Neuroscience and Biobehavioral Reviews 47 (2014) 295–306

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

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

Review

"Eating addiction", rather than "food addiction", better captures addictive-like eating behavior

Johannes Hebebrand[a], Özgür Albayrak[a], Roger Adan[b], Jochen Antel[a], Carlos Dieguez[c,d], Johannes de Jong[b], Gareth Leng[e], John Menzies[e,*], Julian G. Mercer[f], Michelle Murphy[f], Geoffrey van der Plasse[b], Suzanne L. Dickson[g]

[a] Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, Universitätsklinikum Essen (AöR), Wickenburgstr. 21, D-45147 Essen, Germany
[b] Department of Translational Neuroscience, Brain Center Rudolf Magnus, University Medical Center Utrecht, Universiteitsweg 100, 3584 CG Utrecht, The Netherlands
[c] Department of Physiology, School of Medicine, University of Santiago de Compostela, 15782 Santiago de Compostela, Spain
[d] CIBER Fisiopatología de la Obesidad y Nutrición (CIBERobn), Spain
[e] Centre for Integrative Physiology, University of Edinburgh, Hugh Robson Building, 15 George Square, Edinburgh EH8 9XD, UK
[f] Rowett Institute of Nutrition and Health, University of Aberdeen, Greenburn Road, Bucksburn, Aberdeen AB21 9SB, UK
[g] Department Physiology/Endocrine, Institute of Neuroscience and Physiology, The Sahlgrenska Academy at the University of Gothenburg, Medicinaregatan 11, SE-405 30 Gothenburg, Sweden

ARTICLE INFO

Article history:
Received 15 May 2014
Received in revised form 25 August 2014
Accepted 28 August 2014
Available online 6 September 2014

Keywords:
Food addiction
Eating addiction
Obesity
Reward system
Motivation
Fat addiction
Sugar addiction
Salt addiction
Addictive disorders

ABSTRACT

"Food addiction" has become a focus of interest for researchers attempting to explain certain processes and/or behaviors that may contribute to the development of obesity. Although the scientific discussion on "food addiction" is in its nascent stage, it has potentially important implications for treatment and prevention strategies. As such, it is important to critically reflect on the appropriateness of the term "food addiction", which combines the concepts of "substance-based" and behavioral addiction. The currently available evidence for a substance-based food addiction is poor, partly because systematic clinical and translational studies are still at an early stage. We do however view both animal and existing human data as consistent with the existence of addictive eating *behavior*. Accordingly, we stress that similar to other behaviors eating can become an addiction in thus predisposed individuals under specific environmental circumstances. Here, we introduce current diagnostic and neurobiological concepts of substance-related and non-substance-related addictive disorders, and highlight the similarities and dissimilarities between addiction and overeating. We conclude that "food addiction" is a misnomer because of the ambiguous connotation of a substance-related phenomenon. We instead propose the term "eating addiction" to underscore the behavioral addiction to eating; future research should attempt to define the diagnostic criteria for an eating addiction, for which DSM-5 now offers an umbrella via the introduction on *Non-Substance-Related Disorders* within the category *Substance-Related and Addictive Disorders*.

Contents

* Corresponding author. Tel.: +44 131651711.
E-mail address: john.menzies@ed.ac.uk (J. Menzies).

http://dx.doi.org/10.1016/j.neubiorev.2014.08.016

1. Introduction

Almost 60 years ago, Randolph first defined "food addiction" as "[. . .] a specific adaptation to one or more regularly consumed foods to which a person is highly sensitive, produces a common pattern of symptoms descriptively similar to those of other addictive processes"; addictive-like consumption of corn, wheat, coffee, milk, eggs, and potatoes was reported (Randolph, 1956). With the increase in the worldwide prevalence of obesity over the past decades (Finucane et al., 2011; Ogden et al., 2012) the concept of "food addiction" has recently become popular both among researchers and the lay public as a possible way to understand the impact of psychological factors on weight gain (Brownell and Gold, 2013). This concept forms an etiological framework that is centered between chemical or "substance based" and behavioral addictions.

The rise in prevalence rates of obesity in many countries cannot be attributed to genetic factors alone; instead, environmental changes, which interact with our biological make-up, appear to underlie the obesity pandemic. A large proportion of different populations overeat to an extent that threatens physical and mental well-being, and both somatic and psychiatric disorders are associated with obesity. "Food addiction" offers a superficially attractive explanation, and potentially an excuse, for this unhealthy behavior at an individual level. The modern "obesogenic" environment is characterized by the ubiquitous availability of palatable, energy-dense and inexpensive foods, reflecting ongoing efforts of the globalized food industry to increase production and boost sales. As such, the food and beverage industry is perceived as having a powerful role in promoting poor nutrition policies (Davis, 2013). "Food addiction" places blame on the food industry for the production of "addictive foods" and by so doing indicates that obesity prevention strategies should seek to curtail the influence of this industry on eating behavior.

The behavioral, clinical and neurobiological similarities and dissimilarities between addiction and overeating are highlighted in this review. We point out that current evidence in humans suggests that "eating addiction" rather than "food addiction" more precisely circumscribes addictive-like food intake in affected individuals.

2. Definition, classification, and neurobiology of addiction

2.1. Definition of addiction and classification of substance-related and addictive disorders

An overarching scientific delineation of the concept of addiction has proven elusive: "Ideally, we would like to discover the necessary and sufficient conditions for someone to have an addiction, and to do so in such a way as to provide real illumination about the sort of phenomena we have in mind when thinking about addiction" (Sussman and Sussman, 2011). Clinicians and researchers understand addiction in several different ways. Drug addiction has been defined as a chronically relapsing disorder characterized by (1) compulsion to seek and take the drug, (2) loss of control in limiting drug intake, and (3) emergence of a negative emotional state (e.g., dysphoria, anxiety and irritability) reflecting a motivational withdrawal syndrome when access to the drug is prevented; Koob (2013) refers to the term 'reward deficit disorder' for alcoholism and other drug addictions, which are based on multiple motivational mechanisms and progress from impulsivity (positive reinforcement) to compulsivity (negative reinforcement). Compulsive drug seeking can be derived from multiple neuroadaptations. Koob stresses that a key component of addiction is based on the construct of negative reinforcement defined as drug taking that alleviates a negative emotional state. This state is hypothesized to result from the dysregulation of specific neurochemical elements involved in reward and stress within the basal forebrain structures (Koob, 2013).

Sussman and Sussman (2011) identified five elements of addiction that recur in the scientific literature: (1) engagement in the behavior to achieve appetitive effects; (2) preoccupation with the behavior; (3) temporary satiation; (4) loss of control; and (5) suffering negative consequences. They point out the major limitations of conceptualizing addiction via these definitional elements. In particular, there are difficulties in measuring these elements, which might not be independent, but rather related and operative in complex feedback loops. It is also unclear to what quantitative extent 'engagement' must be present before it can be labeled as addictive behavior. Finally, what is perceived as an addiction might be context-dependent.

Until recently, the medically established forms of addiction (APA, 2000) pertained to substance-related disorders only: "Addiction is defined as a chronic, relapsing brain disease that is characterized by compulsive drug seeking and use, despite harmful consequences" (National Institute on Drug Abuse, 2013). Substance-related disorders, which represent a major global public health problem (Whiteford et al., 2013), are classified within the context of mental disorders in the widely used Tenth Edition of the International Classification of Diseases (ICD-10) and the Fifth Edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5; APA, 2013).

The now outdated DSM-IV TR (APA, 2000) avoided the diagnostic use of the term addiction and instead referred to the category "*Substance-Related Disorders*", subdivided into *Substance Use Disorders* and *Substance Induced Disorders* (Table 1). Within *Substance Use Disorders*, *Substance Dependence* referred to "a cluster of cognitive, behavioral, and physiological symptoms". If diagnostic criteria for *Substance Dependence* were not met, but a "maladaptive pattern of substance use manifested by recurrent and significant adverse consequences related to the repeated use of substances" applied, *Substance Abuse* was diagnosed.

After extensive discussions of the definition of the term "addiction", the DSM-5 Substance Use Disorders Workgroup re-titled the previous category as "*Substance-Related and Addictive Disorders*" (APA, 2013; Table 1), which was subdivided into "*Substance-Related Disorders*" and "*Non-Substance-Related Disorders*". Importantly, within the context of *Substance-Related Disorders*, 'addiction' is

Table 1
The transistion from DSM-IV to DSM-5; the novel diagnostic category 'Substance-Related and Addictive Disorders' in DSM 5 for the first time allows the diagnosis of Non-Substance-Related Disorders.

DSM-IV TR (APA, 2000)			DSM 5 (APA, 2013)	
Substance Related Disorders			Substance-Related and Addictive Disorders	
Substance Use Disorders		Substance Induced Disorders	Substance-Related Disorders	Non-Substance-Related Disorders
Substance Dependence	Substance Abuse		Substance Use Disorder	Gambling Disorder

not applied as a diagnostic term. Instead, "the more neutral term *Substance Use Disorder* is used to describe the wide range of the disorder, from a mild form to a severe state of chronically relapsing, compulsive drug taking" (APA, 2013). The DSM-IV subdivision of substance use disorders into 'dependence' and 'abuse' was dropped, because the evidence for this distinction was considered to be insufficient.

Because gambling behaviors activate similar reward systems that are targeted by drugs of abuse, and because they produce behavioral symptoms that overlap with those produced by *Substance Use Disorders*, *Gambling Disorder* was included as the sole *Non-Substance-Related Disorder* in DSM-5 (APA, 2013). The evidence for including other behavioral addictive disorders such as Internet gaming, sex addiction or shopping addiction appeared too weak. For similar reasons, obesity was not included in DSM-5, despite the importance of behavior and the involvement of the same central pathways that are involved in substance use disorders (Volkow and O'Brien, 2007).

The inclusion of *Non-Substance-Related Disorders* within the newly titled category '*Substance-Related and Addictive Disorders*' in DSM 5 represents a paradigm shift, which will also potentially influence ICD-11. The term *addictive disorder* has entered the psychiatric classification system, albeit not (yet) as an umbrella term for both substance use and behavioral addiction. The door is thus now open for the future inclusion of other behavioral addictions into the diagnostic classification schemes.

2.2. Overlap and distinction between exogenous and endogenous substances and between chemical and behavioral addiction

A classic finding in the context of addiction was that substance misuse can alter central nervous system signaling involving peptides with rewarding properties, such as enkephalins, endorphins, and cannabinoids (Feng et al., 2012; Mechoulam and Parker, 2013). However, changes in these endogenous signals can also be associated with non-substance-based addictive behavior. Hence, the general term "chemical addiction" does not necessarily require the substance to be an exogenous chemical. Different receptor genes are expressed in different parts of the brain, conferring the ability to bind these endogenous substances with high affinities. The various systems are each involved in a host of diverse functions–many of which are completely unrelated to reward processes. However, if endogenous "chemicals" can be rewarding or by their actions at specific brain sites in some circumstances and/or in predisposed individuals, such neural mechanisms might represent a link between drug and behavioral addiction. Accordingly, the link of appetite, hunger, satiation and satiety with the reward system (Bellisle et al., 2012) can be viewed as a basis for the development of addictive-like eating behavior. Psychological cues like boredom, perceived stress or a negative mood potentially may trigger overeating in the absence of hunger that would lead to neurobiological alterations in complex central regulatory systems related to addictive behaviors.

