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Food addiction: An analysis of the relationship between obesity, over-eating and addiction behaviours

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Dedicatória

Gostaria de dedicar esta tese ao meu avô Aníbal,
um grande aventureiro,
exímio contador de histórias,
primeiro comediante que conheci,
melhor companheiro de aventuras
e meu eterno mentor.

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Abstract

Introduction: Obesity is a modifiable risk factor with an ever-increasing impact on morbity and mortality worldwide. Efforts to prevent obesity and promote weight loss, like the *Direcção-Geral de Saúde*'s (National Board of Health - DGS) *Programa Nacional para a Promoção da Alimentação Saudável* (National Program for the Promotion of Healthy Eating - PNPAS), have yet to prove their effectiveness. This dissertation reviews recent studies on the impact of food, over-eating and obesity on known neuroanatomical structures of addiction and how the concept of food addiction and addictive processes in eating could impact clinical practice.

What is addiction? The definition of addiction has been broadened, both by scientific literature and popular media to accommodate for new "addictive disorders". Known addiction disorders act on the limbic system, whose dopaminergic circuitry is responsible for prediction of reward and reward value. In these disorders, reduction of dopamine receptors $DRD_{2/3}$ availability and of dopamine release has been described and could translate into a blunted response of the emotional reinforcement circuitry and justify symptoms of withdrawal and tolerance (SRAD pharmacological criteria 10 and 11). Observing these alterations in obese and over-eating individuals could provide significant evidence to the concept of food addiction and provide a new therapeutical target for the treatment and prevention of obesity.

Evidence for food addiction: Several types of studies have been found: 1) Neuroimaging studies testing DA release and/or $DRD_{2/3/4}$ availability; 2) studies using neuroimaging and DA agonists or antagonists; 3) genetic testing on DRD_2 like receptors genes; 4) studies using self-assessment reports and/or scales in different populations. Across the first 3 types of studies small sample sizes were used and results were inconsistent between each study, making it difficult to describe a consistent model for addiction-like behaviour in eating and to validate the concept of food addiction. However, the constant differences observed in dopaminergic pathways between either obese and non-obese or over-eaters and normal eaters, show an undeniable influence of reward and emotion on feeding behaviours and how such mechanisms could undermine motivation and ability to regulate diet and lose weight.

Clinical Implications: The Yale Food Addiction Scale was developed as a diagnostic tool, based on the DSM-5 criteria for SRAD. Studies using the YFAS across different populations showed inconsistent results, supporting the findings of the previously mentioned studies. Additionally, Riva et al developed a therapeutic approach based on addiction and compared it in a clinical trial with two other medically managed intensive inpatient obesity treatments. No differences were observed in the effectiveness of the three approaches. However, they all showed greater weight loss than the control group, indicating that obese patients could largely benefit from an intensive medically and psychologically managed therapeutic approach.

Conclusion: Further research is needed to clarify if and how addiction could impact eating behaviour. Even though, self-assessment scoring scales like the YFAS are greatly put into question, the development of a new, non-addiction-based tool could help differentiate which patients would benefit from a more classical approach of dietary and nutritional counselling,

and which patients would benefit from specific psychological counselling, targeting the emotional and behavioural aspects of eating.

Resumo

Introdução: A obesidade é um factor de risco modificável com crescente impacto global na morbilidade e mortalidade. A eficácia de medidas para prevenir e tratar a obesidade, como o Programa Nacional para a Promoção da Alimentação Saudável da Direcção-Geral de Saúde, está ainda por estabelecer. Esta tese revê literatura recente sobre o impacto de alimentos, alimentação compulsiva e obesidade em estruturas neuroanatómicas associadas a processos de dependência e como o conceito de dependência/compulsão alimentar pode influenciar a prática clínica.

O que é dependência? A definição de dependência tem sido alargada para incluir novas perturbações de dependência, tanto pela comunidade científica como pela comunicação social. Perturbações de dependência associadas ao uso de substâncias atuam no sistema límbico, cujos circuitos dopaminérgicos estão associados à previsão de recompensa e do seu valor subjetivo. Nestas perturbações de dependência, foi observada a diminuição da expressão dos recetores de dopamina $DRD_{2/3}$ e da libertação de dopamina, o que pode indicar uma resposta diminuída dos circuitos de reforço emocional e justificar sintomas de abstinência e tolerância (Critérios farmacológicos de SRAD 10 e 11). A observação destas alterações em indivíduos obesos ou com alimentação compulsiva poderia contribuir para a validação da existência de dependência em alimentação excessiva/compulsiva e demonstrar novas áreas de intervenção terapêutica na obesidade.

Evidências científicas para dependência em alimentação excessiva/compulsiva: Vários tipos de estudo foram encontrados: 1) estudos da libertação de dopamina e da disponibilidade de receptores $DRD_{2/3}$ em estruturas límbicas, especialmente no estriado ventral e núcleos da base, através de neuroimagiologia; 2) estudos dos efeitos de agonistas e antagonistas dopaminérgicos; 3) estudos de polimorfismos genéticos em receptores dopaminérgicos; 4) estudos com escalas e questionários de auto-avaliação de sintomas de dependência/compulsão alimentar. Os três primeiros tipos de estudo usaram maioritariamente amostras de pequenas dimensões e apresentaram resultados inconsistentes entre si, dificultando a definição de um modelo neuropatológico de dependência associado a obesidade. Contudo, estudos que compararam populações com e sem obesidade ou populações com e sem alimentação compulsiva, mostraram diferenças significativas nas vias dopaminérgicas, o que indica uma forte influência de mecanismos emocionais e de recompensa em comportamentos alimentares, nomeadamente na motivação e capacidade de controlar dieta e peso.

Implicações clínicas: A *Yale Food Addiction Scale* foi desenvolvida como ferramenta de diagnóstico, baseada nos critérios de *Substance-Related Addictive Disorders* do DSM-5. Estudos com a aplicação desta ferramenta entre diferentes populações demonstraram resultados inconsistentes entre si, corroborando o padrão observado nos estudos acima mencionados. Adicionalmente, Riva et al, desenvolveram um programa terapêutico baseado em tratamentos de perturbações de dependência e compararam-no num ensaio clínico com outros dois tratamentos de acompanhamento médico intensivo. Embora não tenham sido observadas diferenças estaticamente significativas entre os três tratamentos, todos resultaram em maior

perca de peso que no grupo de controlo (grupo com aconselhamento nutricional e de exercício, sem acompanhamento médico), indicando que alguns pacientes obesos poderão ter melhores resultados com um tratamento médico e psicológico continuado.

Conclusão: São necessários mais estudos para esclarecer a relação entre distúrbios de dependência e comportamento alimentar. Ainda que a validade de ferramentas de auto-avaliação como a YFAS seja incerta, o desenvolvimento de novas ferramentas de diagnóstico, não baseadas em modelos de dependência, poderia contribuir para a diferenciação de pacientes de acordo com a etiologia da sua obesidade e distinguir quais beneficiariam mais de acompanhamento médico e psicológico especializado.

