it is not yet clear whether these differences in terms of GMV contribute to the predisposition to overeating, or if they are rather a consequence of excess body fat (Pannaciulli et al., 2006).

A preliminary answer to this still open issue may derive from the investigation of individuals with overeating behavior, but with a Body Mass Index (BMI) falling within the normal-weight range (from 18.5 to 24.9; Box 2.1; Chapter 2), to remove the possible confounding weight-related effects (Lowe et al., 2009). For this reason, in the present study, we used a VBM approach to investigate GMV

in normal-weight individuals with and without binge eating episodes (BE and non-BE, respectively). Given many studies have demonstrated a clear-cut association between trait impulsivity and overeating behavior regardless of weight status (Jasinska et al., 2012; Lyu et al., 2017; Meule et al., 2013), we expected to observe between-group differences in terms of GMV in impulsivity-related regions (such as, prefrontal and subcortical regions), positively associated with impulsivity trait, as assessed by the Barratt Impulsiveness Scale (BIS-11; Patton et al., 1995). Hence, we hypothesized that binge eating behavior in normal-weight would be associated with regional GMV alterations, even in the absence of a full-blown eating or weight disorder.

7.2. METHODS

7.2.1 Procedure

See Chapter 3 for the 'GENERAL PROCEDURE OF THE EXPERIMENTAL WORK'.

In this experiment, we focused on brain morphometry to examine possible differences in grey matter volumes (GMV) in NW individuals with BE compared to non-BE.

7.2.2 Magnetic Resonance Imaging (MRI) acquisition

The MRI data were collected with a whole body 1.5 T scanner (Siemens Magneton Avanto) equipped with a standard Siemens eight channels coil. High-resolution T1-weighted image were acquired for each subject. Scanning parameters were: 224 contiguous slices; voxel size=0.7*0.7*0.7; Field of view (FOV) 320x320; Repetition Time (TR) 20 ms; echo time (TE) 4.89 ms; band=130 hz/Px.

7.2.3 MRI analysis

MRI data preprocessing and analysis were performed using a Voxel Based Morphometry (VBM) approach that allows for a voxel-by-voxel assessment of differences across the whole brain using standardized anatomical measures of voxel-wise estimations and parametric mapping to determine tissue-type probabilities (Ashburner et al. 2000). Preprocessing was conducted using the Computational Anatomy Toolbox (CAT12, http://dbm.neuro.uni-jena.de/cat/), which is an extension of SPM12 (Statistical Parametric Mapping) (http://www.fil.ion.ucl.ac/spm) implemented in MATLAB 7.12.0 environment. We decided to use CAT12 over VBM8 toolbox because recent evidence indicated that a VBM analysis using CAT12 is more robust and accurate against volumetric alterations than the

VBM8 toolbox (Farokhian et al., 2017). Default settings described in the manual of the CAT12 toolbox (http://dbm.neuro.uni-jena.de/cat12/CAT12-Manual.pdf) were adopted. Preprocessing of MR images included: (i) segmentation into grey matter (GM), white matter (WM), and cerebrospinal fluid (CSF), (ii) normalization according to the Montreal Neurological Institute (MNI) template; (iii) bias correction to remove intensity non-uniformities and (iv) smoothing with a Gaussian kernel of 8*8*8 mm Full Width at Half Maximum (FWHM). The total intracranial volume (TIV) and percentage of global tissue volumes (GM, WM and CSF) of each subject were computed by the CAT 12 toolbox and then compared between the two groups (BE and non-BE) in SPSS 21.

The assessment of between-group differences at a whole brain level focused only on GM volumes (GMV). To this aim, we used the GM images of each participant and performed voxel-wise two-sample t-tests within a General Linear Model (GLM) in SPM 12, using a Whole Brain analysis approach. Statistical images were first assessed for cluster-wise significance with a primary cluster-defining threshold of p= 0.001, then the thresholded cluster was considered significant at a FWE rate of $p < .05$. Only the surviving clusters are reported.

To further investigate these results and their relation with trait impulsivity, we tested the correlation between the GMV in the resulting clusters and the scores of the BIS-11 questionnaire. By means of the SPM toolbox 'MarsBaR' (Brett et al., 2002) we extract the mean GMV values from the cluster showing differential GMV between the groups (i.e., results from the t-test comparison). As a second step, a linear correlation of the resulting values with the scores of the BIS-11 was performed in SPSS 21. Results were considered significant at the level of .05 (two tailed). Non-significant correlations are reported in the Supplementary Materials.

7.3 RESULTS

7.3.1 Descriptive characteristics

See Table 3.1 (Chapter 3; paragraph 3.5).

7.3.2 Voxel-Based Morphometry (VBM)

7.3.2.1 Global Volumes: between-group comparison

Percentage of global volumes of GM, WM, CSF and TIV did not differ between the groups (Table 7.1).

	non-BE	BE	Two sample t-test	
	M ± SD	M ± SD	t	p
(%) GM	19.4 ± 7	19.6 ± 3.3	0.108	0.915
(%) WM	44.6 ± 1.8	44.1 ±3.4	0.623	0.537
(%) CFS	37 ± 1.3	36.3 ± 1.6	1.59	0.12
TIV	1416.6 ±146.8	1482 ± 134.73	1.52	0.136

Table 7.1. Global Volumes: Between-group comparison for global volumes (grey matter, white matter, cerebrospinal fluid) and total intracranial volume. Abbreviations**:** M: Mean; SD: Standard Deviation; t: t-score; BE: binge eaters; non-BE: non binge eaters; GM: Grey Matter; WM: White Matter; CSF: Cerebrospinal fluid; TIV: total intracranial volume.

7.3.2.2 Whole Brain Analysis: between group comparison

The BE > non-BE contrast revealed significant differences in the left Middle and Superior Frontal Gyrus (MFG and SFG, respectively), whereas the opposite comparison did not yield any significant result (Figure 7.1; Table 7.2). Even though the groups did not differ for the Total Intracranial Volume (TIV; See Table 7.1), we conducted the same analysis adding TIV as a covariate of no interest and the BE > non-BE revealed differences in the same cluster within the left MFG (Appendix C, Table C1).

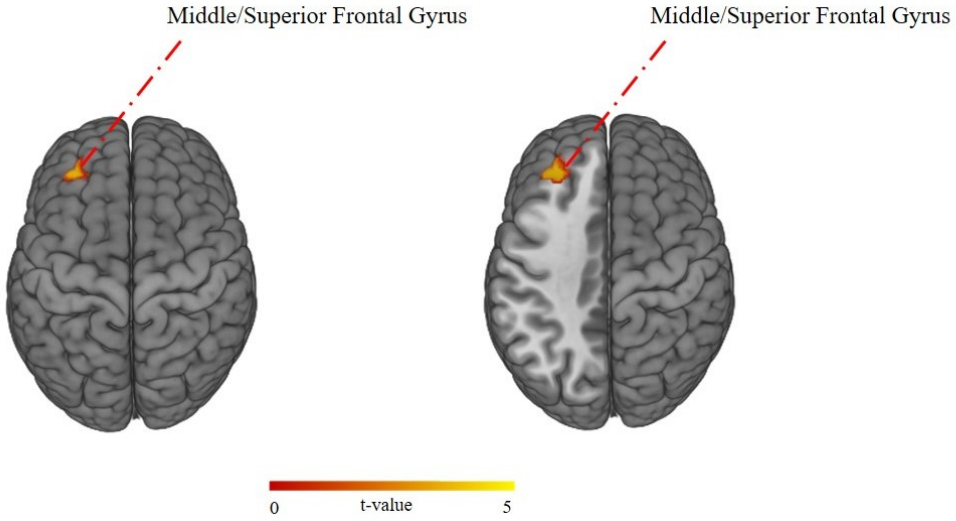

Figure 7.1. Whole Brain Analysis: BE vs non-BE comparison. Figure shows results for the BE > non-BE comparison. Statistical parametric maps were overlaid onto a Montreal Neurological Institute (MNI) render provided by the MRIcroGL software. The color-bar is representative of the *t*-scores given in Table 7.2. Images are shown in neurological convention.