Structural differences between endogenous and exogenous substances of, for example, the opioid agonists result in different conformational, topographical, and stereoelectronic presentations (Hruby and Agnes, 1999) toward the opioid receptors. "Agonist-selective" regulation of opioid receptors is well known (Williams et al., 2013) and entails different signaling efficacies (Kelly, 2013) to multiple downstream pathways and differences in the ability to induce opioid receptor internalization, tolerance and dependence (Koch and Höllt, 2008). Subtle structural modifications, independent of the structural class (opioid peptide based, morphine based, or 4-anilinopiperidin-4-carboxamid [e.g. fentanyl] based) can have a strong impact on the formation of the functional receptor complex and modify efficacy and tolerance development (Stafford et al., 2001); the mechanisms underlying this functional diversity are poorly understood (Williams et al., 2013). The strength of the impact depends strongly on the observable intrinsic efficacy of the ligand/drug and not as much on the structural class or their exogenous or endogenous origin (Williams et al., 2013).

Endogenous "chemicals" similar to neurotransmitters are released within normal physiological concentrations during various activities (e.g. physical exercise, sexual stimulation), but still may eventually lead to a behavioral adaptation accompanied by signs of tolerance and withdrawal in thus predisposed individuals under specific circumstances. In contrast, exogenous drugs can result in responses that are quantitatively and/or qualitatively beyond those experienced in normal physiology.

The route of administration (e.g. inhalation, oral intake, intravenous injection) of an exogenous substance can also determine its addictive properties, for example, the impact of heroin's route of administration on its withdrawal severity is marked, due to differences in bioavailability (Smolka and Schmidt, 1999). In the context of food, it is noteworthy that intravenous infusion of glucose can support conditioning and cause dopamine release in the nucleus accumbens (as do drugs of abuse). However, the effect seems more robust when glucose is administered either in the intestinal tract or in the hepatic-portal vein (Ackroff et al., 2010; Oliveira-Maia et al., 2011).

On a symptomatic level, individuals with behavioral or substance addictions have the urge to engage in their behavioral routine; they feel discomfort if they cease their use, which results in craving and withdrawal symptoms. Some withdrawal symptoms (e.g. anxiety) are common across certain behavioral and chemical addictions, while others (e.g. runny eyes and sneezing in opiate withdrawal) are substance-specific (Morrissey et al., 2008; Bradley, 1990).

Eating is intrinsically rewarding and reinforcing, and food consumption is well-known to activate the reward system in the brain; this applies particularly in the physiological state of hunger. It is easy to see that the rewarding properties of food and their activation of the reward pathway might lead intuitively to the idea that food substances may have addictive properties. However, just because eating behavior engages these reward systems, it does not necessarily follow that specific nutrients (substances) are able to evoke a substance addiction. Instead, the complex activation of the reward system as the initial step of the process ending in addiction can be viewed as being dependent on eating (subjectively)

palatable foods irrespective of their nutritional/chemical composition.

2.3. Neurobiology of the reward pathways and the overlap and interaction between homeostatic and hedonic circuits

Feeding behavior is mediated by a network of interacting neural circuits that include the hypothalamus, the dorsolateral prefrontal cortex (DLPFC), amygdala, striatum and the midbrain (Berthoud, 2011). Together these systems regulate all aspects of feeding behavior, including both homeostatic food consumption (i.e. consumption governed by signals relating to energy stores and energy demands), and hedonic food consumption (i.e. consumption motivated by reward systems). These homeostatic and hedonic neural circuits do not operate independently of one another: they are closely interlinked, and both respond to metabolic signaling. Insight into these neural circuits is leading to novel treatment strategies. For example, a recent meta-analysis concluded that non-invasive neuro-stimulation of the DLPFC is effective in decreasing craving in substance dependence and craving for highly palatable food (Jansen et al., 2013).

Here we outline the putative pathways through which metabolic and reward signals can interact to produce feeding behavior. This serves as a framework for understanding the neurobiological underpinnings of motivation for food and the possible routes by which feeding history can influence behaviors linked to addiction.

Specific neurobiological systems drive attentional and motivational behavior toward important environmental stimuli. Animals show a motivation to find and consume food, which is contrasted with the sensory pleasure of actually eating (in 1996 Berridge coined the terms wanting and liking for these two phenomena). Contextual cues or behaviors related to the initial reinforcer can become more important in maintaining the increasingly addictive behavior than the primary stimulus itself. Primary reinforcers, such as sweet foods, or the environmental cues associated with them, can become increasingly salient as the pleasure associated with their consumption is learned. With repeated exposure, this salience increases, and their prominence as a stimulus to drive behavior becomes greater (Volkow et al., 2013). This may lead to the overconsumption of foods for which there is no metabolic need. It has been argued that this increase in the salience of food parallels the development of addiction to drugs of abuse, particularly because it shares a common neurobiological pathway mediating altered reward salience and motivation – the mesolimbic dopamine system. A subgroup of individuals who, for various reasons, are more “cue reactive” in (i.e. certain reward cues are more likely to attract these individuals), will be more motivated to obtain rewards (Saunders and Robinson, 2013).

Dopamine signaling plays a pivotal role in reward- and addiction-related behavior. Transgenic mice that lack dopamine signaling die of starvation; this is linked to a loss of food-motivated behavior (Szczypka et al., 2001). The ventral tegmental area (VTA) dopamine pathway that projects to the nucleus accumbens (NAc) of the ventral striatum is a key pathway involved in incentive motivation. As reviewed elsewhere (Volkow et al., 2013), these dopamine neurons become activated after delivery of a novel food reward (Norgren et al., 2006) but with repeated exposure to that same reward this activation lessens (habituates) and is induced instead by (predictive) cues associated with that reward (Epstein et al., 2009; Schultz, 2010). Thus, dopamine signaling is crucially important for the formation of associations between rewards and the cues that predict their availability (Schultz et al., 1997; Stuber et al., 2008; Salamone and Correa, 2012). Indeed, firing of these VTA dopamine neurons has been suggested to signal the difference between expected rewards and the actual outcome, i.e. a reward-prediction error (Schultz et al., 1997; Cohen et al., 2012; Steinberg et al., 2013; Boender et al., 2014). This signaling, which involves dopamine release in the NAc, has also been suggested to assign increasing reward value to food cues (Roitman et al., 2004). After extensive training drug seeking becomes more cue-driven as opposed to outcome-driven which is mediated by a transition from dopaminergic activity in the ventral striatum (NAc core and shell) to the dorsal striatum (caudate putamen) (Everitt and Robbins, 2005). It has been postulated that, via this mechanism, food cues may drive palatable food intake in a similar (habitual) fashion over time (Smith and Robbins, 2013). In support of the importance of dopaminergic projections to the NAc, blocking dopaminergic neurotransmission in this target area has been shown to reduce motivated behavior for reward, while local infusion of dopamine agonists improves performance on tests of motivation in a similar fashion to food restriction (Aberman et al., 1998).

Metabolic signals like leptin and ghrelin, which are primary regulators of homeostatic food consumption, also affect the hedonic drive for food (e.g. Egecioglu et al., 2011) and a close relationship between these signals and dopamine activity has been shown experimentally. Domingos et al. (2011) recently showed that the adipocyte-derived anorexigenic hormone leptin modulates the reward value of sucrose. Whereas food-restriction increased the rewarding value of sucrose in rats, treatment with leptin decreased its value, presumably through the modulation of dopaminergic activity. These data indicate that metabolic signals can influence reward-related signaling and drive an animal to adapt motivated behavior in response to changes in energy balance. Also, human subjects with congenital leptin deficiency show increased activity of striatal areas in response to food-cues, but a reversal of this activity following leptin treatment (Farooqi et al., 2007).

These data support earlier work showing that the striatal dopaminergic reward system is sensitive to a range of hormones associated with homeostatic control of food intake. In addition to leptin (Fulton et al., 2006), the stomach-derived orexigenic hormone ghrelin has been shown to have an important role in motivation for food reward in rodents. Ghrelin increases lever-pressing for sucrose in a progressive ratio operant responding paradigm (Skibicka et al., 2012a), an effect that appears to involve the VTA-accumbens dopaminergic pathway (Skibicka et al., 2013) as well as mu-opioid-sensitive pathways (Skibicka et al., 2012b). Interestingly, ghrelin’s effects on food reward behavior and simple intake of chow exerted at the level of the VTA appear to be controlled by divergent circuitry: although accumbens dopamine (Skibicka et al., 2013) and VTA mu-opioid pathways (Skibicka et al., 2012b) have an important role in food reward, they do not alter food intake. The midbrain reward circuitry is also targeted by circulating anorexigenic peptides, several of which have been shown to suppress food-motivated behavior, including GLP-1 (Dickson et al., 2012) and insulin (Figlewicz et al., 2008).

Thus, recent diet history and metabolic signaling impinge upon dopamine-driven motivational aspects of feeding behavior, and the exact mechanisms are now beginning to be elucidated. A recent review by van Zessen et al. (2012) described the evidence for leptin and ghrelin’s actions on the VTA dopamine neurons either to directly modulate dopamine release in target sites, or, like other rewarding substances such as opiates and alcohol, act via GABAergic neurons in the VTA. These metabolic hormones can also affect other components of the brain’s reward pathway including neurones projecting from the lateral hypothalamus, arcuate nucleus and amygdala to the VTA (Narayanan et al., 2010).

But homeostatic signals can also affect circuitry that falls outside these motivation and pleasure-sensing pathways. For instance, Berthoud (2011) pointed out that glucagon-like peptide-1 (GLP-1) signaling might directly alter taste perception. Mice lacking the GLP-1 receptor display reduced sensitivity to sweet tastes but

increased sensitivity to umami (Martin et al., 2009). Similarly, leptin receptor-deficient mice display a heightened sense of smell, and leptin itself, through its actions on leptin receptors expressed on taste receptor cells themselves can alter the threshold for olfactory stimulation (Kawai et al., 2000). Such a direct interaction between metabolic signals and taste perception might strongly affect food choice and subsequent intake.

In contrast to the mesolimbic dopamine system, which has been linked to attention to and motivation for rewards, endogenous opioid systems have been linked to the pleasure associated with food reward (Kelley et al., 2002). While opioids stimulate all food intake, their effects are particularly powerful for palatable food, especially foods that are already preferred. This suggests that opioids reinforce an already established hedonic value (Gosnell et al., 1995; Olszewski et al., 2011). Previously, hedonic "hotspots" were defined in the brain where injections of opioid agonists produced powerful "liking" responses in rats. These areas, which receive dense dopaminergic projections, include the medial shell of the NAc and the ventral pallidum (Berridge, 1996; Peciña et al., 2006; Peciña, 2008). At these sites, modulation of hedonic impact and feeding appear segregated, such that opioids do not affect feeding per se (Olszewski et al., 2011). In general, dopaminergic and opioid mechanisms seem to work together to promote food intake for which dopaminergic mechanisms promote the anticipation and the motivation for food and opioids are involved in the consummation and possibly hedonic evaluation of food (Ackroff et al., 2010; Barbano and Cador, 2007; Oliveira-Maia et al., 2011).