Índice

Lista de Tabelas

Lista de Acrónimos

[^{11}C]NMB	(N-[^{11}C]methyl)benperidol
AEBS	Addiction-like Eating Behaviour Scale
AGRP	Agouti-related Protein
ARC	Arcuate Nucleus
ASL	Arterial Spin Labelling
BED	Binge-eating Disorder
BMI	Body-mass Index
BP	Binding Potential
CBT	Cognitive-Behavioural Therapy
CCK	Cholecystokinin
CNS	Central Nervous System
CREB	cAMP Response Element-Binding Protein
CT	Cognitive Therapy
DA	Dopamine
DGS	Direcção Geral de Saúde
$DRD_{2/3/4}$	$D_2/D_3/D_4$ Dopamine Receptor
fMRI	Functional Magnetic Resonance
G-FCQ-S	General Food Craving Questionnaire State
G-FCQ-T	General Food Craving Questionnaire Trait
GI	Glycaemic Index
GLP1	Glucagon-like Peptide 1
GluR1	Glutamate Receptor 1
LHA	Lateral Hypothalamic Area
MCR-4	Melanocortin Receptor Subtype 4
MPH	Methylphenidate
NAc	Nucleus Accumbens
NSRAD	Non-substance-related Addictive Disorder
NTS	Nucleus of Solitary Tract
PET	Positron Emission Tomography
PNPAS	Programa Nacional para a Promoção de Alimentação Saudável
POMC	Pro-opiomelanocortin
ROI	Region of Interest
SPECT	Single Photon Emission Tomography
SRAD	Substance-related Addictive Disorder
VNTR	Variable Number Tandem Repeat
VTA	Ventral Tegmental Area
YFAS	Yale Food Addiction Scale
α-MSH	α-Melanocyte Secreting Hormone
ΔFosB	Protein FosB Truncated Splice Variant

1. Introduction

Obesity is among the most transversal and common risk factors to the vast majority of chronic diseases[1-3]. Furthermore, obesity has also been associated with greater post-operative risk, greater risk of mental disorders, infections and many acute disorders[1,3]. Considering the total risk of obesity, it becomes of utmost importance to effectively prevent it and to promote weight loss. However, obesity maintains its nationally and globally rising prevalence and incidence, despite many Public Health guided efforts to prevent it[4-7].

Looking at some of the measures taken so far, p.e. at the level of Primary Health Care, the latest manual published by Direcção-Geral de Saúde (National Board of Health - DGS) and Programa Nacional para a Promoção da Alimentação Saudável (National Program for the Promotion of Healthy Eating - PNPAS), "Obesity: Optimizing the therapeutic approach in the national health service", promotes an intervention, by the Family Doctor and Primary Health Care team, based essentially on nutritional advice and exercise planning[7]. Although dietary changes and physical activity are recommended, and have proven efficient in motivated patients[1,3,4,7], this approach implies that the main cause for obesity is simply the caloric imbalance that originates from poor nutrition and lack of exercise.

In recent decades, many studies focused on the behavioural aspects of obesity, and as of 2013, the DSM-5 has listed "Binge-Eating Disorder" (BED) as a feeding disorder[8], categorizing for the first time a mental disorder as a possible etiology for specific cases of obesity. Despite being included in the "Eating and Feeding Disorders" section, some of the criteria for BED diagnosis include "eating an amount of food larger than what most people eat in a similar period of time" and "sense of lack of control over eating"[8], which are remarkably similar to some of the criteria used for addictive disorders. Besides the introduction of BED, the DSM-5 has also introduced the concept of Non-Substance-Related Addictive Disorders (NSRADs)[9], and, even though only Gambling disorder has been described and no other diagnostic criteria have been presented in this category, the inclusion of NSRADs has opened the possibility for many other behavioural conditions to be classified as addictive. Included in these addictive conditions, and again taking into the account the prevalence of obesity, the concepts of "food addiction" and "eating addiction" appear as plausible candidates.

The term "food addiction" was first used by T. Randolph in 1956 to describe "a common pattern of symptoms descriptively similar to those of other addictive processes" related to the consumption of wheat, corn, coffee, milk, eggs and potatoes[10]. Much progress has been made since Randolph's proposed definition, not only in the understanding of addiction and its neurobiological mechanisms but also in the mechanisms of feeding, hunger and their hedonistic roles. The concept of food addiction remains a debated and controversial topic, with many researchers disputing its validity[11-14].

The prevailing scientific views regarding food addiction are divided between considering it a classical Substance-abuse disorder[15-17], a non-substance-related addiction[18,19] or dismissing food addiction and Eating addiction as valid concepts whatsoever[13,14]. In order to shed light on

this debate this dissertation proposes to: 1) present a brief review of the neurobiology and anatomy of addiction, namely of the limbic system and its dopaminergic pathways; 2) review the most recent developments on the addictive properties of palatable foods and the presence of addictive processes in obesity and over-eating; 3) review how the concept of addictive foods and addiction in eating could impact clinical practice.

2. What is addiction?

The term "addiction" is often used in everyday life to characterize a wide variety of behaviours. In the Cambridge English dictionary, addiction is defined as "an inability to stop doing or using something, especially something harmful"[20], and even though this definition may seem broad and overly simplified, the growing list of substances included in every new iteration of the Diagnostic and Statistical Manual of Mental Disorders (DSM), and the recent inclusion of gambling in the new section of Non-Substance-Related Disorders (NSRD) of The DSM-5[9], seem to validate a wider and more inclusive definition of addiction.

Looking through a more clinical perspective, while no general criteria for Non-Substance-Related Disorders have been formulated, the DSM presents 11 general criteria, shown in Table 1, that are applicable to abuse disorders, regardless of what substance is used. Some of these criteria, namely "The substance is often taken in larger amounts or over a longer period than was intended", "Craving, or a strong desire or urge to use the substance", "Recurrent use of the substance in situations in which it is physically hazardous" or "Use of the substance is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance" are often described by overweight patients and patients with different types of disordered eating[21–24].

Table I - Substance Use Disorders Criterion A[9]

Impaired Control
1. The substance is often taken in larger amounts or over a longer period than was intended.
2. There is a persistent desire or unsuccessful efforts to cut down or control use of the substance.
3. A great deal of time is spent in activities necessary to obtain the substance, use the substance, or recover from its effects.
4. Craving, or a strong desire or urge to use the substance.
Social Impairment
5. Recurrent use of the substance resulting in a failure to fulfil major role obligations at work, school, or home.

6. Continued use of the substance despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of its use.
7. Important social, occupational, or recreational activities are given up or reduced because of use of the substance.
Risky Use
8. Recurrent use of the substance in situations in which it is physically hazardous.
9. Use of the substance is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.
Pharmacological criteria
10. Tolerance, as defined by either of the following: a. A need for markedly increased amounts of the substance to achieve intoxication or desired effect. b. A markedly diminished effect with continued use of the same amount of the substance.
11. Withdrawal, as manifested by either of the following: a. The characteristic withdrawal syndrome for other (or unknown) substance. b. The substance (or a closely related substance) is taken to relieve or avoid withdrawal symptoms.

The presence of two to three of these symptom criteria on an individual is enough to diagnose a mild substance disorder, with increasing presence of criteria resulting in an increase in severity. Most of these criteria can easily be adapted and used to quantify many of the behaviours described by compulsive eaters and the obese, as can be seen with the development of self-assessment lists, such as the Yale Food Addiction Scale (YFAS) or the Addiction-like Eating Behaviour Scale (AEBS)[19,25,26]. However, the DSM also presents as an essential characteristic of addictive disorders an "underlying change in brain circuits that may persist beyond detoxification, particularly in individuals with severe disorders"[9].

