Q1 Review

Neuroimaging and neuromodulation approaches to study eating behavior and prevent and treat eating disorders and obesity

Q2

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ABSTRACT

Functional, molecular and genetic neuroimaging has highlighted the existence of brain anomalies and neural vulnerability factors related to obesity and eating disorders such as binge eating or anorexia nervosa. In particular, decreased basal metabolism in the prefrontal cortex and striatum as well as dopaminergic alterations have been described in obese subjects, in parallel with increased activation of reward brain areas in response to palatable food cues. Elevated reward region responsivity may trigger food craving and predict future weight gain. This opens the way to prevention studies using functional and molecular neuroimaging to perform early diagnostics and to phenotype subjects at risk by exploring different neurobehavioral dimensions of the food choices and motivation processes. In the first part of this review, advantages and limitations of neuroimaging techniques, such as functional magnetic resonance imaging (fMRI), positron emission tomography (PET), single photon emission computed tomography (SPECT), pharmacogenetic fMRI and functional near-infrared spectroscopy (fNIRS) will be discussed in the context of recent work dealing with eating behavior, with a particular focus on obesity. In the second part of the review, non-invasive strategies to modulate food-related brain processes and functions will be presented. At the leading edge of non-invasive brain-based technologies is real-time fMRI (rtfMRI) neurofeedback, which is a powerful tool to better understand the complexity of human brain–behavior relationships. rtfMRI, alone or when combined with other techniques and tools such as EEG and cognitive therapy, could be used to alter neural plasticity and learned behavior to optimize and/or restore healthy cognition and eating behavior. Other promising non-invasive neuromodulation approaches being explored are repetitive transcranial magnetic stimulation (rTMS) and transcranial direct-current stimulation (tDCS). Converging evidence points at the value of these non-invasive neuromodulation strategies to study basic mechanisms underlying eating behavior and to treat its disorders. Both of these approaches will be compared in light of recent work in this field, while addressing technical and practical questions. The third part of this review will be dedicated to invasive neuromodulation strategies, such as vagus nerve stimulation (VNS) and deep brain stimulation (DBS). In combination with neuroimaging approaches, these techniques are promising experimental tools to unravel the

intricate relationships between homeostatic and hedonic brain circuits. Their potential as additional therapeutic tools to combat pharmacorefractory morbid obesity or acute eating disorders will be discussed, in terms of technical challenges, applicability and ethics. In a general discussion, we will put the brain at the core of fundamental research, prevention and therapy in the context of obesity and eating disorders. First, we will discuss the possibility to identify new biological markers of brain functions. Second, we will highlight the potential of neuroimaging and neuromodulation in individualized medicine. Third, we will introduce the ethical questions that are concomitant to the emergence of new neuromodulation therapies.

Contents

1. Introduction

A recent study estimated the number of overweight adults in the world as roughly 2.1 billion in 2013 (Ng et al., 2014). In the United States alone, obese individuals have 42% higher health care costs than those with healthy-weight (Finkelstein et al., 2009). Obesity is on the rise, with severe obesity rising at a particularly alarming rate (Flegal et al., 2010; Finkelstein et al., 2012). Because obesity is a multifactorial condition with a complex etiology, and because success of interventions is subject to a large interindividual variability, there is no panacea or "one-fit-all" treatment for obesity. Bariatric surgery (BS) is the treatment of choice for severe obesity due to its effectiveness compared to

behavioral and pharmacological interventions (Buchwald and Oien, 2013). Its utility and success rate is widely accepted. However, 20–40% of those who undergo BS fail to lose sufficient weight (Christou et al., 2006; Livhits et al., 2012) or regain significant weight after treatment (Magro et al., 2008; DiGiorgi et al., 2010; Adams et al., 2012), and can experience a number of complications during and after surgery or medical and psychiatric comorbidities (Shah et al., 2006; Karlsson et al., 2007; DiGiorgi et al., 2010; Bolen et al., 2012; Chang et al., 2014). In addition to existing methods such as BS, which annually helps thousands of people worldwide, there is a clear need for novel approaches to obesity prevention and treatment, including the development of novel diagnostic and phenotyping methods, as well as adjunctive therapies

that may lead to better treatment outcomes for patients who may require invasive procedures such as BS. In comparison to the rising obesity epidemic, eating disorders (ED) are scarcer but also certainly underestimated and increasing at a startling state (Makino et al., 2004). In the United States, up to 24 million people across all ages and genders suffer from ED (anorexia — AN, bulimia — BN and binge eating disorder — BED) (Renfrew Center Foundation for Eating Disorders, 2003), and only 1 in 10 people with ED receives treatment (Noordenbox, 2002), even though ED have the highest mortality rate of any mental illness (Sullivan, 1995). Epidemiology of ED was described in details (including risk factors, incidence, prevalence, and morbidity) in recent reviews (see Smink et al., 2012; Mitchison and Hay, 2014).

In the fight against obesity and eating disorders, improved knowledge about the pathophysiological and neurobehavioral mechanisms underlying these diseases is needed to better prevent risky behaviors, diagnose and treat patients, and develop new therapies that are safer and adjustable to each patient. As noted by Schmidt and Campbell (2013), treatment of eating disorders cannot remain 'brainless', and the same applies to obesity when we consider the growing amount of literature highlighting the behavioral and brain changes/plasticity induced by obesity (Wang et al., 2009b; Burger and Berner, 2014), effective bariatric surgery (Geliebter, 2013; Scholtz et al., 2014), and neuromodulatory interventions (McClelland et al., 2013a; Gorgulho et al., 2014) in animal models and human subjects.

Although several excellent review papers on this subject exist (see McClelland et al., 2013a; Sizonenko et al., 2013; Burger and Berner, 2014; Gorgulho et al., 2014), a comprehensive work comparing a large spectrum of exploratory and therapeutic strategies using neuroimaging and neuromodulation technologies, in terms of advantages and limitations, degree of invasiveness, and applicability to individualized medicine from prevention to treatment is missing and can help provide a road map for future research and applications. Predictive and prevention studies benefiting from neuroimaging are emerging thanks to the characterization of neural vulnerability factors that increase risk for weight gain and risky eating behaviors. The first part of our review will be dedicated to this question, as well as to the role of functional, nuclear, and genetic neuroimaging in fundamental research and prevention programs. A particular focus will be put on obesity, because it is the number one concern, though references to specific ED will be included when relevant. In this first part we will also review for the first time the contribution of a less costly and more portable cortical functional neuroimaging tool (i.e. fNIRS) in the context of research on eating behavior. The second part of our review will provide an overview of the non-invasive neuromodulatory approaches to combat weight problems and ED, including a presentation of real-time fMRI neurofeedback coupled with cognitive therapy, as well as a comparison between transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS). The third section will be dedicated to more invasive neuromodulatory approaches to modulate homeostatic and hedonic mechanisms through the stimulation of the vagus nerve or deep-brain structures. Finally, we will discuss all the data presented in the perspective of obesity/ED phenotyping and individualized medicine, while addressing the ethical questions raised by new therapeutic approaches and their promise.

2. Utility of neuroimaging to investigate eating behavior and elucidate risk and maintenance factors for weight gain and eating disorders: towards new phenotyping and prevention strategies

2.1. Predicting future weight gain and maintenance on the basis of neural responsivity and functioning

An improved understanding of the risk processes that give rise to excess weight gain should guide the design of more effective preventive programs and treatments, which is vital because extant interventions, with the possible exception of bariatric surgery, have limited efficacy.

Theorists have focused on the reward circuitry because eating palatable food increases activation in regions implicated in reward in both humans and other animals, including the ventral and dorsal striatum, midbrain, amygdala, and orbitofrontal cortex (OFC: Small et al., 2001; Avena et al., 2006; Berridge, 2009; Stice et al., 2013) and causes dopamine (DA) release in the dorsal striatum, with the amount released correlating with meal pleasantness (Small et al., 2003) and caloric density of the food (Ferreira et al., 2012) in humans. Both the orosensory properties of palatable food consumption (gustatory stimulation) and direct intragastric infusion of high calorie food induce striatal DA release in reward regions in human and animal studies (Avena et al., 2006; Tellez et al., 2013).

2.1.1. Reward surfeit and incentive sensitization theories of obesity

The reward surfeit model holds that individuals with greater reward region responsivity to food intake are at elevated risk for overeating (Stice et al., 2008b). The incentive sensitization model posits that repeated intake of palatable foods results in an elevated responsivity of reward regions to cues that are associated with palatable food intake via conditioning, prompting elevated food intake when these cues are encountered (Berridge et al., 2010). According to animal studies, firing of striatal and ventral pallidum DA neurons initially occurs in response to receipt of a novel palatable food, but after repeated pairings of palatable food intake and cues that signal impending receipt of that food, DA neurons begin firing in response to reward-predictive cues and no longer fire in response to food receipt (Schultz et al., 1997; Tobler et al., 2005). Elevated reward-related responses to food intake and cues putatively override homeostatic processes of satiety, promoting excess weight gain.

The present review focuses on prospective studies because cross-sectional data cannot differentiate precursors from consequences of overeating, with a focus on human studies unless otherwise indicated. Hyper-responsivity of reward regions (striatum, amygdala, OFC) to palatable food images (Demos et al., 2012), palatable food television commercials (Yokum et al., 2014), geometric cues that signal impending palatable food image presentation (Yokum et al., 2011), palatable food odors that predict impending palatable food receipt (Chouinard-Decorte et al., 2010; Sun et al., 2013), and pictorial cues that predict impending palatable food receipt (Stice et al., 2015) predicted future weight gain. Humans who show elevated dorsal striatum responsivity to palatable food images show greater future weight gain, but only if they are at genetic risk for higher DA signaling capacity due to possessing an A2/A2 genotype of the *TaqIA* polymorphism or a 6-repeat or shorter of the 48-base pair exon 3 variable number tandem repeat (VNTR) polymorphism of the DRD4 gene (Stice et al., 2010b), which are both associated with greater DA signaling and reward region responsivity (Jonsson et al., 1999; Bowirrat and Oscar-Berman, 2005). The evidence from independent laboratories that elevated reward region responsivity to various food cues, including those that predict impending palatable food receipt, predicted future weight gain provides behavioral support for the incentive sensitization theory.