Based on our current knowledge of the pathways involved in the reward system and the mechanisms underlying its activation we can merely speculate that subtle differences account for the inter-individual and intra-individual variation of eating behavior. These differences can be due to genetic, epigenetic, psychological, societal and environmental factors, some of which are interdependent. An eating addiction could thus be viewed as a rather strong perturbation of single or several factors, that result in activation and function of the reward system. Both the industrialization and globalisation of the food industry may conceivably have contributed to an increased risk of such a perturbation via the proliferation of food related factors that render an individual prone to develop such an eating addiction. It is readily evident that the complexity of the factors that shape individual eating behavior preclude an over-interpretation of specific findings including those of animal models.

3. "Food addiction", substance use disorders and eating behavior

3.1. Food: substances of abuse?

Labeling a food or nutrient as "addictive" implies that it contains ingredients and/or possesses an inherent property with the capacity to make susceptible individuals addicted to it, as is the case for chemical substances of abuse. Certain foods have rewarding and reinforcing properties; for example, high sugar-high fat combinations are rewarding for rodents and humans alike. From an evolutionary perspective, these rewarding properties increase motivation to seek out and obtain an adequate and nutritionally diverse energy supply. In our modern obesogenic environment, characterized by ready availability of highly palatable and energy-dense food, it seems that these rewarding properties of particular foods might overwhelm both cognitive restraint and homeostatic mechanisms, and lead to weight gain. Some have thus proposed that the recent increase in the prevalence of obesity reflects the emergence of "food addiction" in a significant fraction of the population (Davis et al., 2011; Gearhardt et al., 2011). Indeed, formulations of processed foods have been designed to maximize palatability and reward; globalization further promotes our exposure to novel sensory combinations. Such properties are not confined to simple taste (sweetness, saltiness) but encompass more complex blends of taste, flavor, smell, texture and even the sounds produced by preparation or consumption (Spence, 2012). However, with the exception of caffeine (DSM-5 for the first time refers to Caffeine-Related Disorders within the category Substance-Related and Addictive Disorders; APA, 2013), there is currently insufficient scientific evidence to label any common food, ingredient, micronutrient, standard food additive or combination of ingredients as addictive.

Per se, foods are nutritionally complex and there is hardly any evidence to suggest that under normal physiological circumstances humans crave specific foods in order to ingest a specific 'substance'. Instead, the diet of subjects who overeat typically contains a broad range of different, subjectively palatable foods. It can be argued that access to a diversity of foods, especially a diverse range of palatable foods, may be a pre-requisite for the development of addictive-like eating behavior. Therefore, one possible approach to overcome this behavior would be to restrict access to only a small number of such foods. Without access, it would be unlikely for such addictive-like behaviors to be expressed. Furthermore, in overweight individuals, this would likely entail a reduced energy intake, because the diversity of rewarding, palatable foods is lacking.

3.2. The diagnosis "food addiction"

The Yale Food Addiction Scale (YFAS; Gearhardt et al., 2009) can be viewed as the first questionnaire to assess addictive eating behavior based on the formal DSM-IV (APA, 2000) diagnostic criteria for substance dependence. The naming of this questionnaire has fueled the controversies related to "food addiction". However, the questionnaire clearly focuses on the assessment of eating behavior and not on substance based addiction. Gearhardt and coworkers described the YFAS as a "sound tool for identifying eating patterns that are similar to behaviors seen in classic areas of addiction". The questionnaire includes 25 items which address eating habits over the past 12 months. Examples include "I eat to the point where I feel physically ill.", and "I have had withdrawal symptoms such as agitation, anxiety, or other physical symptoms when I cut down or stopped eating certain foods." Diagnosis of "food addiction" can be made according to the DSM-IV criteria if at least three items out of seven are fulfilled within the last 12 months and if the symptoms additionally cause significant distress to the patient or impairment in social, occupational, or other important areas of functioning. Despite the fact that the YFAS largely probes for palatable food highly enriched with calories (e.g. chips, pizza, ice cream), it is readily apparent that any of these foods comprises a host of different "substances". Because the substance of abuse is not defined, the classification of YFAS-diagnosed food addiction as a *Substance Use Disorder* is not possible.

The YFAS criteria have been used to explore the prevalence of 'food addiction' in obese subjects from the general population (Davis et al., 2011, 2013) and clinical populations with (Gearhardt et al., 2012, 2013a) and without Binge-Eating Disorder (BED) seeking weight loss treatment (Burmeister et al., 2013; Clark and Saules, 2013; Eichen et al., 2013; Lent et al., 2014; Meule et al., 2012), and from the general population of under-, normal and overweight/obesity (Flint et al., 2014; Gearhardt et al., 2009, 2013b; Mason et al., 2013; Meule, 2012; Meule and Kübler, 2012; Murphy et al., 2014; Pedram et al., 2013). In the latter study by Pedram and colleagues, the prevalence rate of the YFAS diagnosis "food addiction" is approximately 5%; females are affected twice as often as males (6.7% vs. 3.0%; Pedram et al., 2013); in under/normal weight or overweight/obese the rates of "food addiction" were 1.6% and

7.7%, respectively. In conclusion, "food addiction" is more common in both obesity and BED, but can also occur independently of these two disorders.

The strict adherence to criteria used for Substance Related Disorders presumably does not suffice to fully capture the cognitions and behaviors of eating addiction. For example, for Gambling Disorder specific criteria have been laid down in DSM-5 (APA, 2013), which specifically address this addictive behavior and which only partially rest on those for Substance Related Disorders. Thus, disorder-specific behavioral symptoms (see A criterion) include: "after losing money gambling, often returns another day to get even" or "relies on others to provide money to relieve desperate financial situations caused by gambling". In addition, for this behavioral addiction a higher number of symptoms has to be met in order to fulfill mild (4–5 symptoms), moderate (6–7) or severe (8–9) current severity (for alcohol use disorder the respective specifications are met upon presence of 2–3, 4–5, and 6 or more symptoms). Further research is clearly warranted to phenotypically characterize subjects with an eating addiction in an effort to in clinical terms fully delineate this disorder and to eventually come up with stringent diagnostic criteria. We perceive the necessity, and at the same time the difficulty, to clearly separate known causes of overeating, which without knowledge of the underlying process (e.g. leptin deficiency, hypothalamic tumor) could be labeled as an addictive behavior. In light of the polygenic basis of BMI variance in the general population (Hinney and Hebebrand, 2008), we need studies to address if addictive overeating (and obesity) can occur independently of a genetic predisposition to an elevated body weight.

3.3. Disentangling occasional overeating, binge eating and eating addiction

Davis (2013) proposed that overeating is a dimensional prototype reflecting its severity, its degree of compulsiveness, and its clinically significant level of personal impairment. Homeostatic eating reflects a balance between energy intake and output; "passive overeating" entailing a slow but steady increase of body weight reflects the influence of the obesogenic environment (e.g. portion size, overall availability of and easy access to highly palatable energy dense foods) on susceptible individuals. Further down the continuum, mild and intermittent "disinhibited eating" can manifest as episodic binges. At this stage, clinical correlates of "disinhibited eating" include eating in the absence of hunger, emotional eating and loss-of control eating (Tanofsky-Kraff et al., 2008; Vannucci et al., 2013); if a threshold of severity and compulsiveness is exceeded, the diagnosis of BED may be warranted (Davis, 2013). Similarly, Alsiö et al. (2012) postulated a "feed-forward system", according to which adaptations in both homeostatic and non-homeostatic appetite regulation propel the individual from a preference for palatable diets to food craving and compulsive, addiction-like eating behavior. According to Davis (2013) "food addiction" represents the extreme end of the continuum of overeating; she also suggests that "food addiction" reflects a subtype of BED. Like "food addiction", BED also occurs in normal weight individuals albeit less frequently than in overweight or obese individuals.

In our opinion, the equation of "food addiction" with BED must be viewed with caution. The impaired control over eating behavior in "eating addiction" does not necessarily require that the affected individual experiences a sense of lack of control over eating during a single episode of overeating. In this context, the term "grazing" can describe an unplanned and mindless eating behavior that can persist throughout the day, but which does not necessarily include eating binges.

According to the current psychiatric classification scheme, DSM-5, there is a phenomenological overlap between *Substance-related and Addictive Disorders* and *Feeding and Eating Disorders* (APA, 2013), in that 'control' plays a prominent role in the criteria for disorders within these two categories. However, a closer look reveals differences: thus, one of the central behavioral characteristics of *Substance Use Disorders* (APA, 2013) is "impaired control"; in addition, the DSM-5 introductory text for the overall category *Substance-Related and Addictive Disorders* states that ". . .individuals with lower levels of self-control, which may reflect impairments of brain inhibitory mechanisms, may be particularly predisposed to develop substance use disorders, suggesting that the roots of substance use disorders for some persons can be seen in behaviors long before the onset of actual substance use itself". In contrast, a "sense of lack of control over eating during the (binge eating) episode" is a key feature of both Bulimia Nervosa (BN) and BED (APA, 2013; Albayrak et al., 2012). For the former diagnostic category the focus is on the control of behavior before and after initial contact with a substance, and subjective feelings of the loss of control are important in the two eating disorders BN and BED. Accordingly, an outside observer should be able to readily verify the impaired control of subjects with substance use disorders. However, such an observer would need to inquire if an individual affected with BN or BED experiences the sense of lack of control over eating.

3.4. Vulnerable and high risk groups

Genetic factors are important in the development of substance use disorders. For example, the heritability estimates of alcohol use disorders or nicotine dependence are within the range of 40–60%. Meta-analyses of genome-wide association studies have identified non-overlapping genome-wide significant signals for both alcohol and nicotine dependence, which currently explain a small fraction of the respective heritabilities (Wang et al., 2012). Twin or family studies of "food addiction" have not yet been conducted. We are similarly not aware of a study that has systematically assessed the relationship between socio-economic status and "food addiction". Based on its association with obesity, "food addiction" is presumably more prevalent among subjects with low socio-economic status. Alcohol dependence, smoking and illicit drug use have all been associated with markers of social and economic disadvantage (World Health Organization, 2003), as has problem gambling (Welte et al., 2008).

In patients with *Substance Use Disorders*, psychiatric co-morbidity is the rule rather than the exception, with mood, anxiety, and conduct disorders being the most common co-morbid disorders. Such disorders often precede the development of the addiction, but can also develop after its onset. Models of bidirectional relationships or contemporaneous combination of risk factors have addressed this phenomenon (Mueser et al., 1998). The likelihood of co-morbidity of mood or anxiety disorders is 2–3 times higher in adults with drug/alcohol dependency than in the general population (Grant et al., 2004). Similarly, several psychiatric co-morbidities apply to behavioral addictions. For example, pathological Internet use or Internet-dependent individuals have elevated rates of depression and attention deficit/hyperactivity disorder (ADHD) (Peukert et al., 2010).