Regarding substance abuse disorders, it has been established that emotional processing in the limbic system can signal the presence of or prospect for reward and punishment. Most drugs of abuse, by altering the neuromodulatory influence of dopamine, establish consolidated addictive behaviours through this limbic circuity[27]. In order to establish any possible relation between eating and addiction, it is essential to understand the limbic system and its dopaminergic pathways, how they are affected in addiction, and if any of these alterations have been observed in relation to excessive eating.

2.1 Limbic system and addiction

The limbic system includes structures of both telencephalon and mesencephalon. Its structures are comprised of orbital, medial prefrontal and cingulate cortices, parahippocampal gyrus, ventral parts of the basal ganglia, the mediodorsal nucleus of the thalamus and the amygdala. The basal ganglia, although traditionally regarded as motor structures that regulate the initiation of voluntary movements, are also central structures in anatomical circuits, or "loops", that are involved in modulating non-motor aspects of behaviour. One such non-motor structure is the limbic loop, responsible for the regulation of emotional and motivated behaviour as well as mood transitioning[27].

The limbic loop receives inputs from the amygdala, the subiculum (a ventral division of the hippocampal formation), and orbitomedial prefrontal cortex. These cortical regions convey signals relevant to emotional reinforcement to ventral divisions of the anterior striatum, the largest component of which is called the nucleus accumbens (NAc). The NAc, in turn, contains medium spiny neurons that integrate these excitatory inputs under the modulatory influence of dopamine. The NAc dopaminergic projections originate from a collection of neuronal cell bodies that lie just dorsal and medial to the substantia nigra, in a region of the midbrain called the ventral tegmental area (VTA). This relationship between NAc and VTA is represented in Figure 1.

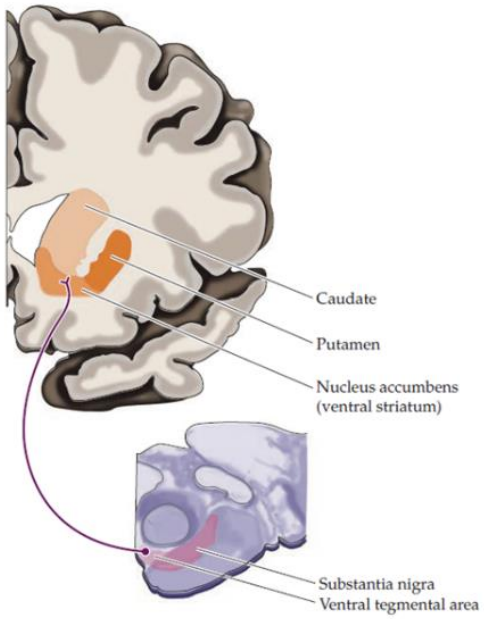

Figure 1 - Neuronal projections between NAc and VTA. Purves, D. (2018), in Neuroscience, 6th Ed, Sunderland, Massachusetts, p. 719)[27]

These dopaminergic neurons are phasically active, releasing dopamine and signalling prediction of reward and reward value, instead of the presence of reward itself. The integration of such signals in the NAc, orbitomedial prefrontal cortex, and amygdala leads to the activation of behaviours directed at obtaining sources of reward and to consolidating the association between the benefits and the rewarding effects of natural agents and experiences such as food, water, sex, and more complex social rewards[27].

This phasic release of dopamine is subject to experience-dependent plasticity, leaving these limbic circuits, namely the NAc and VTA, vulnerable to being affected by chronic exposure to substances of abuse or by repeated engagement in rewarding behaviours. This exposure results from prolonged action of dopamine, either by blocking dopamine transporters, which has been observed with cocaine use[28,29], or by increasing dopamine release, leading to greater amounts of dopamine in the synaptic cleft. The chronic increase in dopamine potentiates the activation of neurons in the ventral tegmental area and NAc, leading to cellular and molecular alterations that promote abnormal regulation. In the VTA these molecular alterations include increased activity of the dopamine-synthesizing enzyme tyrosine hydroxylase, greater neuronal response to excitatory inputs by increased activity of the transcription factor CREB and upregulation of GluR1. In the NAc, increase in transcription factors, such as ΔFosB, and induction of CREB, leads to changes in postsynaptic density proteins which affect receptor traffic and, most importantly, induce shifts in the expression of D_1 and D_2 classes of dopamine receptors[27]. In fact, reduced availability of class D_2 dopamine receptors (DRD_2, DRD_3 and DRD_4) is a common finding observed in many different addictive disorders, such as cocaine[28,29], opioids[30], alcohol[31] and methamphetamine[32] abuse. Additionally, a blunted release of dopamine, during withdrawal has also been observed in many of these disorders[28,31,33].

The reduction of $DRD_{2/3}$ availability and dopamine release is still not fully understood, and debate still remains whether it is an alteration caused by chronic addictive behaviour or a predisposing factor to addiction. Nonetheless, these alterations in neural processing could account for the waning influence of adaptive emotional signals in the operation of decision-making faculties as drug-seeking and drug-taking behaviours become habitual and eventually compulsive[27]. The overall result of addictive diseases is a blunted response of the emotional reinforcement circuitry to less potent natural rewards, while intensifying the response to the target of addiction.

2.2 Eating and reward

Having described many of the possible relationships between reward neurocircuitry and addictive substances, the question of how feeding, a regular behaviour essential to energetic homeostasis, could interact with these hedonistic circuits comes now into focus. Although most, if not all, of the substances we regard as nutrients lack the ability to directly interact with synaptic receptors or directly regulate neurotransmitter release, in the way as the

previously mentioned psychoactive substances do, the feelings of satiety and hunger are intrinsically connected with how the rewarding effects of food are perceived. Reduced perception of food reward is an inherent aspect of satiety, while fasting or caloric restriction increase the rewarding properties of food, stimulating a compensatory hyperphagia. This implies a connection between reward neurocircuitry and the energy homeostasis system.

The energy homeostasis system is comprised of circulating signals, also known as "adiposity negative feedback", that inform the brain of available energy stores, which, in response, will trigger regulatory adjustments to food intake. The principal hormones responsible for adiposity negative feedback are leptin and insulin, secreted by adipocytes and the pancreas, respectively. Both these hormones circulate in proportion to body fat stores, enter the brain in proportion to their plasma level and act on key neurons that regulate energy balance. High levels of these anorexigenic hormones in the CNS, especially leptin, decrease food intake, increase energy expenditure and increase sensitivity to satiety hormones such as cholecystokinin (CCK) and glucagon-like peptide 1 (GLP1), which are secreted by the digestive tract during meals. Low levels of leptin and insulin in the CNS have the reverse effect [27,34,35].

One of the principal targets of leptin is a set of hypothalamic neurons, the arcuate nucleus (ARC). In the ARC two sets of neurons can be found: neurons expressing pro-opiomelanocortin (POMC neurons) and neurons expressing agouti-related protein (AGRP neurons). The POMC neurons are activated in positive energy balance states, i.e., when there is higher adiposity and higher circulating levels of leptin and insulin. The AGRP neurons are activated in negative energy balance states, i.e., when there is lower adiposity and lower circulating levels of leptin and insulin and higher levels of ghrelin, a hormone secreted by the digestive tract before meal onset which stimulates feeding. These two sets of neurons modulate the release of α-melanocyte secreting hormone (α-MSH) – being activated and inhibited by POMC and AGRP neurons, respectively - which, in turn, inhibits appetite and induces satiety by acting on specific receptors, namely the melanocortin receptor subtype called MCR-4, located on the nucleus of the solitary tract (NTS) and other sites of the hypothalamus and brainstem[27,34-36].