Elevated midbrain, thalamus, hypothalamus, and ventral striatum responsivity to milk shake taste also predicted future weight gain (Geha et al., 2013; Sun et al., 2013). Further, individuals who show elevated dorsal striatum responsivity to palatable food intake show greater future weight gain, but only if they are at genetic risk for elevated DA signaling capacity by virtue of possessing an A2/A2 genotype of the *TaqIA* polymorphism (Stice et al., 2008a; Stice et al., 2015). The evidence that individuals who show elevated reward region responsivity to palatable food intake are more likely to enter a prolonged period of positive energy balance and gain weight provides behavioral data in support of the reward surfeit theory.

Although extant data provide support for both the incentive sensitization and reward surfeit theories of obesity, which are not mutually exclusive, future studies should simultaneously examine individual differences in neural response to palatable food taste, cues that signal

impending palatable food taste, and palatable food images to provide a more comprehensive investigation of neural vulnerability factors that predict future weight gain. Results imply that prevention programs that reduce habitual intake of high-calorie foods should attenuate the conditioning process that eventually leads to elevated reward region responsivity to food cues, which may reduce future weight gain. Yet, the fact that behavioral weight loss programs typically result in a transient reduction of high-calorie food intake, but do not produce sustained weight loss implies that it is very difficult to reduce reward region hyper-responsivity to food cues once it has emerged. An uncontrolled study suggested that humans who have been able to sustain their weight loss over long periods of time carefully limit intake of high-calorie foods, exercise daily, and monitor their weight (Wing and Phelan, 2005), implying that it would be useful to test whether interventions that increase executive control, either by direct modification of brain–behavior function or indirectly by modification of the environment, which could offset the risk from elevated reward region responsivity, result in more lasting weight loss.

2.1.2. Reward deficit theory of obesity

The reward deficit model of obesity posits that individuals with lower sensitivity of DA-based reward regions overeat to compensate for this deficiency (Wang et al., 2002). There have only been a few prospective fMRI studies that could have potentially determined whether reduced reward region responsivity preceded weight gain, and there have not been any prospective studies that assessed with DA functioning (e.g. assessed with PET) predicted future weight change. Out of the six prospective studies that examined the relation of BOLD response to palatable food images, cues that signal impending palatable food receipt, and actual palatable food receipt to future weight gain reviewed above (Chouinard-Decorte et al., 2010; Yokum et al., 2011; Demos et al., 2012; Geha et al., 2013; Yokum et al., 2014; Stice et al., 2015), none found a relation between reduced reward region responsivity to these food stimuli and greater future weight gain. Interestingly, however, a prospective study found that young adults who showed lower recruitment of striatal regions in response to milk shake receipt (Stice et al., 2008b, 2015) and palatable food images (Stice et al., 2010b) showed greater future weight gain if they had a genetic propensity for reduced DA signaling capacity. The interactive effects imply that there may be qualitatively distinct reward surfeit and reward deficit pathways to obesity, which should be investigated further.

Obese versus lean adults have shown lower striatal DA D2 receptor availability (Volkow et al., 2008; de Weijer et al., 2011; Kessler et al., 2014) and less striatal responsivity to high-calorie beverage taste (Stice et al., 2008b). Interestingly, Guo et al. (2014) also suggested that obese people have alterations in the DA neurocircuitry that may increase their susceptibility to opportunistic overeating while at the same time making food intake less rewarding, less goal directed and more habitual. Whether the observed neurocircuitry alterations pre-exist or occur as a result of obesity development is still controversial, but considerable evidence suggests that overeating contributes to a down-regulation of the DA-based reward circuitry. Lean younger subjects at risk for future obesity due to parental obesity show hyper- rather than hypo-responsivity of reward regions to palatable food receipt (Stice et al., 2011). Women who gained weight over a 6-month period showed a reduction in striatal responsivity to palatable food receipt relative to baseline and to women who remained weight stable (Stice et al., 2010a). Rats randomized to overeating conditions that result in weight gain versus control conditions show a down-regulation of post-synaptic D2 receptors, and reduced D2 sensitivity, extracellular DA levels in the nucleus accumbens and DA turnover, and lower sensitivity of DA reward circuitry (Kelley et al., 2003; Davis et al., 2008; Geiger et al., 2009; Johnson and Kenny, 2010). Minipigs randomized to a weight gain intervention versus a stable weight condition showed reduced prefrontal cortex, midbrain and nucleus accumbens resting activity (Val-Laillet et al., 2011). The reduced DA signaling capacity appears to occur because habitual intake of high-fat diets causes decreased synthesis of oleoylethanolamide, a gastrointestinal lipid messenger (Tellez et al., 2013). Interestingly, people who report elevated intake of a particular food show reduced striatal response during intake of that food, independent of BMI (Burger and Stice, 2012; Green and Murphy, 2012; Rudenga and Small, 2012).

Geiger et al. (2009) hypothesized that diet-induced down-regulation of the DA circuitry may prompt overeating to increase DA signaling. Yet, mice in which reduced striatal DA signaling from food intake was experimentally induced through chronic intragastric infusion of fat worked less for acute intragastric infusion of fat and consumed less rat chow ad lib than control mice (Tellez et al., 2013). Further, genetically engineered DA-deficient mice are unable to sustain appropriate levels of feeding (Sotak et al., 2005). These data seem incompatible with the notion that an induced down-regulation of DA reward circuitry leads to compensatory overeating. The Tellez et al. (2013) study also provided further evidence that intake of fat can result in reduced DA response to food intake, independent of weight gain per se.

2.1.3. Inhibitory control

Vulnerabilities in reward sensitivity, habit, and inhibitory control appear to interact to produce prolonged hyperphagia of highly palatable foods leading to the development and maintenance of obesity (Appelhans et al., 2011). By extension, lower activation of prefrontal-parietal brain regions implicated in inhibitory control, may lead to greater sensitivity to the rewarding effects of highly palatable foods and greater susceptibility to the pervasive temptation of appetizing foods in our environment, which increases overeating in the absence of meeting homeostatic energy needs (Nederkoorn et al., 2006). In fact, this pattern of food intake behavior appears to occur with only a limited role for homeostatic input in modulating obesogenic food intake behavior (Hall et al., 2014). Inefficient or underdeveloped inhibitory control function may increase the risk for obesity in early childhood at a time when rapid development is occurring in subcortical and prefrontal–parietal brain systems that support reward and inhibitory control functions (see Reinert et al., 2013; Miller et al., 2015 for recent reviews). In addition, obesity-related alterations in adipokines, inflammatory cytokines, and gut hormones may lead to further disruption in neurodevelopment, especially in reward and inhibitory control functions, which may increase the risk for poor academic performance and even dementia risk in later life (Miller et al., 2015). For example, obese versus lean teens showed less activation of prefrontal regions (dorsolateral prefrontal cortex [dlPFC], ventral lateral prefrontal cortex [vlPFC]) when trying to inhibit responses to high-calorie food images and behavioral evidence of reduced inhibitory control (Batterink et al., 2010) and adults who had greater dlPFC activation when instructed to "resist craving" while viewing food images had better weight loss success following gastric bypass surgery (Goldman et al., 2013). Another study found that participants who showed less recruitment of inhibitory control regions (inferior, middle, and superior frontal gyri) during difficult versus easy choices on a delay discounting task showed elevated future weight gain (Kishinevsky et al., 2012; $r = 0.71$); however, individual differences in delay discounting behavior did not explain weight outcomes (Stoeckel et al., 2013b). These results converge with evidence that obese versus lean adults showed reduced gray mater volume in the prefrontal cortex (Pannacciulli et al., 2006), a region that modulates inhibitory control, and with a marginal trend for reduced gray matter volume in the prefrontal cortex to predict weight gain over 1-year follow-up (Yokum et al., 2011). Interestingly, obese versus lean humans also showed less recruitment of inhibitory regions (ventral medial prefrontal cortex [vmPFC]) in response to high-calorie food images (Silvers et al., 2014) and high-calorie food TV commercials (Gearhardt et al., 2014). Further, lower dlPFC response to high-calorie food images predicted greater ad lib food intake over the next 3 days (Cornier et al., 2010). These findings are noteworthy because all but the results from the Batterink, Kishinevsky, and Stoeckel studies emerged in paradigms lacking a behavioral response

component. In some instances (Kishinevsky et al., 2012; Stoeckel et al., 2013b), the neuroimaging data were a better predictor of weight outcomes than the behavioral measure. This example highlights the future potential for "neuromarkers" to improve outcome prediction and individualize intervention strategies to improve weight outcomes (Gabrieli et al., 2015). Finally, it may also be possible to directly target and normalize these brain systems using several of the neuromodulatory tools and techniques described throughout this article, such as transcranial stimulation, to enhance treatment outcomes (Alonso-Alonso and Pascual-Leone, 2007).