WHOLE BRAIN ANALYSIS						
k	**p (FWE)**	**t**	**z-score**	**MNI**	**Side**	**Region**
BE vs non-BE						
496	0.020	4.29	3.87	-26 44 35	L	Middle Frontal Gyrus
		4.01	3.65	-14 36 35	L	Superior Frontal Gyrus
Non-BE > BE						
Ns						

Table 7.2 Whole Brain Analysis: two sample t-test. Abbreviations: k=number of voxels; t and z scores; stereotaxic coordinates according to the MNI space; brain side and region. Statistic threshold: Results were considered significant at p< .001 that additionally met a FWE correction at cluster level (p< .05). BE: Binge Eaters; non-BE: non-binge eaters; FWE: Family Wise Error; L: Left; R: Right; MNI: Montreal Neurological Institute.

7.3.2.3 Correlation between grey matter volumes (GMV) and impulsivity traits

For the cluster in the left MFG – reported in Table 7.2 – the correlation between its mean GMV value and the scores of the BIS-11 questionnaires (motor, attentional, non-planning and total scores) was estimated for both groups. A positive correlation between GMV of the left MFG and the motor impulsivity subscales' scores (r= .35; p= .035; Figure 7.2) was observed. Non-significant correlations with attentional, non-planning and total scores are reported in in Table C2 (Appendix C).

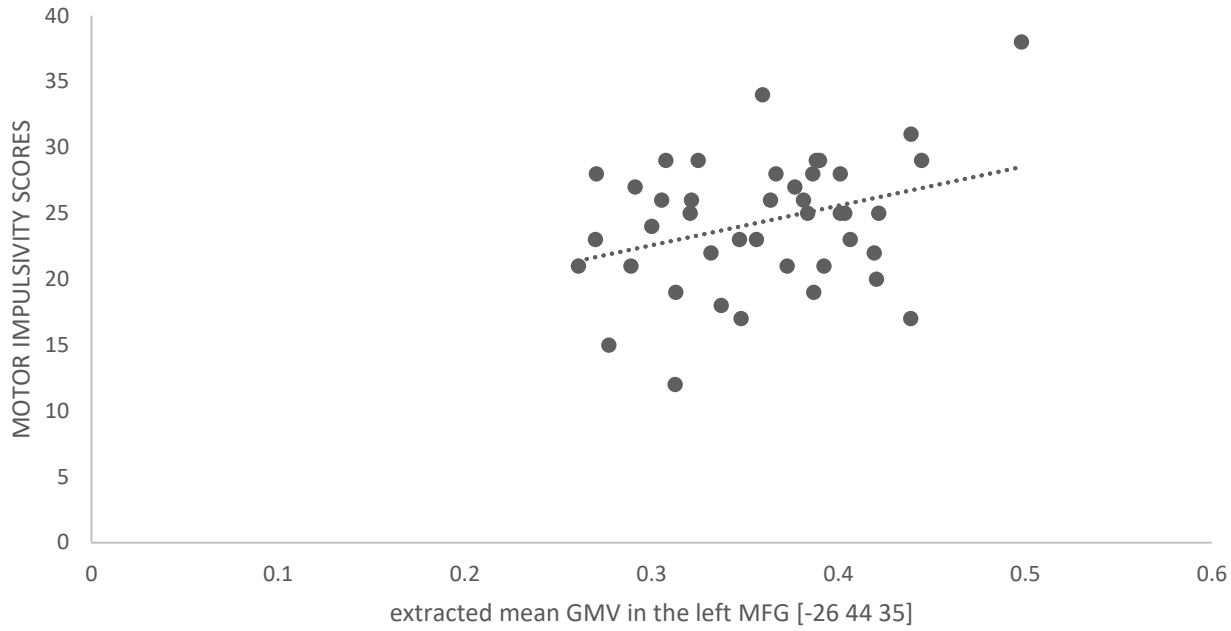

Figure 7.2. Correlation analysis: linear correlation between GMV in the left SFG and Motor Impulsivity scores of the BIS-11 questionnaire for both groups pooled together. BIS-11: Barratt Impulsiveness Scale; GMV: Grey Matter Volume; MFG: Middle Frontal Gyrus. Correlation was considered significant at the level of .05 (2-tailed).

7.4 DISCUSSION

The present research aimed at examining the differences between two groups of normal-weight individuals, with and without binge eating episodes (BE and non-BE), in regional grey matter volumes (GMV) and trait impulsivity. We expected the two groups included in the study to differ in terms of GMV in regions involved in behavioral regulation and inhibitory control (e.g., fronto-striatal regions).

As previously outlined (see Chapter 4 paragraphs 4.4.1), it has to be remembered that the BE group reported greater trait impulsivity compared to non-BE: motor, non-planning and total scores of the BIS-11 resulted to be higher in this group, supporting the theorized driving role of impulsivity in overeating in normal-weight individuals (Meule et al., 2013). In fact, BE has been frequently associated with heightened general impulsivity, and more impulsive individuals are thought to be less able to restrain their eating behavior and to stop when confronted with palatable foods (Lowe et al., 2009).

With regard to morphometry results, the VBM analysis highlighted no differences in the global grey and white matter volumes between the BE and the non-BE group. On the contrary, between-group differences were revealed in regional GMV. Accordingly, BE – compared to non-BE – showed greater regional GMV in a region mainly located within the left MFG and partly in the SFG. In addition, the GMV of this area was positively correlated with the scores of motor impulsivity subscale of the BIS-11: this result indicates that a higher tendency to act (as measured by the BIS-11 subscale) is associated with greater volume of the left MFG. Interestingly, the result of an increased volume of the left MFG associated with measures of trait impulsivity replicated the findings of recent studies on binge drinkers (Doallo et al., 2014; Sousa et al., 2017). Although binge drinking and BE are phenotypically different, they are thought to share some common substrates and behavioral traits (Schulte et al., 2016). Drawing upon a dual-process model of self-regulation (Dawe and Loxton, 2004; Hoffmann et al., 2009), it has been argued that at the roots of both conditions there is a propensity to engage in rash-spontaneous behaviors together with an enhanced sensitivity to reward. Impulsivity, therefore, appears to be a mechanism implicated in both addictions and overeating (Schulte et al., 2016). Crucially, the consistency of our results in normal-weight BE with those in binge drinkers (Sousa et al., 2017) may strengthen the assumption that some common neural basis underlying these conditions exists. Even though this similarity per se does not support the argument that the same processes occur in each of these conditions, it may add further evidence to the idea that there are similar mechanisms involved in both drug and food addiction behavior. It may be possible that greater trait impulsivity, subserved by functional changes in prefrontal and subcortical

brain regions, increases the vulnerability for loss of control over certain stimuli (e.g., food, alcohol, gambling etc.). In this context, one compelling hypothesis would be that higher impulsivity and structural differences in the MFG may be at the roots of the tendency to act impulsively and more specifically, of the bingeing behavior, regardless of the substance involved (alcohol or food).