Bellisle and coworkers (2012) summarize findings on subjects who seemingly eat in the absence of hunger to induce reward. This behavior is related to stress, especially in overweight individuals with visceral adiposity, who may have reward deficiency. The YFAS has not yet been tested systematically in patients with mental disorders; we assume that similar to subjects with *Substance Use Disorders* rates of "food addiction" are higher in individuals who fulfill the diagnostic criteria for "food addiction". Our own studies of adolescent psychiatric in-patients revealed a high rate of approximately 25% for a co-morbid diagnosis of "food addiction", with females being affected twice as often than males. The high

rate of "food addiction" persisted after excluding patients with any eating disorders (Albayrak et al., 2012), suggesting that addictive-like eating patterns might be associated with an adverse mental health. Apart from the association with obesity, an overlap of "food addiction" with the eating disorder BED has been addressed in adults. According to a recent study by Gearhardt et al. (2013a), only 41.5% of obese patients with BED met the "food addiction" threshold, so neither obesity nor BED is synonymous with "food addiction". Overweight BED patients with "food addiction" seem to represent a more severe subgroup than obese BED patients without food addiction in terms of emotional and eating behavior related psychopathology (Gearhardt et al., 2012, 2013a). In a clinical sample of obese BED patients, "food addiction" was associated with elevated depression, negative affect, emotion dysregulation, eating disorder psychopathology and lower self-esteem (Gearhardt et al., 2012). Thus, BED patients that additionally report symptoms of "food addiction" may be exhibiting a more disturbed variant of BED, than those without.

4. A critical review of rodent models of "food addiction"

Addiction research in general has accumulated substantial evidence for the general translation of both pharmacological and non-pharmacological results obtained in rodent models to humans (e.g. Xue et al., 2012; Planeta, 2013). In rat models of drug abuse, *tolerance*, *dependence* and *withdrawal* are essential paradigms of the addictive properties of a given substance. *Tolerance* refers to the behavioral consequences of sub-cellular changes, such as receptor desensitization or down-regulation (Ueda and Ueda, 2009), such that an increase in substance use is required to obtain the same neurobiological effect. A necessary corollary of tolerance, therefore, is an increase in intake. In rat models of food addiction, neither tolerance, nor an accompanying escalation of food intake, has been convincingly demonstrated. There are *transient* increases in intake (often described as "binges"), but the energy consumed is offset by a reduction in food intake at other times, the net result being no change in body weight.

Physical dependence refers to adaptations to drug use that become apparent after cessation of use. Abrupt abstinence results in a withdrawal syndrome. This syndrome is best characterized in opiate dependence, which may have a broader relevance, as some mechanisms underlying food addictions are suggested to involve endogenous opioids (Colantuoni et al., 2002). Opiate dependence is manifested by a withdrawal syndrome that can also be triggered by administration of the opiate antagonist naloxone (Wesson and Ling, 2003). Upon "withdrawal" of specific foods, few studies report such an analogous syndrome in rodents (Avena et al., 2008). Such observations have to our knowledge not been made in humans.

Despite the overall successful translation of several rodent addiction models to humans, it has been argued that it is over-ambitious to attempt to model addiction in animals, and in rodents in particular, where "validity" of such models is often restricted to superficial similarities, referred to as "face validity" that differ substantially in terms of the underlying phenomena and biological processes from the clinical situation (Stephens et al., 2013). Accordingly, caution is also warranted for translating results obtained in rodent models of "food addiction" to humans. Thus, rodents are usually offered single food substances or very simple combinations. Based on such simplistic experiments we need to critically reflect, if and to what degree these models of addiction resemble patterns of eating behavior and food choice in humans. It again needs to be stressed that humans tend not to eat specific nutrients in isolation. While rat experiments on, for instance, "sugar addiction" are necessary to understand how a single nutrient may affect neurobiology and behavior, it is arguable whether they are directly relevant for human pathology.

The mere involvement of endogenous opioid systems in the regulation of food intake does not in itself imply that over-activation of these pathways through excessive eating will result in dependence on endogenous opioids. The opioid pathway that regulates food intake via hypothalamic oxytocin neurons mediates satiety, and is extremely sensitive to inhibition by exogenous opioids. In rats treated chronically with morphine, oxytocin neurons exhibit both tolerance (i.e. a markedly increased threshold to inhibition by morphine) and dependence (as evidenced by a massive and prolonged hypersecretion of oxytocin when morphine withdrawal is acutely provoked by naloxone (Brown et al., 2005)). Accordingly, if the endogenous opioid pathways that regulate oxytocin neurons are activated by the consumption of rewarding food, then an expected consequence would be suppression of satiety leading to overconsumption. However, we would expect that this mechanism would be down-regulated in response to chronic overconsumption (tolerance), and that, if it indeed resulted in endogenous opioid dependence, then fasting should precipitate a hypersecretion of oxytocin with a resulting prolonged potentiation of satiety (withdrawal). To date, this hypothesis has not been tested.

There is currently no evidence that single nutritional substances can elicit a *Substance Use Disorder* in humans according to DSM 5 criteria. In light of the lack of clinical studies that have aimed to detect addictions to specific nutrients, it cannot as yet be ruled out that a predisposed subgroup does indeed develop such a substance based addiction, which in theory may be substantially weaker than in the case of addictions based on well-known exogenous substances such as alcohol, cannabis, nicotine or opiates. The fact, that clinical case studies do not abound on an addiction like intake of specific nutrients or even specific foods, would suggest that such cases are rare, if they exist at all. Alternatively, the addiction is so weak that it is not adequately perceived and reported as such. This leads to the question as to the boundaries between excessive consumption and the beginning of a true addiction.

Animal studies have been performed using palatable food as a stimulus, and some of these foods do appear able to induce an addiction-like phenotype. In rodents, characteristics of food linked to taste and palatability seem to be especially important for the expression of some addiction-like behaviors, including binge-eating. Withdrawal-like behaviors have been reported after terminating access to sugar (Colantuoni et al., 2002). As a surrogate for craving, it is possible to show enhanced motivation for sucrose in rats during periods of abstinence – the rats work increasingly hard (by repeatedly pressing a lever) to obtain sucrose pellet rewards. In this respect it is also noteworthy to mention that a majority of rats will prefer a sweet reward over a cocaine reward and only a subset of rats will start to prefer cocaine after an extended history of cocaine self-administration (Lenoir et al., 2007). Findings such as these suggest that rats can become strongly motivated to consume certain foods. Thus, it is possible that addictive-like *behavior* can be manifest, usually, but not always, directed toward foods high in fat and/or sugar (Kaplan, 1996). The study of foods as *substances* that can be abused is in its early stages. However, it has been shown that rats exposed to the so-called "cafeteria diet" (composed of numerous nutrient combinations in the form of common palatable foods like bacon, cheesecake, and chocolate) develop an apparent compulsivity toward palatable food consumption, a process which may mirror impaired control – a hallmark of addictive behavior (Johnson and Kenny, 2010).

Impaired control is a common phenomenon seen in addictive behaviors. Besides an increased motivation to work for a food reward after extended access to the rewarding substance, rats will seek the reward, even when it is signaled to them that the reward is unavailable. Moreover, after an extended history of cocaine

self-administration, rats will continue to press a lever to obtain a cocaine infusion when a tone is presented that is previously associated with a foot shock (Deroche-Gamonet et al., 2004; Pelloux et al., 2007; Vanderschuren and Everitt, 2004). When compared to cocaine, rats are less motivated to work for a chocolate drink and in contrast to cocaine will not seek the chocolate drink when a tone is presented that was previously associated with a foot shock, even after being exposed to palatable diets for 2 months (de Jong et al., 2013; but see: Johnson and Kenny, 2010). Although some rats may display a tendency to display addictive-like behaviors, exposure to palatable foods high in fat and sugar, did not result increase these behaviors as observed after extended access to cocaine (de Jong et al., 2013).

4.1. Sugar addiction

In all aerobic cells, sugars are subjected to glycolysis to produce pyruvate – the fundamental substrate used to generate chemical energy in the citric acid cycle. As such, mono-, di- and polysaccharides are essential components of our diet. Animals have specialized senses that allow them to readily detect the presence of mono- and disaccharides in potential food sources, and humans perceive these substances as sweet. Rats also prefer sweet-tasting sugar solutions, and solutions of artificial sweeteners perceived as having equivalent sweetness, across a broad range of concentrations without prior training (Sclafani, 1987). Thus, there seems to be an innate (or a quickly learned) motivation to consume sweet foods.

Apart from a single case study (Thornley and McRobbie, 2009), addiction-related behaviors in sugar consumption (such as tolerance and a withdrawal syndrome) have not been observed in humans (Benton, 2010). Instead, most observational and mechanistic evidence for addiction to sugar comes from rat models pioneered in Bart Hoebel's laboratory (Avena et al., 2008). A variety of subtly different approaches have been taken, but most studies involve examining feeding behavior during intermittent access to palatable sugar solutions. For example, repeated 12 h food deprivation followed by 12 h intermittent access to normal food and a sugar solution leads to sugar "binging" (defined operationally as an increased intake compared to rats offered unrestricted access over the same time period). Furthermore, there is evidence that endogenous opioid signaling is active during sugar (but not fat; Bocarsly et al., 2011) binging, as i.p. administration of the opioid receptor antagonist, naloxone, results in somatic effects reminiscent of a withdrawal syndrome (Colantuoni et al., 2002). It was suggested that sugar recruits endogenous opioid pathways, with consequences analogous to those that follow consumption of drugs of abuse. However, these data do not imply that these pathways are being activated by a *substance*. Certain *behaviors* can also recruit endogenous opioid systems. For example, rats subjected to food restriction and given 1hr/day access to a running wheel show a withdrawal syndrome on naloxone administration, whereas much weaker withdrawal-like behaviors were seen in food-restricted or pair-fed rats *not* given access to a running wheel (Kanarek et al., 2009). The underlying endocrine mechanisms relevant in this model which has been used to explain the hyperactivity of patients with acute anorexia nervosa go well beyond the opioid system and include an activation of the hypothalamus-pituitary-adrenal axis induced via hypoleptinemia (Hebebrand et al., 2003); adrenalectomy (Duclos et al., 2009) or exogenous application of leptin (Exner et al., 2000) prevents the development of hyperactivity upon food restriction. This complex model indicates that the combination of an environmental effect (running wheel) with a specific temporal pattern of food restriction entails both a specific behavior (hyperactivity) and profound neuroendocrine alterations that include the engagement of the endogenous opioid system in a manner analogous to opiate drugs of abuse. Thus, under specific conditions addictive-like responses may be attributed not just to substances but also to behaviors. Alternatively, a behavior may become addictive because of the system(s) it activates. In the context of sugar addiction, a *behavioral* addiction rather than an addiction to a *substance* also warrants consideration as an explanation for the observations made in the respective experiments.