2.1.4. Theoretical implications and future research directions

Thus, most prospective and experimental studies have not provided support for the reward deficit theory of obesity, and whereas available data suggest that the reduced DA signaling capacity of the reward circuitry may largely result from overeating, extent data provide little support for the notion that this contributes to compensatory overeating. Yet, there is emerging evidence that there may be qualitatively distinct reward surfeit and reward deficit pathways to obesity that are based on individual differences in genes that affect DA signaling and reward region responsivity to palatable food receipt, implying that it might be useful to refine our working model regarding neural vulnerability factors that contribute to obesity. According to what might be referred to as the *dual pathway model of obesity*, we posit that individuals in the *reward surfeit pathway* initially show hyper-responsivity of reward, gustatory, and oral somatosensory regions to palatable food intake, which increases habitual intake of energy dense foods. The reward surfeit pathway might be more likely for those at genetic risk for greater DA signaling capacity. Habitual intake of palatable foods theoretically leads to the development of hyper-responsivity of attention and reward valuation regions to cues that predict food reward through conditioning (Berridge, 2009), which maintains overeating because exposure to ubiquitous food cues results in craving that prompts eating. Data suggest that the hyper-responsivity of reward regions to palatable food intake contributes to more pronounced cue-reward learning, which increases risk for future weight gain (Burger and Stice, 2014). We further submit that overeating results in a down-regulation of DA-based reward regions, producing a blunted striatal response to food intake that emerges with obesity, but that this may not contribute to further escalation in eating. We also theorize deficits in inhibitory control increase the risk for overeating, and further that overeating leads to a subsequent reduction in inhibitory response to food stimuli, which may also contribute to future escalation in overeating. This prediction is based on evidence that individuals exhibit greater inhibitory control deficits in response to frequently versus infrequently experienced rewards; obese versus lean individuals show a greater immediate reward bias to food stimuli but not monetary reward (Rasmussen et al., 2010). In contrast, individuals in the *reward deficit pathway*, which may be more likely for those with a genetic propensity for lower DA-signaling capacity, might consume more calories per eating episode because the weaker DA-signaling may attenuate feelings of satiety, as reward regions project to the hypothalamus. It is possible that the weaker DA-signaling of reward regions attenuates the effects of gut peptides that relay satiety. It is also possible that the lower DA signaling and reward region responsivity operates through a completely different process, such as by reducing physical activity because these individuals might find exercise less rewarding, contributing to a positive energy balance. More broadly, data imply that too much or too little reward circuitry responsivity, which is referred to as the *Goldilocks Principle*, serves to disrupt homeostatic processes that have evolved to promote sufficient, but not excessive caloric intake. This notion would be consistent with an allostatic load model.

With regard to future research, additional large prospective brain imaging studies should seek to identify neural vulnerability factors that predict future weight gain. Second, environmental, social, and biological factors, including genotypes, that moderate the effects of these vulnerability factors on future weight gain should be examined in more detail. Third, additional prospective repeated-measures studies should attempt to capture the plasticity of reward region responsivity to food images/cues and food receipt, which appears to results from overeating. Randomized controlled experiments could be used to address these research questions, allowing much stronger inferences regarding these etiologic processes. It will also be important to expand research into other relevant neuropsychological functions (e.g. motivation, working memory, multisensory processing and integration, executive function), the neural systems that mediate these functions, their interaction with reward and homeostatic (i.e. hypothalamic, brainstem) brain systems, and how dysfunction in these neural systems and cognitive functions may impact reward and homeostatic functions in order to have a more unified brain–behavior model of food intake behavior (Berthoud, 2012; Hall et al., 2014). For example, inhibitory control and the fronto-parietal brain systems that mediate this function have been studied; however, there are other aspects of executive function (e.g. mental set shifting, information updating and monitoring; Miyake et al., 2000) that are mediated by dissociable, but overlapping regions of the fronto-parietal "executive" network and are understudied in the context of their relationship to food intake behavior. Finally, investigators should continue to translate findings from brain imaging studies into more effective obesity prevention and treatment interventions.

2.2. Dopaminergic imaging

As reviewed above, dopamine (DA) plays an important role in eating behavior. Understanding the neurocognitive mechanisms by which DA influences eating behavior is crucial for prediction, prevention and (pharmacological) treatment of obesity. To infer the involvement of the dopaminergic system, it is important to actually measure DA processing. Findings of increased metabolism or blood flow in a dopaminergic target region do not necessarily imply that DA is directly involved. For example, activation in the striatum could reflect opioid modulation of hedonic 'liking' instead of dopaminergic modulation of 'wanting' (Berridge, 2007). Here, we will go into more detail about results of studies directly investigating DA.

2.2.1. Nuclear tomographic imaging

Nuclear imaging techniques such as positron emission tomography (PET) and single photon emission computed tomography (SPECT) use radioactive tracers and detection of gamma rays to image tissue concentrations of molecules of interest (e.g. DA receptors). PET and SPECT have a very low temporal resolution (tens of seconds to minutes), usually requiring one imaging session for one data point, limiting the kind of research questions that can be targeted with these methods.

Table 1 provides an overview of dopaminergic PET and SPECT studies that have assessed differences as a function of BMI in humans. In line with a downregulation of dopamine signaling with obesity is the relation between lower dopamine synthesis capacity in the dorsal striatum and an elevated BMI (Wilcox et al., 2010; Wallace et al., 2014) and lower striatal DA D2/D3 receptor binding in obese versus lean individuals (Wang et al., 2001; Haltia et al., 2007; Volkow et al., 2008; de Weijer et al., 2011; Kessler et al., 2014; van de Giessen et al., 2014). However, others have found positive associations between striatal D2/D3 receptor binding and BMI (Dunn et al., 2012; Caravaggio et al., 2015), or no association (Eisenstein et al., 2013). From the above-mentioned studies it is also unclear whether differences in DA processing reflect a cause or a consequence of an increased BMI. Some have touched upon this question by assessing changes in DA D2/D3 receptor binding after bariatric surgery and significant weight loss. While one study found increases and the other found decreases in receptor binding after surgery (Dunn et al., 2010; Steele et al., 2010), a study with a larger sample did not find any significant changes (de Weijer et al., 2014).

Another way to investigate the involvement of DA in obesity is to assess changes in extracellular DA levels induced by a psychostimulant or

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Table 1

Summary of studies using SPECT or PET for dopaminergic imaging in lean, overweight or obese human subjects.

Subjects, status	Radioligand	Marker for	Challenge	Main findings	References
SPECT studies					
$n = 15$ obese (BMI 43 ± 5) vs. $n = 15$ non-obese (BMI 22 ± 2)	[123I] iodobenzamide (IBZM)	DA D2/3R	2 sessions[a]: after amphetamine vs. baseline	Obese individuals had lower striatal DA D2/3R binding than controls at baseline; increases in extracellular dopamine were correlated with enhanced trait food craving in obese individuals	van de Giessen et al. (2014)
$n = 19$ bariatric surgery patients (BMI 46 ± 6 before and 41 ± 6 after)	[123I] iodobenzamide (IBZM)	DA D2/3R	None	No significant changes in striatal DA D2/3R binding before vs. 6 weeks after bariatric surgery were found; and no correlation with BMI before or after surgery	de Weijer et al. (2014)
$n = 123$ (BMI 18–41)	[(123)I]FP-CIT	DAT	None	No association between striatal DAT binding and BMI was found	van de Giessen et al. (2013)
$n = 33$ (BMI 21–50)	[123I] PE2I	DAT	None	No association between striatal DAT binding and BMI was found	Thomsen et al. (2013)
$n = 15$ obese (BMI 47 ± 7) vs. $n = 15$ non-obese (BMI 22 ± 2)	[123I] iodobenzamide	DA D2/3R	None	Obese individuals had lower striatal DA D2/3R binding than controls	de Weijer et al. (2011)
$n = 50$ (BMI 19–31)	[99mTc]-TRODAT-1	DAT	None	Lower DAT binding in the striatum was correlated with a higher BMI	Chen et al. (2008)
PET studies					
$n = 13$ obese (BMI 37–49) $n = 24$ non-obese (BMI 23 ± 3)	[11C] carfentanil [11C] raclopride	μ-Opioid R DA D2/3R	None	No difference in D2/D3R availability between obese and non-obese women, but significantly reduced μ-opioid R availability in obese women	Karlsson et al. (2015)
$n = 19$ (BMI 21–35)	[11C] raclopride	DA D2/3R	2 sessions[a]: glucose (caloric) vs. sucralose (non-caloric)	Calorie-induced increases in extracellular dopamine in ventral striatum were correlated with a lower BMI	Wang et al. (2014)
$n = 16$ (BMI 20–33)	6-[18F]-Fluoro-L-m-Tyrosine (FMT)	AADC, DA synthesis	None	Lower dopamine synthesis in caudate nucleus was correlated with 1) greater BMI and 2) greater preference for perceived "healthy", but not actual healthy, foods (independent of BMI)	Wallace et al. (2014)
$n = 33$ ($n = 16$) (BMI 19–35)	[18F] fallypride	DA D2/3R	2 sessions ($n = 16$)[a]: after amphetamine vs. baseline	Lower DA D2/3R binding in caudate and amygdala was correlated with a higher BMI at baseline; amphetamine-induced increases in extracellular dopamine in putamen and substantia nigra were correlated with a higher BMI	Kessler et al. (2014)
$n = 15$ obese (BMI 33 − 47) vs. $n = 15$ non-obese (BMI 19–28)	(N-[(11)C methyl) benperidol ([(11) C] NMB)	DA D2R-specific, non-displaceable	None	No association between striatal DA D2 binding and BMI was found	Eisenstein et al. (2013)
$n = 26$ vs. $n = 35$ (BMI 19–28)	[11C]-(+)-PHNO vs. [11C] raclopride	DA D2/3R (agonist vs. antagonist)	None	Higher DA D2/3R binding in ventral striatum, as measured with [11C]-(+)-PHNO, was correlated with a higher BMI	Caravaggio et al. (2015)
$n = 14$ obese (BMI 40 ± 5) vs. $n = 8$ non-obese (BMI 23 ± 2)	[18F] fallypride	DA D2/3R	None	Lower DA D2/3R binding in caudate was correlated with a lower BMI	Dunn et al. (2012)
$n = 15$ (BMI 25)	6-[18F]-Fluoro-L-m-Tyrosine (FMT)	AADC, DA synthesis	None	Lower DA synthesis capacity in the dorsal striatum was correlated with a higher BMI (caudate) and increased weight loss attempts (putamen)	Wilcox et al. (2010)
$n = 5$ bariatric surgery patients (45 ± 6 before and 38 ± 7 after)	[11C] raclopride	DA D2/3R	None	Four out of five patients showed an increase in DA D2/3R binding in the striatum 6 weeks after bariatric surgery	Steele et al. (2010)
$n = 5$ bariatric surgery patients (BMI 43 ± 3 before and 38 ± 3 after)	[18F] fallypride	DA D2/3R	None	DA D2/3R binding in striatum, (hypo) thalamus, substantia nigra (corrected for multiple comparisons) and amygdala decreased 7 weeks after bariatric surgery	Dunn et al. (2010)
$n = 10$ obese (BMI 51 ± 5) vs. $n = 12$ non-obese (BMI 25 ± 3)	[11C] raclopride and [18F] fludeoxyglucose (FDG)	DA D2/3R; glucose	None	In obese individuals striatal D2/3R binding was lower than controls and was positively correlated with glucose metabolism in frontal and somatosensory cortices	Volkow et al. (2008)
$n = 12$ obese (BMI 33 ± 5) vs. $n = 12$ non-obese (BMI 22 ± 1)	[11C] raclopride	DA D2/3R	2 sessions[a]: after i.v. glucose vs. after i.v. placebo	Obese individuals had lower striatal DA D2/3R binding than controls; glucose increased extracellular striatal dopamine in men and reduced it in women	Haltia et al. (2007)
$n = 10$ obese (BMI 42–60) vs. $n = 10$ non-obese (BMI 21–28)	[11C] raclopride	DA D2/3R	None	Obese individuals had lower striatal DA D2/3R binding than controls; lower striatal DA D2/3R binding was correlated with a higher BMI in obese individuals	Wang et al. (2001)