The MFG – together with the SFG – is indeed part of the dorsolateral prefrontal cortex (DLPFC; Sanches et al., 2009), a brain region involved in executive control (Cumming, 1993), whose role in impulsive behavior has been extensively documented (Crews and Boettinger, 2009). As an example, recent VBM studies have confirmed a clear association between impulsivity and the volume of prefrontal regions, including the left MFG, in healthy individuals (Yokoyama et al., 2015; Matsuo et al., 2009; Cho et al., 2013). This latter region, indeed, exhibited positive correlations with the scores of all the subscales and the total score of the BIS-11 questionnaire (Cho et al., 2013). A support for the involvement of DLPFC regions in impulsive behavior derives also from functional MRI studies, reporting stronger activations of the left DLPFC in response to food pictures in obese versus normal-weight individuals (Beaver et al., 2006; Davids et al., 2009). As pointed out by Davids et al (2009), the more there is need for inhibitory control, the greater is the activation in the PFC regions: thus, in obese individuals confronted with food cues, a stronger top–down control of PFC on subcortical regions may be necessary to produce an appropriate behaviour (Davids et al., 2009). Since greater GMV has been shown to be associated with increased regional brain activation (Brodtmann et al., 2009), greater GMV in the left DLPFC regions might be related with an enhanced attempt to exert cognitive restraint or a greater recruitment of attention needed to control eating behaviour in individuals prone to BE compared to those who are less prone to BE (Brooks et al., 2013).

In light of this evidence, our results might suggest an association between impulsivity tendencies and greater GMV in the left MFG, which in turn may be related to the need of additional top-down control in order to regulate behaviour (Brooks et al., 2013). Overall, these findings provide further support to the compelling hypothesis that MFG may play a crucial role in subserving impulsivity-related behaviours, suggesting a possible implication of this area at the roots of the enhanced tendency to act without forethought.

Chapter 8
CONCLUSIONS

Self-regulation refers to the individual's ability to control its own thoughts, emotions, and actions (Baumeister et al., 1995). Thanks to this ability we can resist a delicious piece of cake when we are on a diet, we can inhibit the urge to make a cutting remark for the sake of harmoniousness or get off the couch to go for a jog in the interest of health. When the capacity to self-regulate fails, impulsive behaviors may derive, leading to unwanted and undesirable outcomes (such as, overeating, substance abuse, rimugination etc.; Baumeister et al., 1995). This inability to inhibit responses (i.e., impulsivity) has been repeatedly recognized as a factor contributing to an enhanced vulnerability for some impulsive disorders, such as drug abuse and cigarette smoking (Kale et al., 2018; Hogart, 2011). Drawing upon the hypothesized common substrates between substance addictions and overeating (Volkow et al., 2013), recently a growing interest has been placed on the still open question of whether impulsivity and inhibitory control deficits may also be at the roots of the symptomatic expression and maintenance of overeating (Atalayer, 2018; Dawe and Loxton, 2004).

Toward clarifying this issue, the experimental work included in the present thesis aimed at extending the actual knowledge on the role of impulsivity in eating-related behaviors, within the general healthy population. In more detail, the main aim of the thesis was to investigate impulsivity in normal-weight binge eaters, capitalizing on different behavioral and neuroimaging approaches. Based on the general definition of impulsivity as a multidimensional construct (Bari and Robbins, 2013), in this experimental work I aimed to unravel its role in binge eating, by investigating: impulsivity (i) as a stable personality trait (i.e., trait impulsivity) with self-reported questionnaires; (ii) as a behavior (i.e., state impulsivity) measured with behavioral paradigms; and (iii) as a neurobiological process using Magnetic Resonance Imaging (MRI) to analyze both brain structure and function.

A first novelty of this work is represented by the investigation of impulsivity in subclinical binge eating, namely in individuals who reported binge eating episodes without having any full-blown eating or weight disorders. The study of non-clinical populations might provide significant hints for the understanding of the mechanisms underlying binge eating in its more severe form, because of the elimination of possible weight-related confounding factors on results' interpretation. Further, the combination of different behavioral and neuroimaging measures is of extreme relevance given the

multidimensional nature of impulsivity and the possible differential impact of its subcomponents in the characterization of impulsive behavior. Accordingly, the use of functional and structural neuroimaging techniques might help find a consistency when describing the neural mechanisms underlying binge eating conditions.

In the following paragraphs, I will briefly summarize the findings in light of the current literature on the topic. Lastly, throughout the discussion below, I will highlight future directions and clinical implications following from my work.

8.1 TRAIT AND STATE IMPULSIVITY

The first aim of the entire project was that of elucidating if more impulsive individuals toward food (binge eaters, BE) showed also enhanced general trait impulsivity. In line with our hypothesis, we revealed that BE reported higher self-reported impulsivity (as assessed by the Barratt Impulsiveness Scale, BIS-11; Patton et al., 1995) compared to those without binge eating behavior (i.e., non-binge eaters, non-BE). Consistently with the assumption that impulsivity is associated with risky behaviors related to substance use (Hogart, 2011; Kale et al., 2018) and binge eating in obesity (Schag et al., 2013), our findings strongly suggest that trait impulsivity could also be considered a hallmark of binge eating in normal-weight individuals, thus regardless of the presence of a weight or eating disorder. Given that self-reported measures of impulsivity are thought to be appropriate tools to assess stable (trait-dependent) aspects of impulsivity, our results may indicate that BE (even when normal-weight) are generally more impulsive (not only toward food) and this may constitute a stable – hypothetically prodromal – factor for the development of overeating and, eventually, weight gain.

Contrary to expectations, despite the differences in impulsivity traits, the performance of two groups did not differ in terms of inhibitory control abilities (Chapters 4 and 5). Neither the Go/No-Go, (GNG; Experiment I) nor the Stop Signal Task (SST; Experiment II) were able to highlight differences between the groups in terms of response inhibition abilities, both toward food and neutral stimuli (e.g., objects, household items etc.). Thus, the hypothesized group differences in inhibitory control – both concerning action restraint and action cancellation – received little support from our results. As already outlined in the discussion of Experiment I and II (Chapters 4 and 5), these findings may be due to methodological issues related to the paradigms (i.e., long inter trial interval between the stimuli, low number of trials, fixed stop signal delay; see paragraphs 4.3.2 and 5.3.2). Nevertheless, it may also possible that deficits in inhibitory control abilities do not become evident in terms of behavior (as

measured by Reaction Times and Accuracy) in subclinical binge eating in normal-weight individuals. Most of the evidence linking inhibitory control deficits to overeating is derived from the study of overweight or obese participants (Lavagnino et al., 2016), therefore, given the well-established effects of weight gain on cognitive processes (Horstmann et al., 2015; Smith et al., 2011; van den Akker et al., 2014), it may be possible that defective inhibitory abilities are consequences of having developed a weight disorder (Lyu et al., 2017). This latter assumption is further supported by a recent investigation in which, similarly to our study, self-reported measures and a food-specific GNG task were employed to assess trait and response impulsivity in normal-weight BE (Lyu et al., 2017). Consistently with our findings, authors described greater trait impulsivity in BE compared to weight-matched non-BE, but no differences between the groups in response inhibition abilities were reported (Lyu et al., 2017). Their interpretation was that BE might be more susceptible to impulse control problems (and thus, inhibitory control deficits) toward food, only under certain conditions. More specifically, it is possible that deficits in inhibitory control emerge in the presence of stressful situations, with an increasing negative affect (e.g., increased anger, boredom or bad mood; Lyu et al., 2017). In general, based on the assumption that response inhibition paradigms are susceptible to state dependent variations and capture what participants do in a given situation (Cyders and Coskunpinar, 2012), it may be possible that the paradigms used in our study were not appropriate to capture differences between the two groups in their inhibitory control abilities.

Overall, the lack of consistency between self-reported and behavioral measures has been already described in the literature (Cyders and Coskunpinar, 2012). This not only confirms the multidimensional nature of impulsivity (i.e., trait and state aspects) but also stresses the need to assess its multiple components with different measures. In the context of our study, the fact that self-reported measures – a reliable tool to investigate trait dependent aspects – revealed differences between the groups, might provide valuable insights on the role of impulsivity as a hallmark at the roots of binge eating conditions. Future studies are warrant to further investigate whether trait impulsivity might also be considered a stable – perhaps risk – factor for binge eating.