Additionally, POMC and AGRP neurons convey this energy homeostasis information to a system of neurons, known as the lateral hypothalamic area (LHA), that also receives neuronal inputs from, and projects to, the NAc. Although the influences of the NAc in feeding are still not clear, the main output target of its GABAergic neurons is the ventral pallidum, which itself is GABAergic and targets the LHA. The LHA is therefore proposed to integrate and coordinate the perception of satiety and food reward[35-37].

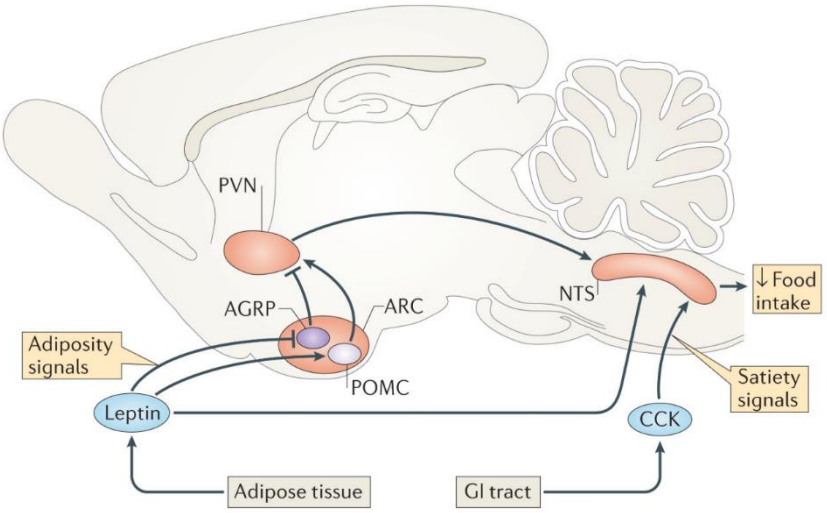

Figure 2 - Morton GJ et al (2014) Figure 2: Integration of long-term homeostatic and short-term satiety signals. In: Neurobiology of food intake in health and disease. Nat Rev Neurosci. 2014 Jun;15(6):367-78[35].

AGRP – Agouti-related Protein; ARC – Arcuate Nucleus; CCK – Cholecystokinin; NTS – Nucleus of Solitary Tract; POMC – Pro-opiomelanocortin; PVN – Paraventricular Nucleus.

This interaction between the energy homeostasis and reward systems offers a possible mechanism for feeding to influence the phasic release of dopamine in the previously mentioned limbic circuits, the NAc and the VTA. Therefore, if the same functional alterations in dopamine release and receptor expression, that are found in chronic exposure to substances of abuse and non-substance-related disorders, could equally be observed in obese and/or over-eating patients, the possibility of overeating as an addiction forming behaviour becomes much more plausible.

3 Methods

The following sections of this dissertation are based on a review of scientific literature found through an extensive search of publications made in the PubMed database using key-words such as “food addiction”, “eating addiction”, “food and reward”, “eating and reward”, “food and dopamine”, “obesity and dopamine”, “obesity and DRD_2”. No publication date restrictions were applied, but preference was given to more recent articles, especially papers published in the last 5 years. Research was made between November 2018 and March 2019. A total of 28 articles were found. From these, 9 articles were selected according to relevance to the subject and preference was given to focus on known neuroanatomical correlates of addiction. These articles are reviewed in chapter 4. An additional 6 articles using self-assessment diagnostic tools, along with a clinical-trial study were selected. Even though these publications did not focus on neuroanatomy or neuroimaging, they offered highly significant data about the clinical relevance of food addiction and were therefore reviewed in chapter 5. In total, 15 articles were selected and reviewed.

4. Evidence for food addiction

As previously established, the behavioural patterns observed in over-eating and obesity are easily comparable to the diagnostic criteria used in SRAD and NSRAD, and these criteria have been adapted to measure and potentially diagnose food addiction. However, and as previously stated, demonstrating the presence of an "underlying change in brain circuits that may persist beyond detoxification"[9] is still necessary to consider food addiction as a valid clinical entity. Having considered the limbic system as a possible target "brain circuit" and diminished DA release and DRD_2 type receptor availability as possible "underlying changes" that occur in addiction processes, demonstrating the presence of these changes in the obese and/or over-eaters becomes an essential step in validating food addiction.

During this review's research, using terms such as "food addiction", "food and dopamine", "eating and reward", "obesity and dopamine", "obesity and DRD2", four major types of studies have been found: 1) Neuroimaging studies assessing DA release and/or $DRD_{2/3/4}$ expression and binding changes in different populations and/or with different conditions (different glycemic indexes, different levels of food related stimulation, etc.); 2) studies using neuroimaging and evaluating the effect of DA agonists or antagonists on weight or eating behaviour; 3) genetic analysis of DRD_2 receptors; 4) studies using self-assessment reports and/or scales in different populations. This chapter will focus on the first three types of studies and aims to analyse their findings to evaluate possible correlations between the DSM pharmacological criteria (SRAD criterion 10 and 11) and symptoms of tolerance and withdrawal, and compare such findings in order to assess consistency across studies.

4.1 Neuroimaging and obesity

Recalling what was discussed in the previous chapter, dopaminergic neurons in the limbic system, namely ventral striatum (NAc) and basal ganglia (VTA), are phasically active and phasic DA release increases to signal reward prediction and value. Over time, DA release can induce changes in proteins of the postsynaptic density and modulate availability of DRD_2 like receptors. Therefore, to determine which components of feeding have greater reward values and higher effects on such mechanisms, dopaminergic signalling, and the function and activity of the mentioned limbic structures, must be tested and evaluated in different feeding contexts, such as varying caloric content, palatability, sweetness and others, and between different populations (lean vs. obese; normal eating behaviour vs. overeating; across BMI; etc.).

In the context of caloric content, Wang et al (2014), hypothesized that in obesity the dopamine response to calorie consumption in striatal brain regions would be attenuated, similarly to the functional alterations in dopaminergic reward circuitry in other addictive disorders. By using positron emission tomography (PET) and [^{11}C]raclopride ($D_{2/3}$ receptor radiotracer sensitive to competition with endogenous DA), they observed dopamine release on 19 subjects, 10 minutes after ingestion of an oral glucose drink and an oral placebo drink of sucralose (sweetener devoid of calories). The drinks were tested on different occasions

and had similar volumes and self-reported quality of sweetness, in order to ensure that any observed differences were attributable to the calorie content independently of the food's palatability. DA release was determined by calculating the difference in DA binding potential between the glucose and placebo tests[38].

A significant correlation between calorie-induced dopamine changes in the ventral striatum and body mass index (BMI) was observed. In lean participants higher DA levels were observed after the glucose drink while in obese participants DA was reduced. Additionally, subjects with higher scores on disinhibition, perception of hunger and binge eating showed a reduction of DA levels with caloric intake, although these scores showed no correlation with BMI[38].

No measurements of baseline (without sweeteners or glucose) $D_{2/3}$ receptor availability were made, so it remains unclear if the calculated DA decrease in the obese represents a blunted dopaminergic response to a caloric stimulus, or if it is caused by reduced basal DA levels in this population. Nevertheless, these findings show reduced dopamine release in ventral striatum with calorie consumption in obese subjects, which might contribute to overeating as a compensatory mechanism to a deficient rewarding effect of food.