BMI: body mass index (kg/m²); "x–x" reflects the range, and "x ± x" reflects the average ± standard deviation; PET: positron emission tomography; DA: dopamine; D2/3R: D2/D3 receptor;

[a] Increases in extracellular dopamine were observed as reductions in binding potential; DEBQ: Dutch Eating Behavior Questionnaire; i.v.: intravenous; SPECT: single photon emission tomography; DAT: dopamine transporter; AADC: aromatic l-amino acid decarboxylase; BED: binge eating disorder.

a food challenge (see Table 1). In such challenge studies, lower receptor binding is interpreted as greater release of endogenous DA leading to greater competition with the radioligand at the receptors. Challenge studies have observed that food- or psychostimulant-induced increases in extracellular striatal DA are associated with a lower BMI (Wang et al., 2014), a higher BMI (Kessler et al., 2014), or have found no differences between BMI groups (Haltia et al., 2007).

In sum, findings from nuclear imaging studies investigating differences in the striatal DA system as a function of BMI are very inconsistent. In an attempt to converge on one theory of dopaminergic hypoactivation in obesity, different authors have used different explanations for their results. For example, DA D2/D3 receptor binding has been interpreted to reflect DA receptor availability (e.g. Wang et al., 2001; Haltia et al., 2007; Volkow et al., 2008; de Weijer et al., 2011; van de Giessen et al., 2014), DA receptor affinity (Caravaggio et al., 2015), or competition with endogenous DA (Dunn et al., 2010; Dunn et al., 2012). Based on the data, it is often unclear whether such differences in interpretation are valid. In addition, a very recent study by Karlsson and colleagues showed a significant reduced μ-opioid receptor availability in obese compared to normal-weight women, without changes in D2-receptor availability, which might be an additional channel that might explain the inconsistent findings in a lot of other studies (Karlsson et al., 2015).

2.2.2. Genetic fMRI

By investigating the effects of common variations in DA genes the role of predisposed vulnerability can be determined. To date, there have only been a few studies that have combined genetics with neuroimaging in the domain of food reward. Most of them are functional magnetic resonance imaging (fMRI) studies.

Most genetic fMRI studies investigating food reward have taken into account a common variation (i.e. polymorphism) referred to as TaqIA, of which the A1 allele has been associated with BMI in several early genetic studies (Noble et al., 1994; Jenkinson et al., 2000; Spitz et al., 2000; Thomas et al., 2001; Southon et al., 2003). The TaqIA polymorphism is located in the *ANKK1* gene, ~10 kb downstream of the DRD2 gene (Neville et al., 2004). A1-allele carriers of the TaqIA polymorphism show reduced striatal D2R expression (Laruelle et al., 1998; Pohjalainen et al., 1998; Jonsson et al., 1999). Genetic fMRI studies have demonstrated that A1-carriers show decreased blood-oxygen-level-dependent (BOLD) responses in DA-rich regions in the brain (dorsal striatum, midbrain, thalamus, orbitofrontal cortex) when consuming a milk shake versus a tasteless solution relative to non-carriers (Stice et al., 2008a; Felsted et al., 2010). Importantly, these decreased responses for food reward consumption, as well as for imagined food intake, predicted future weight gain in the A1 risk allele carriers (Stice et al., 2008a; Stice et al., 2010b). This is in line with the idea that DA modulates the blunted response to food reward in obesity. In contrast, when anticipating a milk shake versus a tasteless solution, A1-carriers have demonstrated *increased* BOLD responses in the midbrain (Stice et al., 2012). A multilocus composite score of dopaminergic genotypes — including *ANKK1* and four others — did not predict decreased striatal responses for the consumption of food reward, but only for the receipt of monetary reward (Stice et al., 2012).

Thus, genetic fMRI studies suggest that individual differences in dopaminergic genes play a role in brain responses to food reward, but their effects are not always replicated and seem to depend on the anticipation or the consumption of food reward.

2.2.3. Future directions for dopaminergic imaging

Together, SPECT, PET, and genetic fMRI studies suggest that brain DA is involved in obesity. However, these neuroimaging findings are not easily interpreted as a simple hypo- or hyper-activation of the DA system in obesity. Moreover, there is an abundance of non-replications and null findings, possibly due to small sample sizes. In order to use dopaminergic imaging as a phenotyping method indicating vulnerability for obesity or for prediction of treatment efficacy, reliability should be increased. Genetic pathway analyses (e.g. Bralten et al., 2013) or genome wide association studies (e.g. El-Sayed Moustafa and Froguel, 2013; Stergiakouli et al., 2014) might be more sensitive and specific in revealing DA's role in obesity. In the context of personalized medicine, DA genetic fMRI studies could be combined with pharmacology (see Kirsch et al., 2006; Cohen et al., 2007; Aarts et al., 2015) to reveal the mechanisms of anti-obesity drugs as well as individual differences in treatment response.

Another reason for the observed inconsistencies might be that obesity (i.e. BMI) is too complex and unspecific as a phenotype (see also Ziauddeen et al., 2012), which is also evident from the fact that studies using polygenic risk scores have only obtained small associations with obesity phenotypes (e.g. Domingue et al., 2014). Neuroimaging studies might more clearly reveal dopaminergic effects when using cognitive paradigms that manipulate food motivation (i.e. effort provision) or the learning of cue-reward associations, as striatal DA is well known for its role in these processes (Robbins and Everitt, 1992; Schultz et al., 1997; Berridge and Robinson, 1998). Assessing task-related responses, however, is a challenge during PET and SPECT due to their low temporal resolution. Nevertheless, PET/SPECT measures could be related to offline task behavior (see, e.g. Wallace et al., 2014). Moreover, combinations of imaging modalities such as PET and fMRI holds a strong potential for future studies (see, e.g. Sander et al., 2013 in non-human primates), making optimal use of the specificity of PET and the temporal and spatial resolution of fMRI.

2.3. The contribution of functional near-infrared spectroscopy (fNIRS)

Unlike the other neuroimaging techniques, such as PET and fMRI, fNIRS does not require subjects to be in a supine position and does not strictly restrict head movements, thus allowing to adopt a wide range of experimental tasks suitable for properly investigating eating disorders and food intake/stimuli. In addition, fNIRS uses a relatively low cost instrumentation (with a sampling time in the order of the ms and a spatial resolution of up to about 1 cm). On the other hand, although EEG is a useful electrophysiological technique, its very low spatial resolution makes it difficult to precisely identify the activated areas of the brain, limiting its application to specific research questions related to eating disorders (Jauregui-Lobera, 2012). Recently, to deal with this problem EEG has been combined successfully with fMRI to overcome the spatial limitations of EEG and the temporal limitations of fMRI, using their complementary features (Jorge et al., 2014). The parallel or sequential use of EEG and fMRI in food related studies may provide additional insights into neural processing cascades. However, combined EEG–fMRI food related studies have not been reported yet. In conclusion, all the above mentioned advantages of using fNIRS and EEG offer the great promise to explore taste-related higher cognitive brain functions, which require tasks involving even the ingestion of food/beverages under more natural situations.

2.3.1. Brief overview of the principles, advantages and limitations of fNIRS

The principles, advantages, and limitations of fNIRS or optical topography or near-infrared (NIR) imaging have been summarized in recent reviews (Hoshi, 2011; Cutini et al., 2012; Ferrari and Quaresima, 2012; Scholkmann et al., 2014). fNIRS is a non-invasive vascular-based neuroimaging technology that measures concentration changes of oxygenated-hemoglobin (O_2Hb) and deoxygenated-hemoglobin (HHb) in cortical microcirculation blood vessels. fNIRS relies on neurovascular coupling to infer changes in neural activity that is mirrored by changes in blood oxygenation in the region of the activated cortical area (i.e. the increase in O_2Hb and the decrease in HHb). Unlike the BOLD signal of fMRI, which is gathered from the paramagnetic properties of HHb, the fNIRS signal is based on the changes in the intrinsic optical absorption of both HHb and O_2Hb (Steinbrink et al., 2006). fNIRS systems vary in

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Table 2
fNIRS cognitive processing studies in patients with eating disorders, as well as healthy subjects/patients upon food intake or food stimuli.