8.2 IMPULSIVITY: NEUROBIOLOGICAL PROCESS

The main objective of the entire project was the exploration of the neural mechanisms of impulsivity in binge eating, with different modalities, in order to better elucidate the role of impulsivity-related processes in the characterization of this condition. First, we assessed the neural correlates of response inhibition by employing a task-based functional Magnetic Resonance Imaging (fMRI) approach during the execution of a food-specific GNG and a food-specific SST (Chapter 4 and 5). Second, we deepened the investigation of the neural differences between the groups by adopting a resting-state fMRI approach (Chapter 6). In this way, we aimed to assess whether the task-related differences were also exhibited in the resting condition (without performing a task). Possible overlapping results in the two approaches might indicate that the differences can be considered stable (across different conditions), giving additional information for results' interpretation. Lastly, we used a Voxel Based Morphometry (VBM) approach to investigate regional and global grey matter volumes (GMV; Chapter 7). The use of this technique allowed us to confirm and possibly extend the functional results, by assessing the presence of between-group differences also in terms of brain morphometry and not only in terms of brain activity.

8.2.1 The fronto-striatal and fronto-parietal networks

Both functional and structural results converged in highlighting between-group differences in brain areas mainly located in prefrontal and subcortical regions. In more detail, when performing response inhibition tasks, individuals with BE, compared to non-BE, showed differences in brain activation located in prefrontal regions (mainly, middle frontal gyrus, MFG) subcortical (i.e., putamen) and parietal regions (Chapters 4 and 5). Resting-state functional connectivity analyses consistently revealed between-group differences in the right MFG and anterior insula (Chapter 6). And lastly, the VBM results indicated between-group differences in the GMV of the left MFG (Chapter 7). In general, this combination of findings confirmed the involvement of impulsivity-related regions (prefrontal and subcortical areas) as substrates of binge eating conditions. As outlined in Chapter 1, a bulk of data indicated a clear involvement of frontal and striatal regions in behavior regulation (Purves et al., 2008). Despite the use of different types of analyses, samples and variations of the paradigms, fMRI evidence has consistently suggested an involvement of the fronto-striatal pathway in response inhibition (for a meta-analysis see Buchsbaum et al., 2005; paragraph 1.3.2) and an association between the cortico-striatal functional connectivity and individual differences in impulsivity traits (e.g., Dalley et al. 2008; Forbes et al. 2009; paragraph 1.3.3). Structural MRI investigations further supported these findings by

showing a positive association between changes in GMV at cortical and subcortical levels with different aspects of trait impulsivity in healthy populations (Cho et al., 2013) and in different clinical conditions, such as Attention Deficit Hyperactivity Disorder (ADHD) or obsessive-compulsive disorder (Koprivova et al., 2009; McAlonan et al., 2007; paragraph 1.3.4). Interestingly, functional and structural alterations within the frontal and striatal regions have also been implicated in the characterization of binge eating disorder (BED) in overweight conditions (Kessler et al., 2016).

Thus, taken together our findings appear to speak in favour of the involvement of impulsivity-related brain regions (cortico-striatal regions) and processes in the characterization of binge eating, even in the absence of full-blown eating or weight disorders. These results imply that impulsive behavior toward food in the general healthy population may be subserved by the involvement of both cortical regions (implicated in cognitive control) and subcortical regions (implicated in approach tendencies; Steinberg 2010). And, most importantly, they suggest that the cortico-striatal differences are not consequences of overweight or weight gain, and may thus be considered plausible candidates for the neural substrates of subclinical binge eating behavior.

8.2.2 The role of the middle frontal gyrus

Crucially, all neuroimaging approaches considered in this work revealed between-group differences located within the MFG (Experiment I-IV). In particular, when comparing BE to non-BE we observed:

- *Decreased* activation in the *right* MFG during action restraint (Experiment I, **Chapter 4**)
- *Increased* activation of the *left* MFG during action cancellation (Experiment II, **Chapter 5**)
- *Decreased* degree centrality (i.e., a measure of the total number of connections for a given node) in the *right* MFG and decreased functional connectivity between the *right* MFG and the anterior insula (Experiment III, **Chapter 6**)
- *Increased* regional GMV in the *left* MFG (Experiment IV, **Chapter 7**).

The involvement of the MFG in the characterization of the differences between the two groups further supports the role of impulsivity-related processes as substrates of binge eating behavior. The MFG – a region located within the dorsolateral prefrontal cortex (DLPFC) – has indeed been reported to participate in different cognitive processes, such as inhibitory control and monitoring of goal-directed behavior (Fuster, 2002). Remarkably, task-based and resting-state functional alterations within the MFG have been revealed in a recent study on obese population (Garçia-Garçia et al., 2015). In this investigation, authors indicated that the decreased activation of

this region during both a visual task of food stimuli and at rest was indicative of the stability of this result across conditions. In addition, they speculated that this results could be a stable trait and hallmark characterizing obesity (Garçia-Garçia et al., 2015). The consistency of their results in obese population with our findings might indicate that differences in the MFG activity may not be dependent only on the weight condition (i.e., obesity) and thus they may not be a consequence of weight gain. A possible speculation would be that the modulation of activity within this region might be a potential trait of overeating in normal-weight individuals, not only in obese conditions (i.e., changes could be more related to overeating behavior rather than to the weight condition itself), and a possible risk factor for the development of weight gain.

Despite the consistency of the neuroimaging results in indicating a clear involvement of the MFG in the characterization of BE, the different approaches pointed out a differential engagement of the two hemisphere (i.e., right and left MFG). In fact, when comparing BE to non-BE, findings indicated a *decreased* – task-related (i.e., action restraint/GNG) and resting-state activity – in the *right* MFG; and an *increased* – task-related activity (i.e., action cancellation/SST) and GMV – in the *left* MFG.

On the one hand, the ***right*** PFC regions – together with parietal areas – have been consistently implicated in response inhibition processes (Aron et al., 2003; 2007; Zhang et al., 2012). A recent theory postulated that the right fronto-parietal network would be specifically associated with the attention to the no-go signal, during response inhibition (Zhang et al., 2012). More specifically, this network (in contrast with the left one) would be associated with the process of *action restraint* (Zhang eta l., 2012). In addition to its role in inhibitory control (Fuster, 2008), the right PFC is also involved in guiding decision making according to comprehension of bodily information at a higher level (Tranel et al., 2002). Consistently, several lines of evidence reported a crucial role of this region in the control of eating behavior and food intake (Alonso-Alonso and Pascal-Leone, 2007). Right PFC dysregulations would indeed be implicated in the failure to appropriately consider the consequences of an action and, in the context of eating behavior, this might result in the indulging in overeating or unhealthy eating, thus facilitating obesogenic habits (Alonso-Alonso and Pascal-Leone, 2007).

The consistency of the association between the right PFC and obesity (see Garcia-Garcia et al., 2015) and the role of this area in cognitive processes relevant for food intake suggest that a dysfunction of the right PFC may represent a central event in the etiology of weight gain and overeating (Alonso-Alonso and Pascal-Leone, 2007). According to this hypothesis (i.e., *the right brain hypothesis for obesity*; Alonso-Alonso and Pascal-Leone, 2007), disruptions of the right PFC could be a critical mechanism sufficient to cause overeating, favoring an increase in body weight in modern

societies. Given the focus on obese population, it remains unclear whether this model could be extended also to the general population with overeating episodes. Nevertheless, the evidence on the topic may inspire future longitudinal studies to unravel a possible role of alterations within the right PFC regions as stable markers for the development and maintenance of overeating.