Other models that evoke binging include a diet and stress model where cycles of food restriction and refeeding with palatable food are paired with acute stressors (Hagan et al., 2002). Given that this model explicitly uses a stressor and others use regular food deprivation (also a physiological stressor), these paradigms may represent a form of stress-evoked eating (Maniam and Morris, 2012). It is worth noting that in most of these sugar addiction models rats do not become obese. These rats down-regulate their energy intake from other sources and maintain a stable body weight (Avena et al., 2012), leading to the hypothesis that sugar addiction in humans – if it occurs at all – may not be relevant for the development of obesity. Since normal food intake is reduced after binges and weight gain does not occur, homeostatic mechanisms are preserved, it could be argued that these paradigms may better represent a form of binge-eating driven by intermittent access to hedonic stimuli.

In humans, addictive behavior is often accompanied by complex psychological/psychiatric constructs like memory, boredom, shame, guilt, habit, impulsivity, restraint, depression and anxiety. Undoubtedly, these contribute to behavioral addiction but this further layer of complexity is difficult to model in rats (Packard, 2009). Based on a rat model for cocaine-craving behavior (Grimm et al., 2001), Grimm and co-workers showed that rats responded to a tone + light cue previously associated with 10% sucrose self-administration; lever pressing during tests for resistance to extinction and cue-induced reinstatement of sucrose seeking in rats progressively increased over the first 2 months of withdrawal (Grimm et al., 2002). Environmental enrichment such as grouping four animals in a large environment with novel objects has been shown to strongly attenuate cue-induced reinstatement of sucrose seeking (Grimm et al., 2008). The beneficial effect of an enriched environment on substance addiction in rodents has led Solinas and coworkers (2008) to suggest that in addition to cognitive and behavioral interventions to target craving-inducing situations, a positive and stimulating environment per se could facilitate abstinence.

4.2. Fat addiction

Maintenance of normal body function requires an adequate daily intake of fat, and the general advice is that a healthy diet should contain about 20–35% fat (Institute of Medicine, 2005). Of note, fat content in the diet improves the palatability of food, through taste, texture and oro-sensory experience in most mammals, including humans, who generally prefer high-fat food to low-fat food. It is unclear to what extent dietary fat is a basic tastant; fatty acid chemoreception has been observed in humans (Newman et al., 2013). Although the evidence is incomplete, it is thought that dietary lipids are detected by a combination of oro-sensory perception, retronasal olfactory and post-ingestive cues (Mizushige et al., 2007). Deciphering the chemical and molecular network within the oral cavity, gastrointestinal tract, hormonal signals and the CNS, all of which are implicated in the palatability and perception of dietary lipids remains as a major challenge.

Because the central effects of many signals involved in energy homeostasis, including leptin, ghrelin, MCH and GLP-1, are markedly influenced by intake of high fat diets, the occurrence of addictive-like behaviors in animals exposed to these diets is not surprising. Mice exposed to ad libitum fat-rich food exhibit signs of anxiety and willingness to endure an aversive environment in order to gain access to the high-fat food, as well as neurochemical

changes in signals related to reward (Teegarden and Bale, 2007; Teegarden et al., 2008). Mice exposed to preferred diets high in fat have decreased stress sensitivity, whereas acute withdrawal from such a diet elevates the stress state and reduces reward (Teegarden and Bale, 2007; Teegarden et al., 2008).

Experiments with binge-type overeating similar to that described above for sugar have been undertaken by different groups. Although some of the neurochemical changes elicited by fat binging appear to be similar to changes elicited by sugar intake (e.g. dopamine release in the NAc; Liang et al., 2006), no signs of opiate-like withdrawal in fat-binging rats were detected (Avena, 2010). In contrast, rats identified as prone to binge-eating will tolerate higher levels of foot shock when it is paired with a fat-containing food, suggesting that binge eating can be associated with an abnormal motivation to consume palatable food (Avena, 2010). The effects appear to depend on the experimental model, being more evident when rats are exposed to calorie restriction or stress exposure (Pankevich et al., 2010). Again, the same limitations apply as described above in relation to sucrose. Finally, and in contrast to sugar addiction models, an important confounding factor is that high-fat diets lead to weight gain and increased adiposity. Therefore, in some instances it is difficult to ascertain which changes are just a consequence of increased adiposity and weight, and which are specifically associated with the intake of fat-rich diets.

4.3. Salt addiction

Salt improves flavor perception and so-called "hidden" salt is often added to foods in relatively high amounts before they reach the table; this even applies to foods perceived by consumers as healthy (Magriplis et al., 2011). Often, despite containing no calories, salt is consumed beyond physiological need. In a healthy individual excess salt intake can be diluted by additional fluid intake, while ultimately the kidneys eliminate excess sodium (and excess water) in urine through natriuretic and diuretic mechanisms. Thus salt intake stimulates fluid intake – and if the most readily available and palatable fluid is energy dense, this can contribute to increased calorie intake. Accordingly if salt itself were addictive, this might promote excessive calorie intake, either directly (by promoting intake of salty energy-dense foods) or as an epiphenomenon (by promoting intake of energy dense fluids).

Evidence for an innate Na^+ (but not NaCl) appetite is very strong in rats. It is driven by hypotonic fluid intake or electrolyte loss, and is a distinct homeostatic process, involving well-defined brain regions – notably the subfornical organ, and specific endogenous neuropeptide messengers (Bertino and Tordoff, 1988). However, the role of salt in increasing directly the rewarding value of food is relatively unexplored. An aversion to high concentrations of dietary salt in rats can be reversed by Na^+-depletion, via mechanisms involving activation of the reward pathway (Robinson and Berridge, 2013). A μ-opioid receptor agonist increases salt consumption after infusion into the NAc (Zhang and Kelley, 2002) and salt consumption competes with electrical stimulation of the lateral hypothalamus in a forced-choice preference test in Na^+-depleted rats (Conover et al., 1994). However, an increased taste preference for salt is not observed in Na^+-depleted rats (Clark and Bernstein, 2006) and lesions of VTA dopamine neurons does not alter Na^+ consumption in Na^+-replete rats (Shibata et al., 2009). Thus it is possible that salt reward may occur only in the depleted state and reflects changes in motivation rather than an increased preference for a salty taste.

In contrast to rats, Na^+-deficient humans do not generally seek to increase their salt intake (Leshem, 2009). Whereas humans have a strong preference for sweet tastes, a strong salt preference may not be innate to humans. Very young children do not discriminate between isotonic salt solutions and water suggesting either that they do not detect salt or that they find the solutions equally palatable. However, a preference toward salt solutions develops in young children only to then disappear between the ages of 3 and 5. From this age on, humans do not find simple salt solutions palatable but rather aversive (Beauchamp et al., 1986). Thus, a strong salt preference is not evident across most of the life-span. As with sweet or fat tasting foods the distinct enjoyment of salty flavored foods in many humans may result from conditioned learning in association with other flavor preferences, rather than having a hedonic drive to consume salt or Na^+. Some rodent studies describe a link between salt intake and reward centers in the brain, but there is little evidence that salt has reinforcing properties unless in conditions of salt depletion (Berridge et al., 1984; Tekol, 2006). Perhaps the distinct enjoyment of salty flavored foods in humans is a result of conditioned learning in association with other flavor preferences, rather than having a hedonic drive to consume salt or Na^+. Nonetheless, it is unclear whether salt can increase the rewarding properties of food and what physiological consequences this might have.

5. Conclusions

The term 'food addiction' is now a part of everyday language. Vocabulary such as "chocoholic" (in use since the 1960s) and "craving" – used to refer to a person's desire and fondness for food – is in common use, and many people believe these conditions approach the severity of an addiction (Bird et al., 2013). Undoubtedly, some people believe that their relationship with problem foods constitutes an addiction, and engage with treatment regimens or approach help groups such as Food Addicts Anonymous – established in 1987. With addiction-related terminology in common use, and treatment, support and recipe books available for "food addicts" it is unsurprising that the media have accepted "food addiction" as fact, with one broadcaster (BBC), for example, having more than 40 news stories related to "food addiction" on its website.

We concur with Hone-Blanchet and Fecteau (2014) that it is premature to conclude validity of the food addiction phenotype in humans from the current behavioral and neurobiological evidence gained in rodent models. Humans who overeat usually do not restrict their diets to specific nutrients; instead the availability of a wider range of palatable foods appears to render prone subjects vulnerable to overeating. Undoubtedly, the food industry needs to act responsibly given that easy access to highly palatable and calorie dense foods promotes overeating and potentially the development of an "eating addiction" in predisposed individuals. It may ultimately be for governments to take action and regulate the food industry, by requesting informative labels and restricting advertising (Bagaric and Erbacher, 2005). At the same time, the medical field, and in particular psychiatry and clinical psychology, should continue to research "eating addiction". In retrospect, the medicalization of tobacco use has proven extremely important in promoting large scale, individual-based, and structural prevention programs, which have successfully led to a reduction in the proportion of adolescents and adults who smoke (Schaap et al., 2008; Levy et al., 2010; White et al., 2011).

To conclude, the society as a whole should be aware of the differences between addiction in the context of substance use versus an addictive behavior. As we pointed out in this review, there is very little evidence to indicate that humans can develop a "Glucose/Sucrose/Fructose Use Disorder" as a diagnosis within the DSM-5 category Substance Use Disorders. We do, however, view both rodent and human data as consistent with the existence of addictive eating behavior. The new DSM-5 (APA, 2013) currently does not allow the classification of an "Overeating Disorder" or an "Addictive Eating Disorder" within the diagnostic category

Substance-Related and Addictive Disorders; indeed, the current knowledge of addictive eating behaviors does not warrant such a diagnosis. However, efforts should be made to operationalize the diagnostic criteria for such a disorder and to test its reliability and validity. It needs to be determined if such a disorder can occur distinct from other mental disorders.

Currently, the assessment of "food addiction" mainly relies on the YFAS questionnaire, which is based on the diagnostic criteria of substance dependence according to DSM-IV (Gearhardt et al., 2009). In our opinion, the term "Eating Addiction" or "Addictive Eating Disorder" would have been more appropriate to avoid the unsubstantiated connotation that food contains chemical substances that can lead to the development of a *Substance Use Disorder*. We have pointed out that the mere application of the criteria used to define substance dependence does not likely appear sufficient to fully capture the phenomenological aspects of an eating addiction. As illustrated above, we are aware of the vague distinctions between substance-based and behavioral-based addictions. Nevertheless, we view the current evidence as being more in favor of addictive-like behaviors to describe the phenomenon of continuous overeating of a variety of foods.

We perceive the need to disentangle the mechanisms underlying an "eating addiction" with and without obesity. The differentiation of subjects who overeat due to increased hunger and/or a reduced satiety from those with an "eating addiction" appears difficult; research is required to uncover biological, physiological, and psychological differences. Obviously, twin and family studies are required to assess heritability of "eating addiction" (or different subgroups of "eating addiction"). Given the increasing number of gene variants known to contribute to the variance in body mass index (BMI; kg/m^2) in the general population, it will be of interest to genotype normal weight and obese subjects with and without "eating addiction" to assess whether the frequencies of relevant alleles differ. As progress is made in uncovering alleles predisposing to diverse substance use disorders or addictive disorders, the overlap with "eating addiction" can be assessed.