Food stimulus or food intake	Task (s)	Subjects, status	Age (years; mean $\pm$ SD)	Range (years)	Device	Ch	Cortical area	Main finding	References
Frontal cortex reactivity in patients with eating disorders									
n.u.	VFT; RPST	14, HC; 10, AN; 14, BN	24.1 $\pm$ 3.0; 26.1 $\pm$ 7.1	n.a.	D8	2	PFC	Higher dlPFC activation in BN	Sutoh et al. (2013)
n.u.	VFT; control: FOT	12, HC; 16, AN	14.3 $\pm$ 1.3; 14.2 $\pm$ 1.3	n.a.	D4	24	PFC	VFT: AN poor PFC activation; FOT: similar PFC activation in AN and HC	Nagamitsu et al. (2011)
n.u.	VFT	27, HC; 27, ED	22.4 $\pm$ 2.0; 23.5 $\pm$ 5.2	n.a.	D4	52	FT	ED: bilateral OFC and right FT smaller activation	Suda et al. (2010)
n.u.	VFT	11, HC; 11, ED	26.9 $\pm$ 2.2; 21.2 $\pm$ 6.0	18–32; 14–38	D3	24	PFC	Lower PFC activation in ED	Uehara et al. (2007)
Effects of food taste									
Sweet taste: sucrose (10%); sour taste: citric acid (10%)	Pleasant/unpleasant tasting task	16, HC	26.3 $\pm$ 5.5	n.a.	D10	16	PFC	Bilateral FP and dlPFC deactivation to both tastes; higher right PFC activation with citric acid	Hu et al. (2014)
Sweet snacks	Taste stimulation	6, HC	21.5 $\pm$ 1.3	19–27	D5	44	PFC	Bilateral primary taste area, inferior frontal gyrus, and dlPFC activation	Ono (2012)
Different liquid taste-stimuli	Encoding and retrieval of taste memory	28, HC	32 $\pm$ 7	21–49	D12	23	PFC	Bilateral FP and right DLPFC larger activation in retrieval	Okamoto et al. (2011)
Bitter: 6-n-propylthiouracil	Tasting task	48, HC	n.a.	24–40	D3	24	dlPFC, vlPFC	dlPFC and vlPFC activation	Bembich et al. (2010)
Different sugar based taste-stimuli; control: VFT, TTT	Taste stimulation	19, HC	32.1 $\pm$ 6.9	23–44	D12	17	PFC	vlPFC is involved in the act of tasting.	Okamoto et al. (2009)
7 green tea samples	Sensory evaluation	12, HC	n.a.	23–42	D12	14	lPFC	Left lPFC and right inferior frontal gyrus activation	Okamoto et al. (2006a)
Different liquid taste-stimuli; control: TTT	Taste encoding task	18, HC	n.a.	25–44	D12	17	PFC	vlPFC activation	Okamoto et al. (2006b)
Effects of food flavor									
Sweet taste/sweet taste-lemon odor/no taste-odor gums	Chewing test	25, HC	27.8 $\pm$ 2.8	n.a.	D8	2	PFC	Combination of taste/odor increases PFC activation	Hasegawa et al. (2013)
Ethylmaltol-flavored 4% sucrose solution	Sensory evaluation tasks	7, HC	31.4 $\pm$ 4.5	n.a.	D4	52	PFC	Ethylmaltol enhances the TC activation when combined with a sweet taste	Saito-Iizumi et al. (2013)
Flavored and odorless broth stimuli	Sensory evaluation task	10, HC	30.5 $\pm$ 4.6	n.a.	D4	52	FP, FT	Bilateral TC activation upon flavored broth taste	Matsumoto et al. (2012)
Effects of odor food components									
Irritating and hedonic odors	Olfactory stimulation test	11, HC; 12, MCS	n.a.	n.a.	D13	42	PFC	PFC activation in MCS and controls	Azuma et al. (2013)
Isovaleric acid (sweet smell)	Olfactory stimulation test	19, HC; 36, D	42.5; 60.9	22–67; 37–81	D3	22	PFC	Activation of the lower part of the PFC in HC; no activation in D subjects	Kobayashi et al. (2012)
2-Phenyl ethanol and citral	Olfactory stimulation test	14, HC	19.6	18–23	D1	2	OFC	Left OFC activation; right OFC activation upon odor recognition	Kokan et al. (2011)
Linalool (mixed olfactory stimulant)	Olfactory stimulation test	22, HC; 27, ADHD	12.4 $\pm$ 1.6; 12.7 $\pm$ 1.4	n.a.	D4	48	PFC	Higher TC activation in ADHD without methylphenidate therapy	Schecklmann et al. (2011a)
2-Phenyl ethanol; linalool (mixed olfactory stimulant)	Olfactory stimulation test	29, HC; 29, ADHD	27.8 $\pm$ 4.1; 28.2 $\pm$ 4.5	n.a.	D4	44	PFC	Methylphenidate normalizes the ADHD TC activation	Schecklmann et al. (2011b)

Stimulus	Task	Subjects	Mean age	Age range	Device	CH	Region	Findings	Reference
Isovaleric acid (sweet smell)	Olfactory stimulation test	8, HC; 5, D	28.9; 46.9	22–39; 17–69	D3	22	PFC	Activation of the lower part of the PFC in HC; no activation in D subjects	Kobayashi et al. (2009)
Isovaleric acid (sweet smell)	Olfactory stimulation test	8, HC	28.9	22–39	D3	22	PFC	Activation of the lower part of the PFC	Kobayashi et al. (2007)
Pleasant: vanilla essence, strawberry essence; unpleasant: scatol	Olfactory stimulation test	13, HC		23–31	D9	2	PFC	PFC activation related to odor strength	Harada et al. (2006)
Pleasant: vanilla substance (1%)	Olfactory stimulation test	8, HC; 13, MA	66; 66	56–79; 56–72	D9	2	TC	Bilateral TC activation only in HC	Fladby et al. (2004)
2-Phenyl ethanol, isovaleric acid	Olfactory stimulation test	12, HC	32.6 ± 14.9	n.a.	D15	2	TC	Bilateral TC activation (right TC higher activation)	Ishimaru et al. (2004)
Effects of nutrition/food components									
7-day essence of chicken/placebo supplementation	Working memory and reaction tasks	12, HC	62.3 ± 2.5	60–68	D4	24	PFC	dlPFC activation only with chicken essence upon working memory task	Konagai et al. (2013a)
12-week krill/sardine oil supplementation	Working memory and calculation tasks	45, HC	67.1 ± 3.4	n.a.	D4	24	PFC	Greater dlPFC activation with krill oil	Konagai et al. (2013b)
Glucose drink (50 mg)	Divided attention task	20, HC	69.4	n.a.	D2	36	PFC	Glucose ingestion enhances the lateral and ventral PFC activation of the right hemisphere to the two concurrent tasks	Gagnon et al. (2012)
12-week docosahaexaenoic acid-rich fish oil supplementation	Battery of cognitive tasks	65, HC	20.6	18–29	D14	2	PFC	Dose response PFC activation	Jackson et al. (2012)
Single dose green tea polyphenol epigallocatechin gallate (135 mg)	Battery of cognitive tasks	27, HC	22	18–33	D14	12	PFC	FC CBF decrease	Wightman et al. (2012)
Single dose soybean peptide	Battery of cognitive tasks	10, HC	n.a.	20–25	D4	52	PFC	FP, dlPFC activation (frequency band amplitude increase)	Yimit et al. (2012)
Single dose caffeine (75 mg)	Battery of cognitive tasks	20, HC	21.4	19–28	D14	12	PFC	FC CBF decrease only in non-habitual consumers	Kennedy and Haskell (2011)
Single dose *trans*-resveratrol (250/500 mg)	Battery of cognitive tasks	22, HC	20.2	18–25	D14	12	PFC	Dose-dependent FC CBF increase	Kennedy et al. (2010)
Casein hydrolysate drink ingestion; carbohydrate drink	n.u.	11, HC	22.5 ± 2.3	21–28	D16	10	PFC	Casein hydrolysate drink does not change [tHb]; carbohydrate drink increases [tHb]	Nakamura et al. (2010)
Single dose caffeine (180 mg)	UKP calculation tests before/after caffeine intake	14, HC	n.a.	21–50	D11	2	PFC	The same PFC activation before and after caffeine intake	Higashi et al. (2004)
5-day creatine supplementation	UKP calculation tests before/after	24, HC	24.3 ± 9.1	n.a.	D6	1	PFC	Reduced left FC activation	Watanabe et al. (2002)
Effects of food images									
Visual stimulation: food photos	Like/dislike test	5, HC	23.4 ± 3.4	n.a.	D4	52	FP, FT	FP activation	Hosseini et al. (2011)
Visual: images of body types/high-calorie food/attachment	Symptom-provocative views task	13, HC; 12, AN	14.3 ± 1.3; 14.4 ± 1.3	n.a.	D4	24	PFC	No difference in PFC activation between HC and AN viewing body types/food; AN higher PFC activation viewing mother–child attachment	Nagamitsu et al. (2010)
Visual stimulation: drinks photos	Preference evaluation task	9, HC	24.0 ± 4.4	n.a.	D7	14	PFC	Medial PFC activation	Luu and Chau (2009)
Visual stimulation: food photos	Preference evaluation task	8, HC	23	18–30	D13	32	PFC	vmPFC activation	Shimokawa et al. (2008)