Overall, the *right brain hypothesis* strongly supports an implication of the right prefrontal hemisphere in overweight conditions, and highlights a possible role of dysfunctions of the right PFC in the development of overeating, and eventually weight gain (Alonso-Alonso and Pascal-Leone, 2007). In support of this notion, many neuro-modulatory interventions, such as Transcranical magnetic stimulation (TMS), have successfully targeted the right PFC to increase self-regulation capacity in eating behavior (Val-Laillet et al., 2015). Nevertheless, effects have also been demonstrated in studies targeting the *left* side of the PFC (Val-Laillet et al., 2015).

Hence, in addition to the well-established role of the right regions of the PFC in overeating and impulsivity, a possible role of the ***left*** lateralized prefrontal areas has been proposed in recent years (Vainik et al., 2018). Accordingly, besides the right fronto-parietal network, also the left fronto-parietal network has been implicated in response inhibition (Zhang et al., 2012). Contrary to the right circuit (involved in *action restraint*), Zhang et al (2012) suggested that the left fronto-parietal regions may be involved in response inhibition itself, hence the canceling of an ongoing action – *action cancellation*. Consistently with our results, this model proposed a role of the right hemisphere in action restraint and left hemisphere in action cancellation (Zhang et al., 2012). Given that our task-based fMRI results highlighted an increased activity in the left MFG in BE (Experiment II, Chapter 5), a fair assumption might be that these individuals needed an additional engagement of this region to successfully cancel the ongoing action, compared to non-BE. As pointed out by Davids et al (2009), the reason for an increase activation during effortful tasks may lie on the need to exert inhibitory control, meaning that in some individuals a stronger top–down control of PFC on subcortical regions may be necessary to produce an appropriate behavior in specific conditions (Davids et al., 2009).

Although speculative, this hypothesis is further support by the VBM results (Experiment IV, Chapter 7) that reveled greater GMV in the left MFG in the BE compared to non-BE, positively associated with self-reported impulsivity. This result replicates the findings of a recent study on binge drinkers, which showed greater GMV in the left MFG in binge drinkers compared to non-binge drinkers, positively associated with trait impulsivity (i.e., BIS-11 scores; Sousa et al., 2017). Based on this evidence, it could be conceivable that higher impulsivity and differences within the MFG may be at the roots of the tendency to impulsively act and more specifically, of the bingeing behavior,

regardless of the substance involved (alcohol or food). Based on the assumption that an increased GMV is generally associated with increased regional brain activation (Brodtmann et al., 2009), this result supports the hypothesis that a greater GMV (Experiment IV, Chapter 7) and an enhanced activation during action cancellation (Experiment II, Chapter 5) in the left MFG could be related with a greater attempt to exert inhibitory control or a general greater recruitment of attention needed to control behavior in individuals prone to loss of control (eating) compared to those who are less impulsive.

Even if further investigation is needed, this left-right differential engagement of PFC regions is remarkable also in light of the growing interest recently placed on the role of the left and right side of the PFC in overweight conditions (Vainik et al., 2018; Alonso-Alonso and Pascal-Leone, 2007). Crucially, a research on the neurobehavioral correlates of obesity revealed that an increased cortical thickness[7] in the *left* PFC and a decreased thickness in the *right* PFC was associated with increased body mass index (BMI; Vainik et al., 2018). Thus, not only they supported the "*right brain hypothesis for obesity*" (Alonso-Alonso and Pascal-Leone, 2007) but they also provided new insights on a possible role of the left hemisphere at the roots of obesity. Despite these results derived from a different population (i.e., obese individuals), studied with different approaches (i.e., cortical thickness analyses), they added a general support to the theory that body weight in humans is partly under control of higher-level brain systems involved in cognition, decision-making and motivation (Vainik et al., 2018). And thus, neurobehavioral factors may intervene in processes involved in eating regulations, such as the ability to resist tempting foods. Hence, the further exploration of the left and right differential prefrontal involvement could help deepen the understanding of the relative contribution of each impulsivity-related aspect in the characterization of binge eating, holding important promises in the prevention and treatment of overeating.

[7] Cortical thickness is a brain morphometric measure commonly determined on the basis of the grey matter set in segmented neuroimaging data, usually from the distance between the white matter surface and the pial surface (He et al., 2007). It represents a viable methodological alternative to volumetric measurements for assessment of subtle cortical changes in the human brain (Hutton et al., 2009).

8.3 FINAL REMARKS

The present research provides new and valuable insights on the role of impulsivity in binge eating among the general population, by outlining behavioral and neural possible hallmarks of this condition. Results reinforce the idea that impulsivity may play a crucial role in the characterization of binge eating behavior, regardless of weight status. In particular, they stress the importance of trait impulsivity as a potential prodromal factor in the development of binge eating and, in particular, the role of bilateral MFG and subcortical regions (e.g., putamen and insula) in the characterization of this condition.

Overall, our findings suggest that impulsivity may constitute a plausible endophenotype of binge eating, predisposing individuals to lose control over palatable foods. It may be possible that a greater trait impulsivity, subserved by functional and structural changes in prefrontal and subcortical brain regions, increases the vulnerability for loss of control over eating behavior. As recently proposed by Loxton (2018), while a greater reward sensitivity may play a role in the initial stages of loss of control behavior, driving the approach toward the stimulus, trait impulsivity plays a crucial role in following stages, when loss of control episodes maintain and eventually, tend to become more frequent over time (Loxton, 2018). Crucially, this framework may be extended to other domains, such as substance and behavioral addictions, providing new insights into the investigation of the substrates of addictive behaviors. In light of this consideration, a further step should consider a fine-grained initial assessment involving also other-than-eating addicted behaviors (such as, alcohol or drug dependence). A comprehensive characterization of addicted behavior traits would allow for testing the possibility of common and shared substrates among addictions and overeating (Volkow et al., 2013), disentangling possible confounding phenomena arising from multi-addiction conditions.

Hence, future studies are warrant to better explore whether the between-group differences, revealed by self-reported and neuroimaging methods, may actually constitute stable features of binge eating and risk factors for the development of clinically relevant weight and eating disorders. Understanding the degree to which impulsivity could be a prodrome for overeating, may allow researchers and health care professionals to adopt appropriate interventions for overeating prevention. In addition, from a theoretical point of view, as subclinical binge eating gains more attention in the literature, the pieces can begin to be put together to form a more comprehensive model of this behavior.

Overall, improved preventions and treatment programs, tailored on the person's specific conditions, are necessary in our cue-laden environment, in which individuals, on a daily basis, have to make immediate decisions on an optimal choice among a vast number of tempting palatable foods (Atalayer et al., 2018).

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APPENDICES

(i) APPENDIX A. Assessment: impulsivity and eating behavior

- Behavioral inhibition/approach (BIS/BAS) scales Carver and White, 1994

Each item of this questionnaire is a statement that a person may either agree with or disagree with. For each item, indicate how much you agree or disagree with what the item says.

1 = very true for me
2 = somewhat true for me
3 = somewhat false for me
4 = very false for me

1. A person's family is the most important thing in life.
2. Even if something bad is about to happen to me, I rarely experience fear or nervousness.
3. I go out of my way to get things I want.
4. When I'm doing well at something I love to keep at it.
5. I'm always willing to try something new if I think it will be fun.
6. How I dress is important to me.
7. When I get something I want, I feel excited and energized.
8. Criticism or scolding hurts me quite a bit.
9. When I want something I usually go all-out to get it.
10. I will often do things for no other reason than that they might be fun.

11. It's hard for me to find the time to do things such as get a haircut.
12. If I see a chance to get something I want I move on it right away.
13. I feel pretty worried or upset when I think or know somebody is angry at me.
14. When I see an opportunity for something I like I get excited right away.
15. I often act on the spur of the moment.
16. If I think something unpleasant is going to happen I usually get pretty "worked up."
17. I often wonder why people act the way they do.
18. When good things happen to me, it affects me strongly.
19. I feel worried when I think I have done poorly at something important.
20. I crave excitement and new sensations.