Although the scientific discussion about "eating addiction" is in its infancy, it has a potentially large public health impact on treatment and prevention strategies. Ultimately, politicians and industrial stakeholders need to be involved in finding solutions to overcome the potential risk of becoming "eating addicted" to industrially processed food highly enriched with carbohydrates, salt or fat. Given that the "food addiction genie" is out of the bottle, the best strategy may be to engage with the public in a debate centering on addictive behavior as a cause of overeating and obesity. We must make clear that there is no evidence that "food addiction" can be considered as a *Substance Use Disorder*. We agree with Stice and coworkers (2013), who have recently suggested that it might be more useful to focus on overeating as a form of food 'abuse'; however, as pointed out above, the diagnosis of a (substance) abuse has been dropped in DSM-V. Stressing "food addiction" as an addiction to eating must be viewed critically, because this focus does not convey an unambiguous and helpful message that is supported by available evidence. Accordingly, we believe that a diagnosis of "eating addiction" is superior to "food addiction" for educational purposes. "Eating addiction" stresses the behavioral component, whereas "food addiction" appears more like a passive process which simply befalls an individual.

Acknowledgements

This review has been compiled by scientists of the NeuroFAST consortium (The Integrated Neurobiology of Food Intake, Addiction and Stress; www.neurofast.eu), a research program that aims to reveal neurobiological and psychological mechanisms underlying habit-forming addictive processes related to the overconsumption of highly palatable food. The research leading to these results has received funding from the European Union's Seventh Framework programme for research, technological development and demonstration under grant agreement no. 245009.

References

Aberman, J.E., Ward, S.J., Salamone, J.D., 1998. Effects of dopamine antagonists and accumbens dopamine depletions on time-constrained progressive-ratio performance. Pharmacol. Biochem. Behav. 61, 341–348.
Ackroff, K., Yiin, Y.M., Sclafani, A., 2010. Post-oral infusion sites that support glucose-conditioned flavor preferences in rats. Physiol. Behav. 99, 402–411.
Albayrak, O., Wölfle, S.M., Hebebrand, J., 2012. Does food addiction exist? A phenomenological discussion based on the psychiatric classification of substance-related disorders and addiction. Obes. Facts 5, 165–179.
Alsiö, J., Olszewski, P.K., Levine, A.S., Schiöth, H.B., 2012. Feed-forward mechanisms: addiction-like behavioral and molecular adaptations in overeating. Front. Neuroendocrinol. 33, 127–139.
American Psychiatric Association, 2000. Diagnostic and Statistical Manual of Mental Disorders, fourth ed. (text rev.). American Psychiatric Association, Washington, DC.
American Psychiatric Association, 2013. Diagnostic and Statistical Manual of Mental Disorders, fifth ed. American Psychiatric Association, Washington, DC.
Avena, N.M., 2010. The study of food addiction using animal models of binge eating. Appetite 55, 734–737.
Avena, N.M., Rada, P., Hoebel, B.G., 2008. Evidence for sugar addiction: behavioral and neurochemical effects of intermittent, excessive sugar intake. Neurosci. Biobehav. Rev. 32, 20–39.
Avena, N.M., Bocarsly, M.E., Hoebel, B.G., 2012. Animal models of sugar and fat bingeing: relationship to food addiction and increased body weight. Methods Mol. Biol. 829, 351–365.
Bagaric, M., Erbacher, S., 2005. Fat and the law: who should take the blame? J. Law Med. 12, 323–339.
Barbano, M.F., Cador, M., 2007. Opioids for hedonic experience and dopamine to get ready for it. Psychopharmacology (Berl.) 191, 497–506.
Beauchamp, G.K., Cowart, B.J., Moran, M., 1986. Developmental changes in salt acceptability in human infants. Dev. Psychobiol. 19, 17–25.
Bellisle, F., Drewnowski, A., Anderson, G.H., Westerterp-Plantenga, M., Martin, C.K., 2012. Sweetness, satiation, and satiety. J. Nutr. 142, S1149–S1154.
Benton, D., 2010. The plausibility of sugar addiction and its role in obesity and eating disorders. Clin. Nutr. 29, 288–303.
Berridge, K.C., 1996. Food reward: brain substrates of wanting and liking. Neurosci. Biobehav. Rev. 20, 1–25.
Berridge, K.C., Flynn, F.W., Schulkin, J., Grill, H.J., 1984. Sodium depletion enhances salt palatability in rats. Behav. Neurosci. 98, 652–660.
Berthoud, H.R., 2011. Metabolic and hedonic drives in the neural control of appetite: who is the boss? Curr. Opin. Neurobiol. 21, 888–896.
Bertino, M., Tordoff, M.G., 1988. Sodium depletion increases rats' preferences for salted food. Behav. Neurosci. 102, 565–573.
Bird, S.P., Murphy, M., Bake, T., Albayrak, O., Mercer, J.G., 2013. Getting science to the citizen – 'food addiction' at the British Science Festival as a case study of interactive public engagement with high profile scientific controversy. Obes. Facts 6, 103–108.
Bocarsly, M.E., Berner, L.A., Hoebel, B.G., Avena, N.M., 2011. Rats that binge eat fat-rich food do not show somatic signs or anxiety associated with opiate-like withdrawal: implications for nutrient-specific food addiction behaviors. Physiol. Behav. 104, 865–872.
Boender, A.J., de Jong, J.W., Boekhoudt, L., Luijendijk, M.C., van der Plasse, G., Adan, R.A., 2014. Combined use of the canine adenovirus-2 and DREADD-technology to activate specific neural pathways in vivo. PLOS ONE 9, e95392.
Bradley, B.P., 1990. Behavioral addictions: common features and treatment implications. Br. J. Addict. 85, 1417–1419.
Brown, C.H., Stern, J.E., Jackson, K.L., Bull, P.M., Leng, G., Russell, J.A., 2005. Morphine withdrawal increases intrinsic excitability of oxytocin neurons in morphine-dependent rats. Eur. J. Neurosci. 21, 501–512.
Brownell, K.D., Gold, M.S., 2013. Food and addiction: scientific, social, legal, and legislative implications. In: Brownell, K.D., Gold, M.S. (Eds.), Food and Addiction. Oxford University Press, Oxford, pp. 439–446.
Burmeister, J.M., Hinman, N., Koball, A., Hoffmann, D.A., Carels, R.A., 2013. Food addiction in adults seeking weight loss treatment. Implications for psychosocial health and weight loss. Appetite 60, 103–110.
Clark, J.J., Bernstein, I.L., 2006. Sensitization of salt appetite is associated with increased wanting "but not liking" of a salt reward in the sodium-deplete rat. Behav. Neurosci. 120, 206–210.
Clark, S.M., Saules, K.K., 2013. Validation of the Yale Food Addiction Scale among a weight-loss surgery population. Eat Behav. 14, 216–219.
Cohen, J.Y., Haesler, S., Vong, L., Lowell, B.B., Uchida, N., 2012. Neuron-type-specific signals for reward and punishment in the ventral tegmental area. Nature 482, 85–88.
Colantuoni, C., Rada, P., McCarthy, J., Patten, C., Avena, N.M., Chadeayne, A., Hoebel, B.G., 2002. Evidence that intermittent, excessive sugar intake causes endogenous opioid dependence. Obes. Res. 10, 478–488.