[tHb]: total hemoglobin concentration; ADHD: attention-deficit/hyperactivity disorder; AN: anorexia nervosa; BN: bulimia nervosa; CBF: cerebral blood flow; CH: channels; D: dysosmia; dlPFC: dorsolateral prefrontal cortex; D1: BOM-L1W (Omega Wave, Japan); D2:CW-6 (Techen, USA); D3: ETG-100 (Hitachi, Japan); D4: ETG-4000 (Hitachi, Japan); D5: ETG-7100 (Hitachi, Japan); D6: HEO-200 (Omron, Japan); D7: Imagent (ISS, USA); D8:NIRO-200 (Hamamatsu Photonics, Japan); D9:NIRO-300 (Hamamatsu Photonics, Japan); D10: OEG-16 (Spectratech, Japan); D11: OM-200 (Shimadzu, Japan); D12: OMM-2000 (Shimadzu, Japan); D13: OMM-3000 (Shimadzu, Japan); D14: OXYMON MkIII (Artinis, The Netherlands); D15:PSA-500 (Bio-medical Sciences, Japan); D16: TRS-10 (Hamamatsu Photonics, Japan); ED: eating disorders; FOT: finger opposition task; FP: frontopolar; FT: frontotemporal; HC: healthy controls; lPFC: lateral prefrontal cortex; MA: mild Alzheimer; MCS: multiple chemical sensitivity; n.a.: not available; n.u.: not utilized; OFC: orbitofrontal cortex; PFC: prefrontal cortex; RPST: rock-paper-scissors intentional loss task; TC: temporal cortex; TTT: tongue tapping task; UKP: Uchida–Kraepelin psychodiagnostic test; VFT: verbal fluency task; vmPFC: ventromedial prefrontal cortex; vlPFC: ventrolateral prefrontal cortex.

complexity from dual channels to 'whole-head' arrays of several dozen channels. Data processing/analysis methods permit topographical assessment of real-time regional cortical hemodynamic changes. However, the relatively low spatial resolution of fNIRS makes it difficult to precisely identify the activated cortical regions. Moreover, the fNIRS measurements, being limited to the cortical surface, cannot examine the primary and secondary taste areas, which are located deep inside the brain (Okamoto and Dan, 2007). Therefore, deeper brain areas, such as ventral striatum and hypothalamus, which would be key for investigating eating behavior, can be explored only by fMRI and/or PET.

2.3.2. Application of fNIRS for mapping human cortical responses in the context of food stimuli/intake and eating disorders

The use of fNIRS in the context of food stimuli/intake and eating disorders studies represents a relatively novel application, as witnessed by the limited number of publications: 39 over the last 10 years. Table 2 summarizes these studies. The related fNIRS results mainly include: 1) a lower frontal cortical activation upon different cognitive conditions/ stimuli in patients with ED, and 2) the different activation patterns over the frontal and temporal cortices upon different conditions/stimuli (i.e. food taste, food flavor, odor food components, nutrition/food components ingestion, and food images) in healthy subjects. So far, few forms of ED have been investigated by fNIRS. Only one study has reported PFC responses to visual stimuli in AN patients (Nagamitsu et al., 2010). The other 4 ED-related studies reported in Table 2, and the extensive fMRI literature (see García-García et al., 2013 review summarizing 86 studies) suggest the existence of neural differences between normal and abnormal eating behavior in response to the sight of food. Recently, Bartholdy et al. (2013) have reviewed the studies in which neurofeedback was combined with neuroimaging techniques, suggesting the potential use of fNIRS for evaluating ED treatments. However, the interpretation of the fNIRS findings might be complicated by the longer scalp-to-cortex distance in some patients with severe AN as a consequence of their brain alteration following gray matter volume reduction and/or cerebrospinal fluid volume increase (Bartholdy et al., 2013; Ehlis et al., 2014). Therefore, an assessment of the degree to which cortical atrophy and scalp perfusion could affect the sensitivity of fNIRS is essential for evaluating the usefulness of this technique first as a research tool in patients with severe AN.

Thirty-four out of the 39 studies have been carried out only in healthy subjects (Table 2). Twenty studies of them have demonstrated how fNIRS can provide a useful contribution to map taste processing mainly localized in the lateral prefrontal cortex (lPFC). Eleven studies are related to the application of fNIRS in nutritional intervention studies in both acute and chronic intervention paradigms (Jackson and Kennedy, 2013; Sizonenko et al., 2013 for reviews). These studies have suggested that fNIRS is capable to detect the effect of nutrients and food components on PFC activation.

Unfortunately, most of the studies reported in Table 2 have been performed in small sample size, and the comparison between patients and controls was often insufficient. In addition, only a single fNIRS study, carried out using a high-cost fNIRS instrument based on time-resolved spectroscopy, has reported absolute concentration values of O_2Hb and HHb.

In most of the reported studies, fNIRS probes covered only frontal brain regions. Therefore, the involvement of other cortical areas including parietal, fronto-temporal, and occipital regions, which might be associated with visuospatial processing, attention, and other perceptive networks, were not investigated. In addition, most of the studies have reported only changes in O_2Hb making a comparison with fMRI findings difficult.

These preliminary studies indicate that, when used in well-designed studies, fNIRS neuroimaging may be a useful tool in helping to elucidate the effects of dietary intake/supplementation. In addition, fNIRS could be easily adopted for: 1) evaluating the efficacy of ED treatment programs and behavioral training programs, and 2) investigating the inhibitory control of the dlPFC to visual food cues in healthy subjects as well as in ED patients.

3. Non-invasive neuromodulation approaches: recent developments and current challenges

3.1. Real-time fMRI neurofeedback and cognitive therapy

3.1.1. Introduction to neurofeedback in cognitive reappraisal

Cognitive reappraisal is an explicit emotion regulation strategy involving the modification of cognitive processes in order to alter the direction and/or magnitude of an emotional response (Ochsner et al., 2012). The brain systems that generate and apply reappraisal strategies include the prefrontal, dorsal anterior cingulate (dACC), and inferior parietal cortices (Ochsner et al., 2012). These regions function to modulate emotional responses in the amygdala, ventral striatum (VS), insula, and ventromedial prefrontal cortex (vmPFC) (Ochsner et al., 2012; Fig. 1). Finally, the use of cognitive reappraisal strategies has been shown to regulate appetitive responses to highly palatable foods via these same neural systems (Kober et al., 2010; Hollmann et al., 2012; Siep et al., 2012; Yokum and Stice, 2013).

Neurofeedback using functional magnetic resonance imaging (fMRI) data is a non-invasive training method used to alter neural plasticity and learned behavior by providing individuals with real time information about their brain activity to support learned self-regulation of this neural activity (Sulzer et al., 2013; Stoeckel et al., 2014; Fig. 2). Combining real time fMRI (rtfMRI) neurofeedback with cognitive reappraisal strategies is a cutting-edge strategy for translating the latest advances in neuroscience, clinical psychology, and technology into a therapeutic tool that may enhance learning (Birbaumer et al., 2013), neuroplasticity (Sagi et al., 2012), and clinical outcomes (deCharms et al., 2005). This approach complements other existing neurotherapeutic technologies, including deep brain and transcranial stimulation, by offering a non-invasive alternative for brain disorders and it may add value above psychotherapy alone, including cognitive behavioral therapy, by providing information about how and where changes in cognitions are causing changes in brain function (Adcock et al., 2005).

There appear to be abnormalities in the use of cognitive reappraisal strategies and the brain systems that implement them that contribute to disorders of ingestive behavior, including AN, BN, BED, obesity, and addiction (Kelley et al., 2005b; Aldao and Nolen-Hoeksema, 2010; Kaye et al., 2013). Across these disorders, there is often dysfunction in two major brain systems that also have key roles in cognitive reappraisal: one involving hypersensitivity to rewarding cues (e.g. VS, amygdala, anterior insula, vmPFC, including orbitofrontal cortex) and the other involving deficient cognitive control over food or other substance use (e.g. anterior cingulate, lateral prefrontal cortex — lPFC, including dorsolateral prefrontal cortex — dlPFC). Novel interventions designed to directly target dysfunctional emotion regulation strategies and patterns of neural activity may provide a new direction and hope for these difficult-to-treat disorders.

3.1.2. Cognitive reappraisal, obesity, and eating disorders

Obesity is one candidate disorder that will be used to illustrate how this novel, neuroscience-driven intervention approach may be implemented. Different studies suggest that obese versus lean individuals show elevated reward region responsivity to images of high-fat/high-sugar foods, which increases risk for weight gain (cf. Section 2.1). Fortunately, cognitive reappraisals, such as thinking of the long-term health consequences of eating unhealthy food when viewing images of such foods, increases inhibitory region (dlPFC, vlPFC, vmPFC, lateral OFC, superior and inferior frontal gyrus) activation and decreases reward region (ventral striatum, amygdala, aCC, VTA, posterior insula) and attention region (precuneus, posterior cingulate cortex — PCC) activation relative to contrast conditions (Kober et al., 2010; Hollmann et al., 2012; Siep et al., 2012; Yokum and Stice, 2013). These data suggest
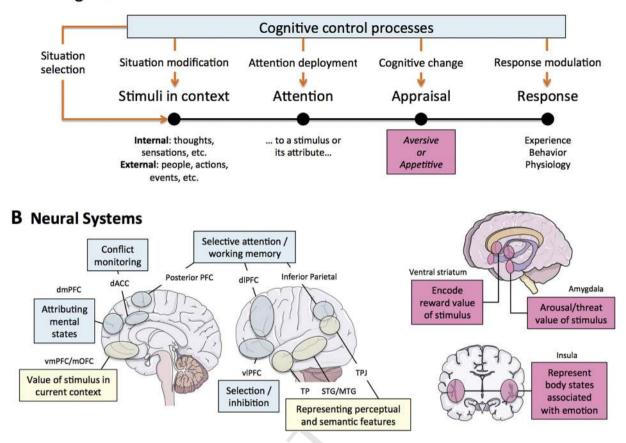
Fig. 1. A model of the cognitive control of emotion (MCCE). (A) Diagram of the processing steps involved in generating an emotion and the ways in which cognitive control processes (blue box) might be used to regulate them. As described in the text, the effects of different emotion regulation strategies (the red arrows descending from the cognitive control processes box) can be understood in terms of the stages of the emotion generation sequence that they influence. The pink box seen at the appraisal stage is meant to indicate that neural systems involved in generating emotion support this process. (B) Neural systems involved in using cognitive strategies, such as reappraisal, to regulate emotion (left, blue boxes), systems involved in generating those responses (left, pink boxes), and systems with an undefined or intermediary role in reappraisal (left, yellow boxes; adapted from Ochsner et al., 2012 with permission). Brain schematic representations were provided by Servier Medical Art (http://www.servier.fr).