21. When I go after something I use a "no holds barred" approach.
22. I have very few fears compared to my friends.
23. It would excite me to win a contest.
24. I worry about making mistakes.

- Barratt Impulsiveness Scale (BIS-11) questionnaire Patton et al., 1995

People differ in the ways they act and think in different situations. For each item, indicate how the right answer for you. .

1 = never/rarely
2 = occasionally
3 = often
4 = always

1. I plan tasks carefully.
2. I do things without thinking.
3. I make-up my mind quickly.
4. I am happy-go-lucky.
5. I don't "pay attention."
6. I have "racing" thoughts.
7. I plan trips well ahead of time. c
8. I am self-controlled.
9. I concentrate easily.
10. I save regularly.
11. I "squirm" at plays or lectures.
12. I am a careful thinker.
13. I plan for job security.
14. I say things without thinking.
15. I like to think about complex problems.
16. I change jobs.
17. I act "on impulse."
18. I get easily bored when solving thought problems.
19. I act on the spur of the moment.
20. I am a steady thinker.
21. I change residences.
22. I buy things on impulse.
23. I can only think about one thing at a time.
24. I change hobbies.
25. I spend or charge more than I earn.
26. I often have extraneous thoughts when thinking.
27. I am more interested in the present than the future.
28. I am restless at the theatre or lectures.
29. I like puzzles.
30. I am future oriented.

- **Binge Eating Scale (BES)** Gormally, 1982

The BES is a 16-item questionnaire assessing the presence of certain binge eating behaviors which may be indicative of an eating disorder. Below are groups of statements about behavior, thoughts, and emotional states. Please indicate which statement in each group best describes how you feel.

- I don't feel self-conscious about my weight or body size when I'm with others.
- I feel concerned about how I look to others, but it normally does not make me feel disappointed with myself.
- I do get self-conscious about my appearance and weight which makes me feel disappointed in myself.
- I feel very self-conscious about my weight and frequently, I feel intense shame and disgust for myself. I try to avoid social contacts because of my self-consciousness.

- I don't have any difficulty eating slowly in the proper manner.
- Although I seem to "gobble down" foods, I don't end up feeling stuffed because of eating too much.
- At times, I tend to eat quickly and then, I feel uncomfortably full afterwards.
- I have the habit of bolting down my food, without really chewing it. When this happens I usually feel uncomfortably stuffed because I've eaten too much.

- I feel capable to control my eating urges when I want to.
- I feel like I have failed to control my eating more than the average person.
- I feel utterly helpless when it comes to feeling in control of my eating urges.
- Because I feel so helpless about controlling my eating I have become very desperate about trying to get in control.

- I don't have the habit of eating when I'm bored.
- I sometimes eat when I'm bored, but often I'm able to "get busy" and get my mind off food.
- I have a regular habit of eating when I'm bored, but occasionally, I can use some other activity to get my mind off eating.
- I have a strong habit of eating when I'm bored. Nothing seems to help me break the habit.

- I'm usually physically hungry when I eat something.
- Occasionally, I eat something on impulse even though I really am not hungry.
- I have the regular habit of eating foods that I might not really enjoy, to satisfy a hungry feeling even though physically, I don't need the food.
- Even though I'm not physically hungry, 1 get a hungry feeling in my mouth that only seems to be satisfied when I eat a food, like a sandwich, that fills my mouth. Sometimes, when I eat the food to satisfy my mouth hunger, I then spit the food out so I won't gain weight.

- I don't feel any guilt or self-hate after I overeat.
- After I overeat, occasionally I feel guilt or self-hate.
- Almost all the time I experience strong guilt or self-hate after I overeat.

- I don't lose total control of my eating when dieting even after periods when I overeat.
- Sometimes when I eat a "forbidden food" on a diet, I feel like I "blew it" and eat even more.
- Frequently, I have the habit of saying to myself, "I've blown it now, why not go all the way" when I overeat on a diet. When that happens I eat even more.
- I have a regular habit of starting strict diets for myself, but I break the diets by going on an eating binge. My life seems to be either a "feast" or "famine."

- I rarely eat so much food that I feel uncomfortably stuffed afterwards.
- Usually about once a month, I eat such a quantity of food, I end up feeling very stuffed.
- I have regular periods during the month when I eat large amounts of food, either at mealtime or at snacks.
- I eat so much food that I regularly feel quite uncomfortable after eating and sometimes a bit nauseous.

- My level of calorie intake does not go up very high or go down very low on a regular basis.
- Sometimes after I overeat, I will try to reduce my caloric intake to almost nothing to compensate for the excess calories I've eaten.
- I have a regular habit of overeating during the night. It seems that my routine is not to be hungry in the morning but overeat in the evening.
- In my adult years, I have had week-long periods where I practically starve myself. This follows periods when I overeat. It seems I live a life of either "feast or famine."

- I usually am able to stop eating when I want to. I know when "enough is enough."
- Every so often, I experience a compulsion to eat which I can't seem to control.
- Frequently, I experience strong urges to eat which I seem unable to control, but at other times I can control my eating urges.
- I feel incapable of controlling urges to eat. I have a fear of not being able to stop eating voluntarily.

- 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.
- 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.

- I seem to eat just as much when I'm with others (family, social gatherings) as when I'm by myself.
- Sometimes, when I'm with other persons, I don't eat as much as I want to eat because I'm self-conscious about my eating.
- Frequently, I eat only a small amount of food when others are present, because I'm very embarrassed about my eating.
- I feel so ashamed about overeating that I pick times to overeat when I know no one will see me. I feel like a "closet eater."

- I eat three meals a day with only an occasional between meal snacks.
- I eat 3 meals a day, but I also normally snack between meals.
- When I am snacking heavily, I get in the habit of skipping regular meals.
- There are regular periods when I seem to be continually eating, with no planned meals.

- I don't think much about trying to control unwanted eating urges.
- At least some of the time, I feel my thoughts are pre-occupied with trying to control my eating urges.
- I feel that frequently I spend much time thinking about how much I ate or about trying not to eat anymore.
- It seems to me that most of my waking hours are pre-occupied by thoughts about eating or not eating. I feel like I'm constantly struggling not to eat.

- I don't think about food a great deal.
- I have strong cravings for food but they last only for brief periods of time.
- I have days when I can't seem to think about anything else but food.
- Most of my days seem to be pre-occupied with thoughts about food. I feel like I live to eat.

- I usually know whether or not I'm physically hungry. I take the right portion of food to satisfy me.
- Occasionally, I feel uncertain about knowing whether or not I'm physically hungry. At these times it's hard to know how much food I should take to satisfy me.
- Even though I might know how many calories I should eat, I don't have any idea what is a "normal" amount of food for me.

- Yale Food Addiction Scale (YFAS) Gearhardt et al., 2011

This survey asks about your eating habits in the past year. People sometimes have difficulty controlling their intake of certain foods such as:
- Sweets like ice cream, chocolate, doughnuts, cookies, cake, candy, ice cream
- Starches like white bread, rolls, pasta, and rice
- Salty snacks like chips, pretzels, and crackers
- Fatty foods like steak, bacon, hamburgers, cheeseburgers, pizza, and French fries
- Sugary drinks like soda pop

When the following questions ask about "CERTAIN FOODS" please think of ANY food similar to those listed in the food group or ANY OTHER foods you have had a problem with in the past year

IN THE PAST 12 MONTHS:

0= Never; 1= Once a month; 2= 2-4 times a month; 3= 2-3 times a week; 4= 4 or more times or daily

1. I find that when I start eating certain foods, I end up eating much more than planned

2. I find myself continuing to consume certain foods even though I am no longer hungry

3. I eat to the point where I feel physically ill

4. Not eating certain types of food or cutting down on certain types of food is something I worry about

5. I spend a lot of time feeling sluggish or fatigued from overeating

6. I find myself constantly eating certain foods throughout the day

7. I find that when certain foods are not available, I will go out of my way to obtain them. For example, I will drive to the store to purchase certain foods even though I have other options available to me at home.