Conover, K.L., Woodside, B., Shizgal, P., 1994. Effects of sodium depletion on competition and summation between rewarding effects of salt and lateral hypothalamic stimulation in the rat. Behav. Neurosci. 108, 549–558.
Davis, C., 2013. From passive overeating to "food addiction": a spectrum of compulsion and severity. ISRN Obes. 2013, 435027.
Davis, C., Curtis, C., Levitan, R.D., Carter, J.C., Kaplan, A.S., Kennedy, J.L., 2011. Evidence that 'food addiction' is a valid phenotype of obesity. Appetite 57, 711–717.
Davis, C., Loxton, N.J., Levitan, R.D., Kaplan, A.S., Carter, J.C., Kennedy, J.L., 2013. 'Food addiction' and its association with a dopaminergic multilocus genetic profile. Physiol. Behav. 118, 63–69.
de Jong, J.W., Meijboom, K.E., Vanderschuren, L.J., Adan, R.A., 2013. Low control over palatable food intake in rats is associated with habitual behavior and relapse vulnerability: individual differences. PLOS ONE 8, e74645.
Deroche-Gamonet, V., Belin, D., Piazza, P.V., 2004. Evidence for addiction-like behavior in the rat. Science 305, 1014–1017.
Dickson, S.L., Shirazi, R.H., Hansson, C., Bergquist, F., Nissbrandt, H., Skibicka, K.P., 2012. The glucagon-like peptide 1 (GLP-1) analogue, exendin-4, decreases the rewarding value of food: a new role for mesolimbic GLP-1 receptors. J. Neurosci. 32, 4812–4820.
Domingos, A.I., Vaynshteyn, J., Voss, H.U., Ren, X., Gradinaru, V., Zang, F., Deisseroth, K., de Araujo, I.E., Friedman, J., 2011. Leptin regulates the reward value of nutrient. Nat. Neurosci. 14, 1562–1568.
Duclos, M., Gatti, C., Bessière, B., Mormède, P., 2009. Tonic and phasic effects of corticosterone on food restriction-induced hyperactivity in rats. Psychoneuroendocrinology 34, 436–445.
Egecioglu, E., Skibicka, K.P., Hansson, C., Alvarez-Crespo, M., Friberg, P.A., Jerlhag, E., Engel, J.A., Dickson, S.L., 2011. Hedonic and incentive signals for body weight control. Rev. Endocr. Metab. Disord. 12, 141–151.
Eichen, D.M., Lent, M.R., Goldbacher, E., Foster, G.D., 2013. Exploration of "food addiction" in overweight and obese treatment-seeking adults. Appetite 67, 22–24.
Epstein, L.H., Temple, J.L., Roemmich, J.N., Bouton, M.E., 2009. Habituation as a determinant of human food intake. Psychol. Rev. 116, 384–407.
Everitt, B.J., Robbins, T.W., 2005. Neural systems of reinforcement for drug addiction: from actions to habits to compulsion. Nat. Neurosci. 8, 1481–1489.
Exner, C., Hebebrand, J., Remschmidt, H., Wewetzer, C., Ziegler, A., Herpertz, S., Schweiger, U., Blum, W.F., Preibisch, G., Heldmaier, G., Klingenspor, M., 2000. Leptin suppresses semi-starvation induced hyperactivity in rats: implications for anorexia nervosa. Mol. Psychiatry 5, 476–481.
Farooqi, I.S., Bullmore, E., Keogh, J., Gillard, J., O'Rahilly, S., Fletcher, P.C., 2007. Leptin regulates striatal regions and human eating behaviour. Science 317, 1355.
Feng, Y., He, X., Yang, Y., Chao, D., Lazarus, L.H., Xia, Y., 2012. Current research on opioid receptor function. Curr. Drug Targets 13, 230–246.
Figlewicz, D.P., Bennett, J.L., Aliakbari, S., Zavosh, A., Sipols, A.J., 2008. Insulin acts at different CNS sites to decrease acute sucrose intake and sucrose self-administration in rats. Am. J. Physiol. Regul. Integr. Comp. Physiol. 295, R388–R394.
Finucane, M.M., Stevens, G.A., Cowan, M.J., Danaei, G., Lin, J.K., Paciorek, C.J., Singh, G.M., Gutierrez, H.R., Lu, Y., Bahalim, A.N., Farzadfar, F., Riley, L.M., Ezzati, M., Global Burden of Metabolic Risk Factors of Chronic Diseases Collaborating Group (Body Mass Index), 2011. National, regional, and global trends in body-mass index since 1980: systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9.1 million participants. Lancet 377, 557–567.
Flint, A.J., Gearhardt, A.N., Corbin, W.R., Brownell, K.D., Field, A.E., Rimm, E.B., 2014. Food-addiction scale measurement in 2 cohorts of middle-aged and older women. Am. J. Clin. Nutr. 99, 578–586.
Fulton, S., Pissios, P., Manchon, R.P., Stiles, L., Frank, L., Pothos, E.N., Maratos-Flier, E., Flier, J.S., 2006. Leptin regulation of the mesoaccumbens dopamine pathway. Neuron 51, 811–822.
Gearhardt, A.N., Corbin, W.R., Brownell, K.D., 2009. Preliminary validation of the Yale Food Addiction Scale. Appetite 52, 430–436.
Gearhardt, A.N., Grilo, C.M., DiLeone, R.J., Brownell, K.D., Potenza, M.N., 2011. Can food be addictive? Public health and policy implications. Addiction 106, 1208–1212.
Gearhardt, A.N., White, M.A., Masheb, R.M., Morgan, P.T., Crosby, R.D., Grilo, C.M., 2012. An examination of the food addiction construct in obese patients with binge eating disorder. Int. J. Eat. Disord. 45, 657–663.
Gearhardt, A.N., White, M.A., Masheb, R.M., Grilo, C.M., 2013a. An examination of food addiction in a racially diverse sample of obese patients with binge eating disorder in primary care settings. Compr. Psychiatry 54, 500–505.
Gearhardt, A.N., Roberto, C.A., Seamans, M.J., Corbin, W.R., Brownell, K.D., 2013b. Preliminary validation of the Yale Food Addiction Scale for children. Eat. Behav. 14, 508–512.
Gosnell, B.A., Lane, K.E., Bel l, S.M., Krahn, D.D., 1995. Intravenous morphine self-administration by rats with low versus high saccharin preferences. Psychopharmacology (Berl.) 117, 248–252.
Grant, B.F., Stinson, F.S., Dawson, D.A., Chou, S.P., Dufour, M.C., Compton, W., Pickering, R.P., Kaplan, K., 2004. Prevalence and co-occurrence of substance use disorders and independent mood and anxiety disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. Arch. Gen. Psychiatry 61, 807–816.
Grimm, J.W., Hope, B.T., Wise, R.A., Shaham, Y., 2001. Incubation of cocaine craving after withdrawal. Nature 412, 141–142.
Grimm, J.W., Shaham, Y., Hope, B.T., 2002. Effect of cocaine and sucrose withdrawal period on extinction behavior, cue-induced reinstatement, and protein levels of the dopamine transporter and tyrosine hydroxylase in limbic and cortical areas in rats. Behav. Pharmacol. 13, 379–388.
Grimm, J.W., Osincup, D., Wells, B., Manaois, M., Fyal l, A., Buse, C., Harkness, J.H., 2008. Environmental enrichment attenuates cue-induced reinstatement of sucrose seeking in rats. Behav. Pharmacol. 19, 777–785.
Hagan, M.M., Wauford, P.K., Chandler, P.C., Jarrett, L.A., Rybak, R.J., Blackburn, K., 2002. A new animal model of binge eating: key synergistic role of past caloric restriction and stress. Physiol. Behav. 77, 45–54.
Hebebrand, J., Exner, C., Hebebrand, K., Holtkamp, C., Casper, R.C., Remschmidt, H., Herpertz-Dahlmann, B., Klingenspor, M., 2003. Hyperactivity in patients with anorexia nervosa and in semistarved rats: evidence for a pivotal role of hypoleptinemia. Physiol. Behav. 79, 25–37.
Hinney, A., Hebebrand, J., 2008. Polygenic obesity in humans. Obes. Facts 1, 35–42.
Hone-Blanchet, A., Fecteau, S., 2014. Overlap of food addiction and substance use disorders definitions: analysis of animal and human studies. Neuropharmacology 85C, 81–90.
Hruby, V.J., Agnes, R.S., 1999. Conformation-activity relationships of opioid peptides with selective activities at opioid receptors. Biopolymers 51, 391–410.
Institute of Medicine, 2005. Dietary Reference Intakes for Energy, Carbohydrate. Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids. http://www.nal.usda.gov/fnic/DRI/DRI_Energy/energy_full_report.pdf
Jansen, J.M., Daams, J.G., Koeter, M.W., Veltman, D.J., van den Brink, W., Goudriaan, A.E., 2013. Effects of non-invasive neurostimulation on craving: a meta-analysis. Neurosci. Biobehav. Rev. 37, 2472–2480.
Johnson, P.M., Kenny, P.J., 2010. Dopamine D2 receptors in addiction-like reward dysfunction and compulsive eating in obese rats. Nat. Neurosci. 13, 635–641.
Kanarek, R.B., D'Anci, K.E., Jurdak, N., Mathes, W.F., 2009. Running and addiction: precipitated withdrawal in a rat model of activity-based anorexia. Behav. Neurosci. 123, 905–912.
Kaplan, R., 1996. Carrot addiction. Aust. N. Z. J. Psychiatry 30, 698–700.
Kawai, K., Sugimoto, K., Nakashima, K., Miura, H., Ninomiya, Y., 2000. Leptin as a modulator of sweet taste sensitivities in mice. Proc. Natl. Acad. Sci. U. S. A. 97, 11044–11049.
Kelley, A.E., Bakshi, V.P., Haber, S.N., Steininger, T.L., Will, M.J., Zhang, M., 2002. Opioid modulation of taste hedonics within the ventral striatum. Physiol. Behav. 76, 365–377.
Kelly, E., 2013. Ligand bias at the μ-opioid receptor. Biochem. Soc. Trans. 41, 218–224.
Koch, T., Höllt, V., 2008. Role of receptor internalization in opioid tolerance and dependence. Pharmacol. Ther. 117, 199–206.
Koob, G.F., 2013. Theoretical frameworks and mechanistic aspects of alcohol addiction: alcohol addiction as a reward deficit disorder. Curr. Top. Behav. Neurosci. 13, 3–30.
Lenoir, M., Serre, F., Cantin, L., Ahmed, S.H., 2007. Intense sweetness surpasses cocaine reward. PLoS ONE 2, e698.
Lent, M.R., Eichen, D.M., Goldbacher, E., Wadden, T.A., Foster, G.D., 2014. Relationship of food addiction to weight loss and attrition during obesity treatment. Obesity (Silver Spring) 22, 52–55.
Leshem, M., 2009. Biobehavior of the human love of salt. Neurosci. Biobehav. Rev. 33, 1–17.
Levy, D.T., Mabry, P.L., Graham, A.L., Orleans, C.T., Abrams, D.B., 2010. Reaching healthy people 2010 by 2013: a SimSmoke simulation. Am. J. Prev. Med. 38, S373–S381.
Liang, N.C., Hajnal, A., Norgren, R., 2006. Sham feeding corn oil increases accumbens dopamine in the rat. Am. J. Physiol. Regul. Integr. Comp. Physiol. 291, R1236–R1239.
Magriplis, E., Farajian, P., Pounis, G.D., Risvas, G., Panagiotakos, D.B., Zampelas, A., 2011. High sodium intake of children through 'hidden' food sources and its association with the Mediterranean diet: the GRECO study. J. Hypertens. 29, 1069–1076.
Maniam, J., Morris, M.J., 2012. The link between stress and feeding behaviour. Neuropharmacology 63, 97–110.
Martin, B., Dotson, C.D., Shin, Y.K., Ji, S., Drucker, D.J., Maudsley, S., Munger, S.D., 2009. Modulation of taste sensitivity by GLP-1 signalling in taste buds. Ann. N. Y. Acad. Sci. 1170, 98–101.
Mason, S.M., Flint, A.J., Field, A.E., Austin, S.B., Rich-Edwards, J.W., 2013. Abuse victimization in childhood or adolescence and risk of food addiction in adult women. Obesity (Silver Spring) 21, E775–E781.
Mechoulam, R., Parker, L.A., 2013. The endocannabinoid system and the brain. Annu. Rev. Physiol. 64, 21–47.
Meule, A., 2012. Food addiction and body-mass-index: a non-linear relationship. Med. Hypotheses 79, 508–511.
Meule, A., Kübler, A., 2012. Food cravings in food addiction: the distinct role of positive reinforcement. Eat. Behav. 13, 252–255.
Meule, A., Hecke l, D., Kübler, A., 2012. Factor structure and item analysis of the Yale Food Addiction Scale in obese candidates for bariatric surgery. Eur. Eat. Disord. Rev. 20, 419–422.
Mizushige, T., Inoue, K., Fushiki, T., 2007. Why is fat so tasty? Chemical reception of fatty acid on the tongue. J. Nutr. Sci. Vitaminol. (Tokyo) 53, 1–4.
Morrissey, J., Keogh, B., Doyle, L., 2008. Psychiatric Mental Health Nursing. Gill & Macmillan Ltd., Dublin.
Mueser, K.T., Drake, R.E., Wallach, M.A., 1998. Dual diagnosis: a review of etiological theories. Addict. Behav. 23, 717–734.
Murphy, C.M., Stojek, M.K., MacKillop, J., 2014. Interrelationships among impulsive personality traits, food addiction, and Body Mass Index. Appetite 73, 45–50.