that cognitive reappraisals may reduce hyper-responsivity of reward regions to food cues and increase inhibitory control region activation, which is crucial because our environment is replete with food images and cues (e.g. ads on TV) that contribute to overeating. Accordingly, Stice et al. (2015) developed an obesity prevention program that trained participants to use cognitive reappraisals when confronted with unhealthy foods, reasoning that if participants learn to automatically apply these reappraisals, they will show reduced reward and attention region responsivity and increased inhibitory region responsivity to food images and cues for high-fat/high-sugar food, which should reduce caloric intake. Young adults at risk for weight gain by virtue of weight concerns ($N = 148$) were randomized to this new *Minding Health* prevention program, a prevention program promoting gradual reductions in caloric intake and increases in exercise (the *Healthy Weight* intervention), or an obesity education video control condition (Stice et al., 2015). A subset of *Minding Health* and control participants completed an fMRI scan pre and post intervention to assess neural responses to images of high-fat/sugar foods. *Minding Health* participants showed significantly greater reductions in body fat than controls and percentage of caloric intake from fat and sugar than *Healthy Weight* participants, though these effects attenuated by 6-month follow-up. Further, *Minding Health* participants showed greater activation of an inhibitory control region (inferior frontal gyrus) and reduced activation of an attention/expectation region (mid cingulate gyrus) in response to palatable food images relative to pretest and controls. Although the *Minding Health* intervention produced some of the hypothesized effects, it only affected some outcomes and the effects often showed limited persistence.

It is possible that the addition of rtfMRI neurofeedback training to the *Minding Health* intervention may lead to more persistent effects and improved treatment outcomes. Given the emphasis on the use of cognitive reappraisal in the *Minding Health* intervention, fMRI-based neurofeedback was preferred compared to other, complementary technologies such as electroencephalography (EEG) due to the superior spatial resolution of fMRI, including the ability to target subcortical brain structures critical to the regulation of food intake behavior for neurofeedback. The first study demonstrating the *therapeutic* potential of rtfMRI neurofeedback was published in 2005 (deCharms et al., 2005). There have been several studies now demonstrating rtfMRI neurofeedback-induced changes in brain function in multiple structures of relevance to disorders of ingestive behavior, including the amygdala (Zotev et al., 2011; Zotev et al., 2013; Bruhl et al., 2014), insula (Caria et al., 2007; Caria et al., 2010; Frank et al., 2012), aCC (deCharms et al., 2005; Chapin et al., 2012; Li et al., 2013), and PFC (Rota et al., 2009; Sitaram et al., 2011). Several groups have also reported successful application of rtfMRI to modify cognitive and behavioral processes relevant for the treatment of clinical disorders (for review of these studies see deCharms, 2007; Weiskopf et al., 2007; deCharms, 2008; Birbaumer et al., 2009; Caria et al., 2012; Chapin et al., 2012; Weiskopf, 2012; Sulzer et al., 2013), including an application in the area of obesity (Frank et al., 2012). For a review of potential applications of rtfMRI
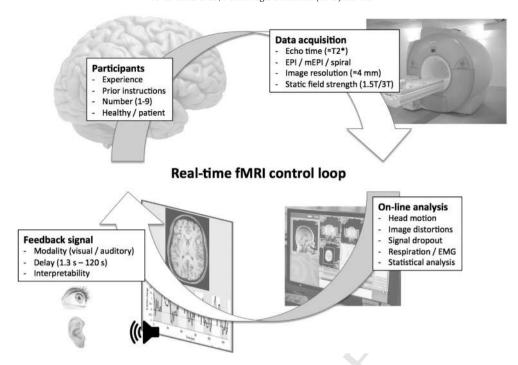
Fig. 2. Schematic of real-time functional magnetic resonance imaging (rtfMRI) control loop. Typically, echo planar imaging (EPI) images are extracted from the magnetic resonance (MR) scanner online, analyzed by third-party software, and then presented back to the subject for the purposes of neural self-regulation (adapted from Weiskopf et al., 2004) mEPI: multi-echo EPI; EMG: electromyography.

neurofeedback for disorders of ingestive behavior, see Bartholdy et al. (2013).

3.1.3. Proof-of-concept for the use of rtfMRI neurofeedback with cognitive reappraisal for the regulation of food intake behavior
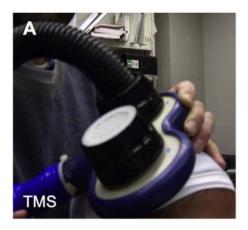
As a proof-of-concept, Stoeckel et al. (2013a) completed a study combining the use of cognitive reappraisal strategies (described above) and rtfMRI neurofeedback in 16 healthy-weight participants (BMI < 25) without a history of disordered eating who were acutely fasted. In a pilot study, an independent sample of 5 participants were able to improve control of inhibition-related (lateral inferior frontal cortex), but *not* reward-related (ventral striatum), brain activation using rtfMRI neurofeedback (Stoeckel et al., 2011). Therefore, lateral inferior frontal cortex was selected as the target brain region of interest for neurofeedback. Participants completed two neurofeedback visits, 1 week apart. At each visit, participants initially performed a functional localizer task, the stop signal task, which is a well-known test of inhibitory control (Logan et al., 1984) that activates lateral inferior frontal cortex (Xue et al., 2008). Participants then attempted to self-regulate brain activity within this region of interest using cognitive regulation strategies (cognitive reappraisal and upregulation) while viewing highly palatable (high-fat/sugar) food images. At the end of each neurofeedback training trial, participants received feedback from the brain region identified by the localizer scan using custom in-house software developed at the Massachusetts Institute of Technology (for technical details, see Hinds et al., 2011). Participants also recorded their subjective cravings in response to the food images throughout the session. Compared to upregulation trials, participants had less reward circuit activity (ventral tegmental area (VTA), VS, amygdala, hypothalamus, and vmPFC) and decreased craving when using reappraisal strategies (ps < 0.01). In addition, the difference in activity in the VTA and hypothalamus during upregulation *vs.* reappraisal was correlated with craving ($rs = 0.59$ and 0.62, ps < 0.05). Neurofeedback training led to improved control of lateral inferior frontal cortex; however, this was not related to mesolimbic reward circuit activation or craving. rtfMRI neurofeedback training led to increased control of brain activity in healthy-weight participants; however, neurofeedback did not enhance the effect of cognitive regulation strategies on mesolimbic reward circuit activity or craving after two sessions (Stoeckel et al., 2013a).

3.1.4. Consideration for rtfMRI neurofeedback experiments targeting disorders of ingestive behavior

Before testing this protocol in individuals with disorders of ingestive behavior, including obesity, it will be important to consider which brain region(s) are good targets for rtfMRI neurofeedback training and how best to represent neuropsychological functions at the neural systems level. For example, the hypothalamus has a central role in the regulation of ingestive behavior; however, it is a relatively small structure with several subnuclei with heterogeneous functional properties that contribute to the regulation of hunger, satiety, and metabolism, but also less closely related functions such as sleep. Given the resolution of rtfMRI, it is possible that a neurofeedback signal from the hypothalamus would include information from a combination of these subnuclei, which may impact the effectiveness of efforts to improve voluntary regulation of a specific function (e.g. hunger). It is also important to consider the likelihood that the targeted function is amenable to training. For example, it is possible that targeting the homeostatic control of feeding represented in the hypothalamus and brainstem may lead to compensatory behaviors to defend the set point of body weight given that these are central, highly conserved neural circuits that control normal energy homeostasis. However, it may be possible to target hedonic, cognitive control, or other "non-homeostatic" mechanisms (and their supporting neural circuits) that may help individuals more effectively to adapt to their environment while minimizing compensatory behaviors that may lead to persistent obesity. It is also unclear whether better outcomes would be expected from neurofeedback from an anatomically-restricted brain region or set of brain regions or whether a network approach using connectivity-based feedback or multi-voxel pattern classification (MVPA) may be preferable given the regulation of ingestive behavior involves both homeostatic and non-homeostatic mechanisms represented in a distributed neural circuitry in the brain (Kelley et al., 2005a). An ROI-based approach could be used to target a specific **Q4** brain region (e.g. vmPFC for the regulation of subjective reward value of highly palatable food cues) or to normalize disrupted functional
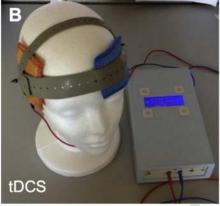
Fig. 3. Pictures of (A) butterfly coils for transcranial magnetic stimulation (TMS) and (B) electrodes and battery for transcranial direct current stimulation (tDCS).

connections between a set of brain regions instantiating a well-characterized function (e.g. the entire mesocorticolimbic reward system consisting of VTA-amygdala-VS-vmPFC); however, MVPA may be preferable if there is a distributed set of multiple brain networks that underlie a complex neuropsychological construct such as cue-induced food craving. It may also be necessary to augment rtfMRI neurofeedback training by including a psychological or cognitive training intervention, such as *Minding Health*, prior to neurofeedback. Finally, it may be necessary to augment cognition with adjunctive pharmacotherapy to enhance the efficacy of neurofeedback training. For a more detailed discussion of these and other issues of relevance to the design of rtfMRI neurofeedback studies of disorders of ingestive behavior, see Stoeckel et al. (2014).