Similarly, van de Giesse et al, also hypothesized that a blunted striatal dopamine release, resulting in less reward from food, could be present in obesity. Using [^{123}I]iodobenzamide single photon emission computed tomography (SPECT), they measured striatal dopamine $D_{2/3}$ receptor ($DRD_{2/3}$) availability and amphetamine-induced striatal dopamine release in 15 obese and 15 age-matched, normal-weight women. The participants also completed the General Food Craving Questionnaire Trait (G-FCQ-T), the General Food Craving Questionnaire State (G-FCQ-S) and visual analogue scales assessing self-reported hunger and craving in order to examine any possible correlations between this study's findings and food craving[39].

This study found that there was no significant amphetamine-induced striatal DA release in obese subjects, whereas there was significant release in normal-weight controls. Even though these findings seem to corroborate the initial hypothesis of this study, the difference in dopamine release was not statistically significant. On the other hand, a positive association between dopamine release and food craving (SRAD Criterion 4) within obese subjects was found, which suggests a significant involvement between these two processes.

Additionally, van de Giesse et al, found that the obese group had significantly lower baseline levels of striatal $DRD_{2/3}$ compared to the normal-weight group, even though no correlation was found between $DRD_{2/3}$ availability, food craving, BMI, insulin resistance or leptin resistance[39].

Wang et al (2011), assessed how dopamine was involved in the motivation for food consumption in patients with Binge-Eating Disorder (BED), a condition characterized by compulsive eating and often associated with obesity. They used PET scanning with [^{11}C]raclopride, focusing on the cerebellum, dorsal and ventral striatum regions, in 10 obese BED participants and 8 obese non-BED participants. The participants were scanned on two separate days with and without administration of oral methylphenidate (MPH), a drug that blocks DA reuptake and amplifies its signals, and under both neutral stimulation (presented with toys,

clothes, neutral taste and smell tests) and food stimulation (presented with foods described as their favourite, with according taste and smell tests), leading to four experimental conditions: food/MPH; food/placebo; neutral/MPH; neutral/placebo. Basal levels ofDRD_2 were also assessed in both groups.

This study found that the BED group presented higher release of DA in food stimulation with MPH than the non-BED group and that higher scores in binge eating questionnaires (Gormally Binge Eating Scale) were associated with higher DA release. Additionally, the BED group showed no DA release in neutral stimulation with or without MPH, while the non-BED group showed increased DA release in the neutral/MPH condition. However, unlike the previously discussed studies, most of the changes in DA release were only observed in the dorsal striatum, while no statistically significant differences were observed in the ventralstriatum. Lastly, similar to previously mentioned studies, basal levels of DRD_2 were independent of BMI and did not differ between the BED and non-BED groups[40].

Despite the increased DA release when food stimulation was presented, in a condition characterized by uncontrolled eating, the fact that basal DA release (equivalent to neutral/MPH and neutral/placebo) was completely blunted lends support to the previously suggested state of reward deficiency and compensatory overeating. Additionally, the fact that the BED group had increased release of DA under food stimulation, could mean a process of increased DA release during planning, and increased motivation to engage in feeding.

The findings of these three studies[38-40] seem to support a process of blunted DA release and deficient reward that leads to compensatory overeating. This process, in turn, is similar to the pharmacological criterion of "tolerance" (SRAD criterion 10) that is observed in substance abuse disorders, where there is a "need for markedly increased amounts of the substance to achieve intoxication or desired effect" and a "markedly diminished effect with continued use of the same amount of the substance"[9].

Focusing on structural activity, rather than dopaminergic pathways, Lennerz et al, conducted a randomized, blinded, crossover study in 12 healthy overweight and obese young men, using arterial spin labelling (ASL) functional magnetic resonance (fMRI) to compare the effects of high and low glycaemic index (GI) test meals on reward circuitry, during the postprandial period (4 hours after ingestion). Each participant was tested with a high-GI (84%) and a low-GI (37%) test meals, each on separate occasions. The test meals had similar ingredients, macronutrient composition, food form and calorie content, differing only in GI. Using the ASL method, which determines cerebral arterial blood flow in prespecified regions of interest (ROI), 4 hours after ingestion would enable to observe the effects of GI during the late postprandial period, a phase in which the regulation of eating behaviour regarding a next meal occur. It was observed that during this period the cerebral blood flow was greater in the NAc after the high-GI meal. Additionally, during this period plasma glucose levels were lower and self-reported hunger (through a visual analogue scale) were higher after high-GI as well[41].

This late NAc activation could indicate, not a direct rewarding effect of food itself, but a late activation of rewarding mechanisms which, together with increased feelings of hunger and lower glycemia, potentiates craving and impulsivity, akin to the "Impaired control" group of

diagnostic criteria (SRAD criteria 1-4) and to one of the "Withdrawal" criteria (SRAD criterion 11.b: "The substance (or a closely related substance) is taken to relieve or avoid withdrawal symptoms")[9].

In order to determine if certain eating behaviours, pertaining to emotion and reward, could be more prevalent in the obese and overweight, and if such behaviours were related to striatal dopaminergic signalling, Eisenstein et al, assessed obesity-associated behavioural patterns, using self-report questionnaires in 22 obese and 17 normal weight participants, evaluating 4 different areas: 1) eating behaviour related to emotion; 2) eating behaviour related to reward including craving for palatable foods and inability to limit intake of sweet foods; 3) non-food reward behaviour; 4) punishment avoidance. The questionnaires used to assess each characteristic can be seen on Table 2.

Table II– Questionnaires used for each behavioural domain[42]

Behavioural Domain	Included Questionnaires
Eating Related to Emotion	Emotional Eating Scale (EES)
	Dutch Eating Behaviour Questionnaire Emotional Scale (DEBQ ES)
	Sweet Taste Questionnaire Mood Altering Effects (STQ MAE)
Eating Related to Reward	Binge Eating Scale (BES)
	Sweet Taste Questionnaire Impaired Control over Eating (STQ IC)
	Food Craving Inventory (FCI)
Reward	Behavioural Activation System (BAS)
	Generalized Reward and Punishment Expectancy Scales (GRAPES)
	Sensitivity to Punishment and Reward Questionnaire (SPSRQ)
	Temperament and Character Inventory (TCI-R)
Punishment	Behavioural Inhibition System (BIS)
	GRAPES
	SPSRQ
	TCI-R

To determine the correlation between these characteristics and striatal DRD_2, Eisenstein et al, used PET with (N-[^{11}C]methyl)benperidol ([^{11}C]NMB), a PET radioligand DRD_2 receptor antagonist that is highly selective for DRD_2 over DRD_3 and other G-protein receptors and not displaced by endogenous DA. Using ([^{11}C]NMB), allows for measurements of DRD_2 binding not confounded by these factors. This study found that emotion and reward related behaviour linearly correlated with striatal and midbrain DRD_2 binding, specifically self-reported rates of eating to avoid negative emotion, in both the obese and normal weight group. However, both eating related behavioural domains were found to be independent of BMI, and no statistically significant difference was found between the lean and obese groups[42]. DRD_2 binding and availability was also found to be independent of BMI, which is in accordance to previously described studies[39,40].