8. There have been times when I consumed certain foods so often or in such large quantities that I started to eat food instead of working, spending time with my family or friends, or engaging in other important activities or recreational activities I enjoy.

9. There have been times when I consumed certain foods so often or in such large quantities that I spent time dealing with negative feelings from overeating instead of working, spending time with my family or friends, or engaging in other important activities or recreational activities I enjoy.

10. There have been times when I avoided professional or social situations where certain foods were available, because I was afraid I would overeat.

11. There have been times when I avoided professional or social situations because I was not able to consume certain foods there.

12. I have had withdrawal symptoms such as agitation, anxiety, or other physical symptoms when I cut down or stopped eating certain foods. (Please do NOT include withdrawal symptoms caused by cutting down on caffeinated beverages such as soda pop, coffee, tea, energy drinks, etc.)

13. I have consumed certain foods to prevent feelings of anxiety, agitation, or other physical symptoms that were developing. (Please do NOT include consumption of caffeinated beverages such as soda pop, coffee, tea, energy drinks, etc.)

14. I have found that I have elevated desire for or urges to consume certain foods when I cut down or stop eating them.

15. My behavior with respect to food and eating causes significant distress.

16. I experience significant problems in my ability to function effectively (daily routine, job/school, social activities, family activities, health difficulties) because of food and eating.

IN THE PAST 12 MONTHS:

0= NO; 1= YES

17. My food consumption has caused significant psychological problems such as depression, anxiety, self-loathing, or guilt.

18. My food consumption has caused significant physical problems or made a physical problem worse.

19. I kept consuming the same types of food or the same amount of food even though I was having emotional and/or physical problems.

20. Over time, I have found that I need to eat more and more to get the feeling I want, such as reduced negative emotions or increased pleasure.

21. I have found that eating the same amount of food does not reduce my negative emotions or increase pleasurable feelings the way it used to.

22. I want to cut down or stop eating certain kinds of food.

23. I have tried to cut down or stop eating certain kinds of food.

24. I have been successful at cutting down or not eating these kinds of food

25. How many times in the past year did you try to cut down or stop eating certain foods altogether?

1 or fewer times; 2 times; 3 times; 4 times; 5 or more times

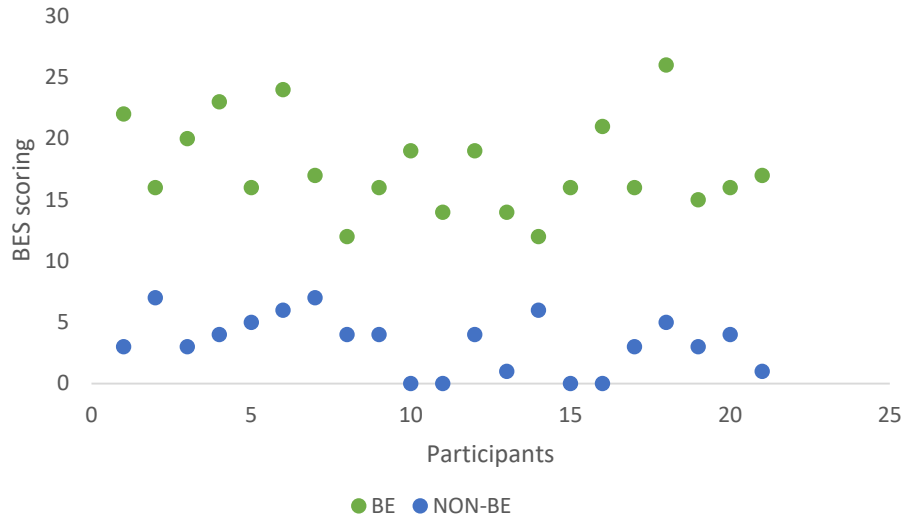

Figure A1. Graphical representation of Binge Eating Scale (BES) scorings for both groups. BE: Binge Eaters; non-BE: non Binge Eaters.

APPENDIX B. Supplementary Materials Experiment I and II (Chapter 4 – 5).

(i) GO/NO-GO TASK

	non-BE		BE	
	M	SD	M	SD
Food	450,7	±126,18	440,47	±124,43
Non-food	482,45	±135,92	463,4	±120,54

Table B1. Mean Reaction Times (ms) for GO FOOD and GO NON-FOOD conditions in both groups. BE= Binge Eaters; non-BE= non-binge eaters; M= Mean; SD= Standard Deviation

	BE		Non-BE	
	Food	**Non-food**	**Food**	**Non-food**
COMMISSION ERRORS	12%	5,5%	10%	5%

Table B2. Percentage of commission errors for GO FOOD and GO NON-FOOD conditions in both groups. BE= Binge Eaters; non-BE= non-binge eaters.

cluster		peak			MNI			BRAIN REGION	
k	p(FWE-corr)	F	z	p(unc)	x	y	z	SIDE	LABEL
39	0,0023	33,206	5,35	0,0000	36	-87,5	-6	R	IOG
64	0,0001	33,018	5,33	0,0000	-44,5	-66,5	-22	L	Cerebellum
		23,38	4,51	0,0000	-34	-84	-38	L	Cerebellum
22	0,0373	29,497	5,05	0,0000	18,5	-91	30	R	SOG
44	0,0011	24,977	4,66	0,0000	1	-63	42	R	Precuneus
26	0,0186	22,724	4,44	0,0000	43	52,5	-2	R	MFG
23	0,0313	22,721	4,44	0,0000	36	-73,5	46	R	Angular Gyrus
		21,994	4,37	0,0000	29	-66,5	58	R	Angular Gyrus
13	0,2015	18,829	4,04	0,0000	-13	-70	-46	L	Cerebellum
14	0,1661	18,589	4,02	0,0000	-23,5	42	-2	L	Anterior Insula
12	0,2445	18,542	4,01	0,0000	-27	-77	30	L	SOG
10	0,3583	17,545	3,90	0,0000	-13	-52,5	-46	L	Cerebellum
17	0,0936	17,358	3,88	0,0001	25,5	14	-2	R	Putamen
11	0,2963	16,757	3,81	0,0001	18,5	42	2	R	ACC
14	0,1661	16,438	3,77	0,0001	4,5	-28	58	R	Precentral Gyrus

Table B3. Go/No-Go Task: Main effect of Group**.** In the table the following details are reported: k=number of voxels; t and z scores; stereotaxic coordinates according to the Montréal Neurological Institute (MNI); brain side and region. Statistical parametric maps are thresholded at p< .001, k> 10. IOG: Inferior Occipital Gyrus; SOG: Superior Occipital Gyrus MFG: Middle Frontal Gyrus; ACC: Anterior Cingulate Gyrus.

cluster		peak			MNI			BRAIN REGION	
k	p(FWE-corr)	F	z	p(unc)	x	y	z	SIDE	LABEL
8	0,996	10,428	2,69	0,0015	22	-60	-22	R	Cerebellum
6	0,998	10,266	2,93	0,0016	-34	-18	-66	L	Precentral G.
11	0,961	9,454	2,81	0,002	-55	-18	46	L	Postcentral G.
		9,073	2,74	0,003	-41	-18	54	L	Precentral G.
		8,831	2,71	0,003	-45	-18	46	L	Postcentral G.