Narayanan, N.S., Guarnieri, D.J., DiLeone, R.J., 2010. Metabolic hormones, dopamine circuits, and feeding. Front. Neuroendocrinol. 31, 104–112.
Newman, L., Haryono, R., Keast, R., 2013. Functionality of fatty acid chemoreception: a potential factor in the development of obesity? Nutrients 5, 1287–1300, NIDA: www.nida.nih.gov/scienceofaddiction/sciofaddiction.pdf
Norgren, R., Hajnal, A., Mungarndee, S.S., 2006. Gustatory reward and the nucleus accumbens. Physiol. Behav. 89, 531–535.
Ogden, C.L., Carroll, M.D., Kit, B.K., Flegal, K.M., 2012. Prevalence of obesity in the United States, 2009–2010. NCHS Data Brief 82, 1–8.
Oliveira-Maia, A.J., Roberts, C.D., Walker, Q.D., Luo, B., Kuhn, C., Simon, S.A., Nicolelis, M.A., 2011. Intravascular food reward. PLoS ONE 6, e24992.
Olszewski, P.K., Alsiö, J., Schiöth, H.B., Levine, A.S., 2011. Opioids as facilitators of feeding: can any food be rewarding? Physiol. Behav. 104, 105–110.
Packard, M.G., 2009. Anxiety, cognition, and habit: a multiple memory systems perspective. Brain Res. 1293, 121–128.
Pankevich, D., Teegarden, S.L., Hedin, A.D., Jensen, C.L., Bale, T.L., 2010. Caloric restriction experience reprograms stress and orexegenic pathways and promotes binge-eating. J. Neurosci. 30, 16399–16407.
Peciña, S., 2008. Opioid reward 'liking' and 'wanting' in the nucleus accumbens. Physiol. Behav. 94, 675–680.
Peciña, S., Smith, K.S., Berridge, K.C., 2006. Hedonic hot spots in the brain. Neuroscientist 12, 500–511.
Pedram, P., Wadden, D., Amini, P., Gulliver, W., Randell, E., Cahill, F., Vasdev, S., Goodridge, A., Carter, J.C., Zhai, G., Ji, Y., Sun, G., 2013. Food addiction: its prevalence and significant association with obesity in the general population. PLoS ONE 8, e74832.
Pelloux, Y., Everitt, B.J., Dickinson, A., 2007. Compulsive drug seeking by rats under punishment: effects of drug taking history. Psychopharmacology (Berl.) 194, 127–137.
Peukert, P., Sieslack, S., Barth, G., Batra, A., 2010. Internet and computer game addiction. Psychiatr. Prax. 37, 219–224.
Planeta, C.S., 2013. Animal models of alcohol and drug dependence. Rev. Bras. Psiquiatr. 35, S140–S146.
Randolph, T.G., 1956. The descriptive features of food addiction; addictive eating and drinking. Q. J. Stud. Alcohol 17, 198–224.
Robinson, M.J., Berridge, K.C., 2013. Instant transformation of learned repulsion into motivational "wanting". Curr. Biol. 23, 282–289.
Roitman, M.F., Stuber, G.D., Phillips, P.E., Wightman, R.M., Carelli, R.M., 2004. Dopamine operates as a subsecond modulator of food seeking. J. Neurosci. 24, 1265–1271.
Salamone, J.D., Correa, M., 2012. The mysterious motivational functions of mesolimbic dopamine. Neuron 76, 470–485.
Saunders, B.T., Robinson, T.E., 2013. Individual variation in resisting temptation: implications for addiction. Neurosci. Biobehav. Rev. 37, 1955–1975.
Schaap, M.M., Kunst, A.E., Leinsalu, M., Regidor, E., Ekholm, O., Dzurova, D., Helmert, U., Klumbiene, J., Santana, P., Mackenbach, J.P., 2008. Effect of nationwide tobacco control policies on smoking cessation in high and low educated groups in 18 European countries. Tob. Control 17, 248–255.
Schultz, W., 2010. Dopamine signals for reward value and risk: basic and recent data. Behav. Brain Funct. 6, 24.
Schultz, W., Dayan, P., Montague, P.R., 1997. A neural substrate of prediction and reward. Science 275, 1593–1599.
Sclafani, A., 1987. Carbohydrate taste, appetite, and obesity: an overview. Neurosci. Biobehav. Rev. 11, 131–153.
Shibata, R., Kameishi, M., Kondoh, T., Torii, K., 2009. Bilateral dopaminergic lesions in the ventral tegmental area of rats influence sucrose intake, but not umami and amino acid intake. Physiol. Behav. 96, 667–674.
Skibicka, K.P., Hansson, C., Egecioglu, E., Dickson, S.L., 2012a. Role of ghrelin in food reward: impact of ghrelin on sucrose self-administration and mesolimbic dopamine and acetylcholine receptor gene expression. Addict. Biol. 17, 95–107.
Skibicka, K.P., Shirazi, R.H., Hansson, C., Dickson, S.L., 2012b. Ghrelin interacts with neuropeptide Y Y1 and opioid receptors to increase food reward. Endocrinology 153, 1194–1205.
Skibicka, K.P., Shirazi, R.H., Rabasa-Papio, C., Alvarez-Crespo, M., Neuber, C., Vogel, H., Dickson, S.L., 2013. Divergent circuitry underlying food reward and intake effects of ghrelin: dopaminergic VTA-accumbens projection mediates ghrelin's effect on food reward but not food intake. Neuropharmacology 73, 274–283.
Smith, D.G., Robbins, T.W., 2013. The neurobiological underpinnings of obesity and binge eating: a rationale for adopting the food addiction model. Biol. Psychiatry 73, 804–810.
Smolka, M., Schmidt, L.G., 1999. The influence of heroin dose and route of administration on the severity of the opiate withdrawal syndrome. Addiction 94, 1191–1198.
Solinas, M., Chauvet, C., Thiriet, N., El Rawas, R., Jaber, M., 2008. Reversal of cocaine addiction by environmental enrichment. Proc. Natl. Acad. Sci. U. S. A. 105, 17145–17150.
Spence, C., 2012. Auditory contributions to flavour perception and feeding behaviour. Physiol. Behav. 107, 505–515.
Steinberg, E.E., Keiflin, R., Boivin, J.R., Witten, I.B., Deisseroth, K., Janak, P.H., 2013. A causal link between prediction errors, dopamine neurons and learning. Nat. Neurosci. 16, 966–973.
Stafford, K., Gomes, A.B., Shen, J., Yoburn, B.C., 2001. Mu-Opioid receptor downregulation contributes to opioid tolerance in vivo. Pharmacol. Biochem. Behav. 69, 233–237.
Stephens, D.N., Crombag, H.S., Duka, T., 2013. The challenge of studying parallel behaviors in humans and animal models. Curr. Top Behav. Neurosci. 13, 611–645.
Stice, E., Figlewicz, D.P., Gosnell, B.A., Levine, A.S., Pratt, W.E., 2013. The contribution of brain reward circuits to the obesity epidemic. Neurosci. Biobehav. Rev. 37, 2047–2058.
Stuber, G.D., Klanker, M., de Ridder, B., Bowers, M.S., Joosten, R.N., Feenstra, M.G., Bonci, A., 2008. Reward-predictive cues enhance excitatory synaptic strength onto midbrain dopamine neurons. Science 321, 1690–1692.
Sussman, S., Sussman, A.N., 2011. Considering the definition of addiction. Int. J. Environ. Res. Public Health 8, 4025–4038.
Szczypka, M.S., Kwok, K., Brot, M.D., Marck, B.T., Matsumoto, A.M., Donahue, B.A., Palmiter, R.D., 2001. Dopamine production in the caudate putamen restores feeding in dopamine-deficient mice. Neuron 30, 819–828.
Tanofsky-Kraff, M., Ranzenhofer, L.M., Yanovski, S.Z., Schvey, N.A., Faith, M., Gustafson, J., Yanovski, J.A., 2008. Psychometric properties of a new questionnaire to assess eating in the absence of hunger in children and adolescents. Appetite 51, 148–155.
Teegarden, S.L., Bale, T.L., 2007. Decreases in dietary preference produce increased emotionality and risk for dietary relapse. Biol. Psychiatry 61, 1021–1029.
Teegarden, S.L., Nestler, E.J., Bale, T.L., 2008. Delta FosB-mediated alterations in dopamine signaling are normalized by a palatable high-fat diet. Biol. Psychiatry 64, 941–950.
Tekol, Y., 2006. Salt addiction: a different kind of drug addiction. Med. Hypotheses 67, 1233–1234.
Thornley, S., McRobbie, H., 2009. Carbohydrate withdrawal: is recognition the first step to recovery? N. Z. Med. J. 122, 133–134.
Ueda, H., Ueda, M., 2009. Mechanisms underlying morphine analgesic tolerance and dependence. Front. Biosci. 14, 5260–5272.
van Zessen, R., van der Plasse, G., Adan, R.A., 2012. Contribution of the mesolimbic dopamine system in mediating the effects of leptin and ghrelin on feeding. Proc. Nutr. Soc. 71, 435–445.
Vanderschuren, L.J., Everitt, B.J., 2004. Drug seeking becomes compulsive after prolonged cocaine self-administration. Science 305, 1017–1019.
Vannucci, A., Tanofsky-Kraff, M., Crosby, R.D., Ranzenhofer, L.M., Shomaker, L.B., Field, S.E., Mooreville, M., Reina, S.A., Kozlosky, M., Yanovski, S.Z., Yanovski, J.A., 2013. Latent profile analysis to determine the typology of disinhibited eating behaviors in children and adolescents. J. Consult. Clin. Psychol. 81, 494–507.
Volkow, N.D., O'Brien, C.P., 2007. Issues for DSM-V: should obesity be included as a brain disorder? Am. J. Psychiatry 164, 708–710.
Volkow, N.D., Wang, G.J., Tomasi, D., Baler, R.D., 2013. Obesity and addiction: neurobiological overlaps. Obes. Rev. 14, 2–18.
Wang, J.C., Kapoor, M., Goate, A.M., 2012. The genetics of substance dependence. Annu. Rev. Genomics Hum. Genet. 13, 241–261.
Welte, J.W., Barnes, G.M., Tidwell, M.C., Hoffman, J.H., 2008. The prevalence of problem gambling among U.S. adolescents and young adults: results from a national survey. J. Gambl. Stud. 24, 119–133.
Wesson, D.R., Ling, W., 2003. The Clinical Opiate Withdrawal Scale (COWS). J. Psychoactive Drugs 35, 253–259.
White, V.M., Warne, C.D., Spittal, M.J., Durkin, S., Purcell, K., Wakefield, M.A., 2011. What impact have tobacco control policies, cigarette price and tobacco control programme funding had on Australian adolescents' smoking? Findings over a 15-year period. Addiction 106, 1493–1502.
Whiteford, H.A., Degenhardt, L., Rehm, J., Baxter, A.J., Ferrari, A.J., Erskine, H.E., Charlson, F.J., Norman, R.E., Flaxman, A.D., Johns, N., Burstein, R., Murray, C.J., Vos, T., 2013. Global burden of disease attributable to mental and substance use disorders: findings from the Global Burden of Disease Study 2010. Lancet 382, 1575–1586.
Williams, J.T., Ingram, S.L., Henderson, G., Chavkin, C., von Zastrow, M., Schulz, S., Koch, T., Evans, C.J., Christie, M.J., 2013. Regulation of μ-opioid receptors: desensitization, phosphorylation, internalization, and tolerance. Pharmacol. Rev. 65, 223–254.
World Health Organization, 2003. Addiction. In: Wilkinson, R.G., Marmot, M.G. (Eds.), Social Determinants of Health: The Solid Facts. World Health Organization, Denmark, pp. 24–25.
Xue, Y.X., Luo, Y.X., Wu, P., Shi, H.S., Xue, L.F., Chen, C., Zhu, W.L., Ding, Z.B., Bao, Y.P., Shi, J., Epstein, D.H., Shaham, Y., Lu, L., 2012. A memory retrieval-extinction procedure to prevent drug craving and relapse. Science 336, 241–245.
Zhang, M., Kelley, A.E., 2002. Intake of saccharin, salt, and ethanol solutions is increased by infusion of a mu opioid agonist into the nucleus accumbens. Psychopharmacology (Berl.) 159, 415–423.