Considering that self-reported behaviour was not associated with BMI, and was correlated with higher DRD_2, instead of lower, doubts concerning the model of reward deficiency and compensatory over-eating are raised. However, the fact that self-reported behaviour could predict DRD_2 binding in dorsal and ventral striatum, supports the theory of striatal and mesostriatal dopaminergic systems having fundamental roles in eating motivation. Additionally, the higher scores of self-reported behaviours were in the categories of "eating to avoid negative emotion", which is similar to the SRAD criterion of withdrawal: "The substance (or a closely related substance) is taken to relieve or avoid withdrawal symptoms" (SRAD Criterion 11.b).

In the context of taste and palatability, Pepino et al conducted a study with the hypothesis that the age-related decline in sweet preferences is directly related to an age-related decline in striatal DRD_2 and that this relationship is disrupted in obese people. They evaluated sucrose preferences in 20 non-obese subjects and 24 obese, using the Monell two-series, forced-choice tracking, where subjects were given two solutions with different sucrose concentration and had to choose one[43]. To prevent confounding by perception of sweetness intensity, subjects rated sweetness on a magnitude scale. On a separate occasion, subjects underwent PET scan with administration of [^{11}C]NMB in order to measure striatal DRD_2 binding potential (BP) in the ventral and dorsal striatum.

This study found that obese subjects lack the normal associations between age and sucrose preference, as hypothesized. However, they also found that striatal DRD_2 BP did not correlate with sucrose preference, and age-related decline between these two variables was also not associated. Most importantly, and contrary to initial predictions, this study found that lower sucrose preferences were actually associated with higher DRD_2 BP, with a strong statistical correlation. This was only found, however, in the lean group, with no such association observed in obese subjects[43].

These findings give significant understanding to the role of DRD_2 binding in eating behaviours and seem to support the hypothesis that blunted DRD_2 binding, and/or availability, may lead to reward deficiency and to preference for more palatable and more caloric foods. However, the fact that such findings were exclusively observed in lean subjects, and not in the obese, gives no evidence that these associations culminate in an addictive process.

4.2 Studies using dopaminergic agonists and antagonists

The results shown in neuroimaging studies lead to significant insight to the disruption of dopaminergic reward signalling, and the occurrence of tolerance and withdrawal symptoms, on obesity and over-eating. An effective method of determining how relevant such disruptions can be to weight and feeding control consists in assessing the effects of know dopaminergic agonists and antagonists on eating behaviour.

Having observed weight loss in patients with prolactin secreting pituitary adenomas treated with cabergoline, a dopamine receptor agonist, Gibson et al, aimed to study if cabergoline, by possibly correcting blunted dopaminergic signalling observed in previous studies, could have an effect on body weight and glucose tolerance in obese, non-diabetic individuals,

with normal plasma prolactin levels. They provided 40 male and female volunteers with a high fibre diet plan with 500 kcal deficit and advised for maintained stable physical activity level. Participants were assigned to carbegoline (0.25mg) or placebo group using a randomized double-blind scheme. Waist circumference and weight measurements were taken every 4 weeks, during a total of 16 weeks. Prolactin measurements were taken at study completion to verify subject compliance.

This study found that weight loss was apparent in both groups, with carbegoline showing no relevant improvement in treatment effectiveness. Additionally, even though the cabergoline group showed decreased post-prandial glucose and insulin levels, and the placebo group showed higher tendency for insulin resistance, there were no statistically significant changes in glucose homeostatic parameters between both groups[44].

These results suggest that changes in body weight in prolactinoma patients are caused mainly by normalization of prolactin levels and other hormonal deficiencies, rather than by effects on dopaminergic reward mechanisms. Most importantly, in both groups dietary compliance was lacking, as the observed weight loss was less than predicted with the prescribed diet. Therefore, cabergoline showed no effect in regulating motivation to eat, has would be expected with overeating driven by blunted dopamine release and reward deficiency.

Taking into account the role of dopamine in determining the reward value of food, Mogg et al evaluated the effect of the D_3 receptor antagonist, GSK598809, in brain activation and attentional bias to food-related cues in obese and overweight subjects. This study consisted of a double-blind, placebo-controlled design, with 26 overweight and obese, male and female participants. The participants underwent a stimulus-response compatibility (SRC) manikin task to evaluate approach bias. Approach bias is indicative of the extent to which certain stimuli (food, drug, p.e.) have high incentive salience for an individual, i.e., how strongly the stimuli can "capture" attention and influence motivation and behaviour. The SRC task requires participants to move a small stickman figure (manikin) as quickly as possible either towards or away from a picture, which may be food-related (cake, pizza, cookies, etc.) or unrelated (common household items with similar shape and colour to the food-related images). An approach bias for food-related images is indicated when time responses to move the manikin towards the food are faster than moving it away, or faster than responses to control stimuli.

As would be expected, participants placed in placebo group showed a significantly higher approach bias for food cues, showing increased incentive salience for food stimuli. Even though the GSK598809 group showed an approach bias score for food cues higher than zero, it was a significantly lower than the placebo group[45].

Even though these findings do not elucidate on how DA release and $DRD_{2/3}$ availability are implicated in obesity and eating behaviour, they give significant evidence for the role of D_3 receptor modulation in processing reward-related cues, motivation and behavioural responses to palatable foods.

4.3 Dopamine receptor gene polymorphisms

Despite the results from the previously analysed studies, it is still unclear if the variations in DA release and DRD_2 like receptor availability are in fact caused by chronic exposure to obesity and over-eating, or if there are pre-existing states that predispose to the development of these conditions. In fact, several studies found DRD_2 levels to be independent of BMI[39,40,42] which seems to support the later. Several genes have been found to encode phenotypes similar to the discussed dopaminergic signalling variations and using genetic testing to compare their presence between different populations (lean vs. obese; normal eating behaviour vs. overeating; across BMI) could shed new light on this question.

Two dopamine receptor genes have been implied in regulation of reward circuitry: rs1800497, a DRD_2 polymorphism and the DRD_4 exon III variable number tandem repeat. A low DRD_2 density is associated with the rs1800497 T-allele (the risk allele T is also known as the TaqI A1 allele), possibly causing individuals to be less sensitive to the activation of dopamine-based reward circuitry. A deficient dopamine functioning has been linked to variable number tandem repeat (VNTR) "7 repeats or longer" allele (DRD_4 7R+)[46].

Roth et al, studied these polymorphisms in 451 obese and over-weight children who underwent a 1-year intervention program based on physical exercise, nutrition education, and behavioural therapy, in order to evaluate whether the previously described polymorphisms of dopamine receptors could moderate treatment responses and predict the intervention's success. They hypothesized that the presence of DRD_2 rs1800497 T and/or DRD_4 7R + alleles were more frequent in obese subjects and correlated negatively with weight loss after the 1-year program. Additionally, they also studied the two alleles in a control group of 583 lean young adults. Using an obese population not yet chronically exposed to a calorie dense diet and over-eating ensured less confounding results by unknown epigenetic processes[46].

Table III– Distribution of participants by genotype and study group(46). CC, CT, TT – no alleles, one T allele and two T alleles at the rs1800497, respectively

		Overweight children	Control adults
DRD_2 rs1800497	**CC**	308	407
	CT	132	161
	TT	11	15
DRD_4 7R+	**No repeats**	285	357
	One repeat	148	198
	Two repeats	18	15

The distribution of genotypes was similar between obese children and lean controls (Table III). No association was found between the DRD_2 rs1800497 and DRD_4 7R+ alleles and obesity, and the presence of these alleles could not predict BMI as initially hypothesized. Nevertheless, children with DRD_2 TT genotype (homozygous), had a reduced or no weight loss at all, as was predicted. Regarding DRD_4 7r+ genotypes, no association was found to weight loss success[46].