Table B4. Go/No-Go Task: Main effect of Response (Go/No-Go conditions). In the table the following details are reported: k=number of voxels; t and z scores; stereotaxic coordinates according to the Montréal Neurological Institute (MNI); brain side and region. Statistical parametric maps are thresholded at p< .005. G.: Gyrus

cluster		peak			MNI			BRAIN REGION	
k	p(FWE-corr)	F	z	p(unc)	x	y	z	SIDE	LABEL
ns									

Table B5. Go/No-Go Task: Main effect of stimulus. In the table the following details are reported: k=number of voxels; t and z scores; stereotaxic coordinates according to the Montréal Neurological Institute (MNI); brain side and region. Statistical parametric maps are thresholded at p< .001. ns: not significant.

(ii) STOP SIGNAL TASK

	non-BE		BE	
	M	SD	M	SD
Food	975,39	±223,24	957,31	±244,86
Non-food	957,8	±234,56	960,67	±242,65

Table B6. Mean Reaction Times (ms) for GO FOOD and GO NON-FOOD conditions in both groups. BE= Binge Eaters; non-BE= non-binge eaters; M= Mean; SD= Standard Deviation.

	BE		Non-BE	
	Food	**Non-food**	**Food**	**Non-food**
COMMISSION ERRORS	25%	24%	25%	23%

Table B7. Percentage of commission errors for GO FOOD and GO NON-FOOD conditions in both groups. BE= Binge Eaters; non-BE= non-binge eaters.

cluster		peak			MNI			BRAIN REGION	
k	p(FWE-corr)	F	z	p(unc)	x	y	z	SIDE	LABEL
43	0,001	32,963	5,29	0,000	-17	-74	-18	L	Cerebellum
35	0,002	28,989	4,98	0,000	36	-28	46	R	Postcentral G
		19,094	4,06	0,000	22	-28	42	R	Precentral G
		12,47	3,26	0,001	47	-32	42	R	SMG
12	0,193	26,571	4,78	0,000	-48	39	18	L	MFG
17	0,067	26,015	4,73	0,000	-27	52	26	L	MFG
		21,979	4,35	0,000	-34	42	22	L	MFG
10	0,296	22,049	4,36	0,000	-48	-67	-26	L	Cerebellum
23	0,020	20,742	4,23	0,000	-10	-18	54	L	Precentral G
		16,121	3,72	0,000	-20	-21	70	L	Precentral G
10	0,296	20,280	4,18	0,000	-6	-88	14	L	Cuneus
13	0,156	20,197	4,17	0,000	32	-7	46	R	Precentral G
10	0,296	18,851	4,03	0,000	5	28	46	R	MeSFG
10	0,296	15,728	3,67	0,000	54	32	-2	R	TrIFG
		13,738	3,42	0,000	43	42	-2	R	TrIFG
10	0,296	13,830	3,44	0,000	47	-18	54	R	Postcentral G
		13,717	3,42	0,000	50	-25	46	R	Postcentral G

Table B8. Stop Signal Task: Main effect of Group. In the table the following details are reported: k=number of voxels; t and z scores; stereotaxic coordinates according to the Montréal Neurological Institute (MNI); brain side and region. Statistical parametric maps are thresholded at p< .001, k> 10. G: Gyrus; SMG: Supramarginal Gyrus; MFG: Middle Frontal Gyrus; MeSFG: Medial Superior Frontal Gyrus; TrIFG: Inferior Frontal Gyrus (pars triangularis).

cluster		peak			MNI			BRAIN REGION	
k	p(FWE-corr)	F	z	p(unc)	x	y	z	SIDE	LABEL
329	0,000	37,75	5,64	0,000	-38	-25	58	L	Precentral G
		28,25	4,92	0,000	-55	-18	42	L	Postcentral G
303	0,000	36,51	5,55	0,000	61	-49	14	R	MTG
		33,69	5,35	0,000	50	-56	46	R	Angular G
142	0,000	36,49	5,55	0,000	-55	-56	30	L	Angular G
		25,76	4,71	0,000	-48	-60	46	L	Angular G
		22,19	4,37	0,000	-48	-53	50	L	Angular G
120	0,000	27,96	4,90	0,000	-59	-18	14	L	Central Operculum
		23,27	4,48	0,000	-38	0	6	L	Anterior Insula
		10,08	3,95	0,000	-41	-14	14	L	Posterior Insula
31	0,001	23,76	4,52	0,000	12	35	54	R	SFG
		15,77	3,68	0,000	15	39	46	R	SFG
10	0,068	22,22	4,38	0,000	-34	21	-14	L	POrG
39	0,001	20,21	4,18	0,000	19	49	38	R	MeSFG
		16,20	3,73	0,000	5	49	34	R	MeSFG
		12,18	3,21	0,000	1	39	30	R	MeSFG
38	0,001	19,34	4,08	0,000	8	-60	-18	R	Cerebellum
33	0,003	19,14	4,06	0,000	57	-14	4	R	Central Operculum
		15,98	3,71	0,000	54	-25	6	R	Postcentral G
45	0,000	18,33	3,97	0,000	-3	-7	50	L	SMA
25	0,014	18,19	3,96	0,000	36	21	-118	R	POrG
		17,12	3,84	0,000	43	28	-14	R	OrIFG
11	0,239	17,59	3,89	0,000	-3	42	8	L	ACC
11	0,239	15,25	3,62	0,000	57	-4	-2	R	STG
17	0,067	14,25	3,49	0,000	47	21	46	R	MFG
		14,13	3,48	0,000	40	11	46	R	MFG

Table B9. Stop Signal Task: Main effect of Response. In the table the following details are reported: k=number of voxels; t and z scores; stereotaxic coordinates according to the Montréal Neurological Institute (MNI); brain side and region. Statistical parametric maps are thresholded at p< .001, k> 10. G: Gyrus; STG: Superior Temporal Gyrus; SFG: Superior Frontal Gyrus; POrG: Posterior Orbital Gyrus; MeSFG: Medial Superior Frontal Gyrus; OrIFG: Orbital Inferior Frontal Gyrus; SMA: Supplementary Motor Area; ACC: Anterior Cingulate Cortex.

cluster		peak			MNI			BRAIN REGION	
k	p(FWE-corr)	F	z	p(unc)	x	y	z	SIDE	LABEL
ns									

Table B10. Stop Signal Task: Main effect of stimulus. In the table the following details are reported: k=number of voxels; t and z scores; stereotaxic coordinates according to the Montréal Neurological Institute (MNI); brain side and region. Statistical parametric maps are thresholded at p< .001. ns: not significant.

(iii) APPENDIX C. Supplementary Materials Experiment IV (Chapter 7).

WHOLE BRAIN ANALYSIS						
k	p	t	z-score	MNI	Side	Region
BE vs non-BE						
115	0.000	4.18	3.77	-26 44 35	Left	MFG
Non-BE > BE						
ns						

Table C1. Whole Brain Analysis: two sample t-test with Total Intracranial Volume (TIV) as a covariate of no interest. **Notes**: k=number of voxels; t and z scores; stereotaxic coordinates according to the MNI space; brain side and region. Statistic threshold: Results were considered significant at p< .001 with a cluster size (k) > 100. BE: Binge Eaters; non-BE: non-binge eaters; FEW: Family Wise Error; MFG: Middle Frontal Gyrus.

	Extracted mean GMV in left MFG [MNI: -26, 44, 35]	
	Pearson correlation (r)	p-value
BIS-11 Total score	.064	.685
BIS-11 Attentional Impulsivity	.012	.938
BIS-11 Motor Impulsivity	.329	.034*
BIS-11 Non-planning Impulsivity	.190	.227

Table C2. Correlation analysis between BIS-11 and GMV in the left MFG [MNI: -26, 44, 35]. **Notes:** BIS-11: Barratt Impulsiveness Scale; GMV: Grey Matter Volume; MFG: Middle Frontal Gyrus; MNI: Montreal Neurological Institute. Correlation was considered significant at the level of .05 (2-tailed).