These findings give support to the hypothesis of diminished DRD_2 like receptor availability as a pre-existing state with increased risk and predisposition to obesity and over-eating. As previously stated, this is line with previously discussed findings of DRD_2 availability independent of BMI[39,40,42]. Furthermore, the fact that genotype (rs1800497 TT homozygous) could predict weight loss and therapeutic success, seems to suggest a possible distinct category or phenotype of obesity, in this case, with a more significant emotional component, driven by reward deficiency, rather than by sedentarism and poor nutrition.

4.4 Discussion

Taking into perspective all the studies analysed so far, some consistent findings, as well as contradicting ones, can be observed. Regarding DA release, three studies evaluated this parameter [38–40], across different populations, such as lean vs. obese[38,39] and obese BED vs. obese non-BED[40], and with different stimuli, such as caloric content[38], drug induced[39] and with food cues (taste and smell)[40]. Overall, the data suggest a reduction in DA release in the obese and BED-related obesity, but they do so in an inconsistent manner. Firstly, Wang et al (2014), found, not a blunted DA release in the obese group, compared to lean subjects, but reported that DA content decreased in response to caloric stimuli, which was not hypothesized[38]. Secondly, van de Giessen et al, found blunted DA release, but their findings did not reach statistical significance[39]. Lastly, Wang et al (2011), found that the basal release of dopamine was reduced, but after food stimulation there was an increase of DA levels in BED patients, compared to non-BED, and these variations of DA release were not observed in the ventral striatum, as expected, but only in the dorsal striatum[40]. Furthermore, in a model of reward deficiency due to reduced DA release, it would be expected that correction of this deficiency by a DA agonist would potentiate adherence to a diet of caloric deficiency, leading to weight loss. However, Gibson et al showed no difference in weight loss between subjects taking the DA agonist and the placebo[44]. Also contradicting this model are Wang et al's (2011) findings, together with Mogg et al's, which found that administration of a DRD_3 antagonist, GSK598809, diminished attentional bias to food cues, may suggest that certain reward and regulatory mechanisms involved in pathological eating behaviour could be associated with increased DA release, instead of decreased[40,45]. Alternatively, the findings of these two studies, which do not test DA release in response to ingestion, but rather to visual and sensory stimuli, could also signify a process of increased DA release in regulation of planning and motivation of feeding. Also lending support to this possibility, are the findings of Lennerz et al, of increased NAc activation in the late post-prandial period in the obese and overweight, together with van de Giessen et al's results of association between increased dopamine release and higher self-reported feelings of food craving[39,41].

The inconsistencies between these studies and the small sample sizes used in most of them, difficult any sort of definite conclusion regarding DA release in obesity and over-eating. Blunted DA release cannot, therefore, satisfyingly justify the symptoms of tolerance and withdrawal that

would be observed in an addictive process.

Regarding DRD_2 like receptors, several studies evaluated $DRD_{2/3}$ availability[39,40,42,43]. Three of these found $DRD_{2/3}$ availability to be independent from BMI[39,40,42], with only van de Giessen observing lower $DRD_{2/3}$ availability in the obese (even though still independently from BMI)[39]. Additionally, Pepino et al, found that $DRD_{2/3}$ availability was also independent from preference for sweet tastes[43]. These findings contradict the model of $DRD_{2/3}$ receptor downregulation as a mechanism for reward deficiency. Other correlations with $DRD_{2/3}$ were however found. Firstly, in Eisenstein et al's study, it was observed that higher rates of self-reported eating and reward related eating behaviours were associated with, not lower, but higher $DRD_{2/3}$ availability[42]. Secondly, and akin to Eisenstein et al's results, Wang et al found that higher BED scores were also positively correlated with $DRD_{2/3}$ availability[40]. Both these findings put in question the model of reward deficiency and compensatory over-eating as well. However, the fact that $DRD_{2/3}$ availability could predict eating behaviour in these two studies, could suggest either not yet understood disfunction of eating behaviour regulation or a new phenotype within obesity. The latter is also supported by Roth et al's findings, where presence of a genotype associated with lower DRD_2 availability predicted weight loss success (homozygous subjects for the rs1800497 had less success in losing weight) and distribution of such genotype was likewise independent of BMI, which suggests that dopaminergic circuitry variations could be specific to a separate phenotype of obesity and that such variations could be, not caused by chronic addictive behaviour, like it was previously mentioned in SRAD, but rather a risk factor or a predisposing condition to obesity[46].

Like the findings regarding DA release, many inconsistencies are also found between the observations regarding $DRD_{2/3}$ availability, and, with exception of Roth et al's study, relatively small sample sizes were also used. Likewise, downregulation of DRD_2 like receptors is not yet confirmed to be an "underlying change in brain circuits" in obesity and cannot yet be presented as a possible mechanism for tolerance development.

Regarding mechanisms of withdrawal, both Eisenstein et al, measuring higher scores of pathological eating behaviour, namely "eating to avoid negative emotion", with higher $DRD_{2/3}$ availability, and Lennerz et al, observing higher NAc activation in the late post-prandial period (a period 4 hours after ingestion, where next meal planning is occurring), could indicate the presence of "withdrawal" symptoms in obese and over-eaters (or those at risk of developing these conditions), and eating in order to relieve or avoid such symptoms (SRAD criterion 11.b)[9,41,42]. However, a "characteristic withdrawal syndrome" (SRAD criterion 11.a) of over-eating, or other possible "addictive substances", such as highly palatable foods, high caloric content or high GI, is yet to be described[9]. Further studies, especially on populations introducing calorie deficient or low palatability diets, need to be undertaken in order to determine if over-eating and obesity can lead to withdrawal syndromes.

Overall, the results of the analysed studies make it difficult to describe a consistent model for addiction-like behaviour in eating and to validate the concept of food addiction itself. Moreover, and as previously stated, most of the analysed studies involved small samples, impeding any possible generalizations. Further research is therefore needed to clarify if, and how, addiction could impact eating behaviour.

Nonetheless, the constant differences observed in dopaminergic pathways between either obese and non-obese, or over-eaters and normal eaters, show an undeniable influence of reward and emotion on feeding behaviours and how such mechanisms could undermine motivation and ability to regulate diet and lose weight.

5. Clinical implications

As previously stated, further evidence is needed to validate the construct of "food addiction", and no relationship has been established between obesity and addictive behaviour. Nevertheless, the psychological component observed so far in obesity and overweight cannot be ignored. New tools to quantify and measure behavioural pathology in eating have surfaced in recent years, most prominently the Yale Food Addiciton Scale[25,26]. The YFAS consists of a self-assessment questionnaire, divided in different items, extrapolated from the previously discussed 11 DSM criteria for Substance-abuse. Like the DSM, the YFAS defines diagnostic threshold at a minimum of 3 criteria present. Likewise, the presence of additional criteria translates into increasingly severe FA diagnosis. This extrapolation of diagnostic has been the target of many criticisms, as it assumes food addiction as an accepted neurobiological disease despite insufficient and inconsistent data, akin to the studies we have discussed previously[11,12].

During this study's research, several studies were found that used the YFAS in different populations. Two studies, Lawson et al and Ivezaj et al (2019), used the YFAS on large groups of obese patients seeking bariatric surgery and patients seeking for help with weight/eating concerns after bariatric surgery, respectively[21,23]. Both these studies found that YFAS scoring had no correlation with BMI[21,23]. Ivezaj et al (2019) also found that YFAS correlated positively with eating behaviour scales (Eating Disorder Examination-Bariatric Surgery Version) and the Beck Depression Inventory[23]. Additionally, Ivezaj et al (2017), conducted a systematic review of 19 studies testing pre- and post-bariatric surgery obese patients for FA symptoms, using YFAS and other self-assessment tools. Data from these studies suggest that rates of food addiction diagnosed by YFAS decrease during the first post-operative year, and the presence of presurgical food addiction was linked to higher pre-operative eating disorder psychopathology, problematic eating behaviours, and broad levels of psychopathology. However, the pre-surgical YFAS scores were unrelated to pre-surgical BMI and post-surgical weight loss[22].

On the other hand, Şengör et al, using the YFAS in a population of 370 university students, found that YFAS scores correlated positively with weight, hip circumference, BMI and with scores in the Eating Attitude Test (EAT)-26[24]. Likewise, Beyer et al, using MRI on 625 subjects (participants of the LIFE – Adult study), together with the YFAS, the Three Factor Eating Questionnaire (TFEQ), waist-to-hip ratio and BMI measurements, aimed to determine how these variants related to cortical thickness in orbitofrontal cortex (OFC), NAc and other ROI. The YFAS score positively correlated with BMI, with TFEQ and waist-to-hip, but did not show any correlation with cortical thickness. Higher BMI was, however, associated with reduced cortical thickness in the right prefrontal, orbitofrontal, parahippocampal, left temporal and occipital cortex and increased left NAc volume[47].

Furthermore, the validity of a therapeutic approach to obesity based on addiction is also highly controversial, as it may signify an "over-pathologisation" of common behaviour[13]. It can also be argued that attributing addictive properties to food and eating may, in patients attempting to lose weight or with relapsing weight gain, induce the perception of inevitable

"failure of control" when eating, and therefore offering an excuse for continued behaviour[14].

Attempting to evaluate how effective an approach similar to the treatment of addiction would be, Riva et al, developed an integrated approach to the treatment of morbid obesity, labelled "experiential cognitive therapy" (experiential CT). This approach focused on maintaining/relapse mechanisms, using virtual reality, to guide the patient in simulated critical situations related to such mechanisms (Home, Supermarket, Pub, Restaurant, Swimming Pool, Beach, Gymnasium) and to practice eating/emotional/relational management and general problem-solving skills. Additionally, this approach used simulated changes in body experience to facilitate changes in body image[48].

Using a controlled clinical trial with a sample of 221 morbid obese women (BMI >40) with a story of previously failed weight loss attempts, Riva et al compared their experiential CT approach with two other obesity treatments: psycho-educational nutritional groups and cognitive-behavioural therapy (CBT); and with a "waiting list" control group. All three treatments had a duration of 6 weeks, and patient evaluations were made before treatment, posttreatment and 6 months after treatment[48].

All three approaches showed greater weight loss and improvement of psychological symptoms than the waiting list group. Weight reduction was slightly higher for the CBT group and improvement of psychological symptoms was greater in the experiential CT group, even though these differences between the three treatments were not statistically significant. Additionally, the nutritional group showed overall higher weight at follow-up assessment[48].

5.2 Discussion

The results of Riva et al's study, give little support to a specific addiction-like approach to obesity. However, they do show that medically managed intensive inpatient obesity treatments can, in a relatively brief time period, and with an hard to treat population (morbidly obese women), result in substantially more effective weight loss and improvement of psychological well-being[48].

Furthermore, the reviewed studies using YFAS have shown mixed and inconsistent results, which supports the previously mentioned criticisms of this scoring system. Therefore, the validity of the YFAS as a diagnostic tool cannot be accurately ascertained. As stated in the previous chapter, known mechanisms of tolerance and withdrawal cannot be clearly determined to be associated to food and eating, and further research is needed to clarify if addiction could impact eating behaviour and, most importantly, through which mechanisms such impact could occur.

Regardless of the validity of the concept of "food addiction" there is, as previously stated, an undeniable influence of reward and emotion on feeding behaviours. Many of the findings in the previously analysed neuroimaging, agonist/antagonist and genetic studies seem to support, not necessarily addiction-driven obesity and over-eating but rather a more specific separate phenotype of obesity, which, as seen in Riva et al, could largely benefit from an alternative therapeutic approach. Even though, self-assessment scoring scales like the YFAS are greatly put into question, perhaps a new, non-addiction-based tool could help differentiate which patients

would benefit from a more classical approach of dietary and nutritional counselling, and which patients would benefit from specific psychological counselling, targeting the emotional and behavioural aspects of eating.

6. Conclusion

When reviewed separately, evidence for food addiction appears to be rather compelling. At first glance, many studies show possible neuroanatomical correlates to symptoms of tolerance and withdrawal[38-40,42,45]. However, these correlates are inconsistent and often contradictory when compared amongst themselves, making it impossible to describe a neuropathological model of food addiction. The role of $DRD_{2/3}$ availability and dopamine release is still not fully understood in obesity and over-eating. Even though there is a lack of consistency across studies, significant differences have been observed in dopaminergic pathways between either obese vs. non-obese or over-eaters vs. normal eaters[39,42,43,46]. For this reason, the emotional component of obesity and over-eating should not be ignored and taking it into consideration in a clinical context has, as shown by Riva et al, showed significant benefit[48].

Going back to the definition of addiction, namely the DSM criteria, an "underlying change to brain circuits" remains yet to be clearly defined related to food addiction. Attempting to define or diagnose food addiction solely based on patient self-report of the DSM criteria, without establishment of a consistent neuropathological model, represents a misuse of these criteria and serves small purpose in proving the existence of an addictive processes in obesity. Some newly developed diagnostic tools, such as the YFAS, engage in this misuse and the inconsistent results, observed across the previously discussed studies using the YFAS, seem to reflect this flaw[21-24,47].

Significant data has been presented to support altered reward and emotion regulation as a significant etiological factor of obesity[42,43,46]. The development of new self-assessment diagnostic tools, not based on DSM criteria, that focus on identifying emotionally and reward driven eating, rather than on behaviour labelled as "addiction", could be an extremely powerful tool in clinical practice in several ways. Being of aware of the influence palatable foods can have over oneself, could be a tool of empowerment critical to a successful and sustained weight-loss. Most importantly, it could help differentiate patients who would benefit from a medically and psychologically assisted weight-loss from those who would benefit from a more classical approach of dietary and nutritional counselling.

In conclusion, there is not enough data to determine if addiction processes occur in relation to obesity and over-eating, and the clinical usefulness of an addiction-based approach to obesity remains to be proven. However, the findings reviewed in this dissertation seem to support the existence of distinct phenotypes in obesity, some of which related to altered reward and emotion, and thus more effectively treated and managed through a more specialized and intensive therapeutic approach. Further research is needed to better characterize the role of emotion and reward in eating behaviour. New clinical tools need to be developed to help differentiating different types of patients and more clinical trials are necessary to determine better and more efficient treatments for different types of obesity.

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