3.2. Transcranial magnetic stimulation (TMS) and transcranial direct-current stimulation (tDCS)

3.2.1. Introduction to TMS and tDCS

Non-invasive neuromodulation techniques allow the external manipulation of the human brain in a safe manner, without the requirement of a neurosurgical procedure. Over the past two decades there has been growing interest in the use of non-invasive neuromodulation in neurology and psychiatry, motivated by the shortage of effective treatments. The most commonly used techniques are transcranial magnetic stimulation (TMS) and transcranial direct current simulation (tDCS). TMS is based on the application of rapidly changing magnetic fields that are delivered with a coil encased in plastic that is placed over the scalp of the subject (Fig. 3A). These varying magnetic fields cause an induction of secondary currents in the adjacent cortex that can be strong enough to trigger neuronal action potentials (Barker, 1991; Pascual-Leone et al., 2002; Hallett, 2007; Ridding and Rothwell, 2007). TMS can be administered in single or multiple pulses, also called repetitive TMS (rTMS). In the case of tDCS, mild DC currents (typically in the order of 1–2 mA) are applied directly over the head through a pair of saline-soaked electrode pads connected to a battery-like device (Fig. 3B). Approximately 50% of the current delivered by tDCS penetrates the scalp and can raise or decrease the resting membrane potential of neurons in underlying areas (anodal or cathodal tDCS stimulation, respectively), causing changes in spontaneous firing (Nitsche et al., 2008). rTMS and tDCS can induce transient/lasting changes that are believed to be mediated by changes in synaptic strength. A comprehensive overview of these techniques and their mechanisms of action are beyond the scope of this section and can be found elsewhere (Pascual-Leone et al., 2002; Wassermann et al., 2008; Stagg and Nitsche, 2011). Table 3 presents a summary of key differences between TMS and tDCS. While TMS and tDCS have been and still remain the dominant techniques in the field, other novel or modified forms of non-invasive neuromodulation have been developed in recent years and are actively under investigation, such as deep TMS (dTMS) (Zangen et al., 2005), high-definition tDCS (HD-tDCS) (Datta et al., 2009), transcranial alternate current simulation (tACS) (Kanai et al., 2008), or transcranial random noise stimulation (tRNS) (Terney et al., 2008). Additional techniques for neuromodulation are those that are invasive (cf. Section 4), such as deep brain stimulation (DBS), or those that target peripheral nerves, such as vagus nerve stimulation (VNS).

Over the past two decades there has been remarkable progress in our understanding of the neurocognitive basis of human eating behavior, obesity and eating disorders. A number of neuroimaging and neuropsychology studies have identified the crosstalk between reward and cognition as a central component in the regulation of eating behavior and body weight in humans (Alonso-Alonso and Pascual-Leone, 2007; Wang et al., 2009a; Kober et al., 2010; Hollmann et al., 2012; Siep et al., 2012; Vainik et al., 2013; Yokum and Stice, 2013). As research continues in this field, the available knowledge makes it possible to begin exploring interventions that shift from behavior to neurocognition as the primary target. Overall, neuromodulatory techniques can bring

Table 3

Comparative between TMS and tDCS.

Characteristics	Transcranial magnetic stimulation (TMS)	Transcranial direct current stimulation (tDCS)
Spatial resolution	Very good (approximately 1 cm³)	Poor (conventional tDCS) to good (HD-tDCS)
Temporal resolution	Excellent (ms)	Poor (s)
Tolerability	Very good to fair, depending on protocols	Excellent to very good
Safety	Good (can rarely cause seizures)	Excellent
Cost	High range (typically $30,000–$100,000)	Low to middle range ($250–$10,000)
Portability	Fair	Excellent
Regulatory status	Cleared for some specific devices and applications (depression, cortical mapping, migraine)	Not cleared. Only off label application
Consumer versions	No	Yes

Table 4

Summary of studies with TMS and tDCS in the field of human eating behavior.

Study characteristics	Subjects, status	Stimulation protocol	Main outcome measures	Main findings	References
TMS studies					
Acute effects (single session); parallel design, randomized, double-blind, sham-controlled	n = 37 subjects (mean age: 30; 86.8% of women) with bulimic-type eating disorders	Target: DLPFC; two groups: active (left DLPFC, 5 cm anterior to hand motor area) and control (sham rTMS); parameters: 1000 pulses, 10 Hz rTMS, 20 min, intensity 110% motor threshold	Food craving (VAS) while exposed to real food and a movie of food; frequency of bingeing in a 24-hour follow-up period	Decrease in food craving; reduction in bingeing in 24 h post rTMS	Van den Eynde et al. (2013)
Acute effects (single session); crossover design, randomized, single-blind, sham-controlled; improved sham condition matched for perceived painfulness of the stimulation	n = 10 women (mean age: 28.3) with frequent food cravings (≥3 times/week during the past month); 3-hour fasting	Target: DLPFC; two conditions: active (left DLPFC) and control (sham rTMS); Parameters: 3000 pulses, 10 Hz rTMS, 15 min, intensity 100% motor threshold	Food craving (VAS) while exposed to food images	No differences between conditions	Barth et al. (2011)
3-week intervention; parallel design, randomized, double-blind, sham-controlled; preceded by 1-week of sham rTMS in all participants	n = 14 women (mean age: 27.4) with bulimia nervosa	Target: DLPFC; 1 week with sham rTMS before randomization to avoid high placebo responders; two groups: active (left DLPFC) and control (sham rTMS); parameters: 3 weeks, 15 sessions, 2000 pulses per session. 20 Hz rTMS, intensity 120% motor threshold	Change in binges and purges; mood and compulsive symptoms	No differences between groups	Walpoth et al. (2008)
Acute effects (single session); parallel design, randomized, double-blind, sham-controlled	n = 28 women (mean age: 25.8) with frequent food cravings (≥3 times/week); 3–4 h fasting	Target: DLPFC; two groups: active (left DLPFC) and control (sham rTMS); parameters: 1000 pulses, 10 Hz rTMS, 20 min, intensity 110% motor threshold	Food craving (VAS); consumption of snack foods	Decrease in food craving; no effect on snack consumption	Uher et al. (2005)
tDCS studies					
Acute effects (single session); crossover design, randomized, double-blind, sham-controlled	n = 9 women (mean age: 23.4); all lean with frequent food cravings (≥3 times/day); 3-hour fasting	Target: DLPFC; two conditions: active (anode over F4/cathode over F3) and control (sham tDCS); parameters: 2 mA, 20 min, 35 cm² sponge electrodes	EEG event-related potentials during an Go/No-Go task; food craving (VAS) while exposed to real food and a movie of food; snack intake; attentional bias for food (eye tracking)	Reduction of the frontal N2 component and enhancement of the P3a component of No-Go responses; reduction in caloric intake	Lapenta et al. (2014)
8-day intervention; crossover design, randomized, single-blind, sham-controlled	n = 14 men (mean age: 24.8), all lean, with low scores in three-factor eating questionnaire; 6-hour fasting	Target: DLPFC; two conditions: active (anode over an area 5 cm anterior to the right motor cortex/cathode over the left forehead) and control (sham tDCS); parameters: 1 mA, 20 min, 35 cm² sponge electrodes	Subjective appetite (ratings and VAS); free eating from a standardized multi-choice test buffet	14% decrease in total calorie consumption, at the expense of carbohydrates; decrease in appetite: nonspecific and specific (sweets and savory food)	Jauch-Chara et al. (2014)
Acute effects (single session); crossover design, randomized, double-blind, sham-controlled	n = 17 women (mean age: 26.4; 29.4% of overweight) with frequent food cravings (≥1/day)	Target: DLPFC; two conditions: active (anode over F4/cathode over F3) and control (sham tDCS); parameters: 2 mA, 20 min, 4 cm² sponge electrodes	Food craving ratings while viewing movies of food; temporal discounting task; free eating test	Decrease in craving for sweets; no effect on temporal discounting no change in free eating; moderating effect of temporal discounting: participants with more reflective choice behavior showed more susceptibility to anticraving effects of tDCS	Kekic et al. (2014)
Acute effects (single session), in combination with an exercise bout of about 200 calories; crossover design, randomized, single-blind, sham-controlled	n = 9 subjects (mean age: 24; 55% of men; all overweight or obese), 2- to 3-hour fasting	Target: DLPFC; two conditions: active (anode over F3/cathode over Fp2) and control (sham tDCS); parameters: 2 mA, 20 min, 35 cm² pads	Subjective appetite (VAS)	Decrease in desire to eat with tDCS; greater appetite suppression with the combination of tDCS and exercise	Montenegro et al. (2012)
Acute effects (single session); crossover design, randomized, single-blind, sham-controlled	n = 19 subjects (mean age: 32.5; 68.4% of women; about 58% of overweight or obese) with frequent food cravings (≥3 times/week during the past month); 4-hour fasting	Target: DLPFC; two conditions: active (anode over F4/cathode over F3) and control (sham tDCS); parameters: 2 mA, 20 min, standard sponge electrodes	Food craving and ability to resist tasting (VAS) while viewing food images; free consumption of previously presented foods	Decrease in food craving, particularly for sweets and carbohydrates; no change in food consumption	Goldman et al. (2011)
Acute effects (single session); crossover design, randomized, double-blind, sham-controlled	n = 23 subjects (mean age: 23.7; 91% of women) with frequent food cravings (≥3 times/day); 3-hour fasting	Target: DLPFC; three conditions: active 1 (anode over F3/cathode over F4), active 2 (anode over F4/cathode over F3), control (sham tDCS); parameters: 2 mA, 20 min, 35 cm² sponge electrodes	Food craving (VAS) while exposed to real food and a movie of food; snack intake; attentional bias for food (eye tracking)	Decrease in food craving only in condition active 1; decrease in snack intake in conditions active 1 and 2; decrease in attentional bias for food only in condition active 1	Fregni et al. (2008)

rTMS: repetitive transcranial magnetic stimulation; tDCS: transcranial direct current stimulation; DLPFC: dorsolateral prefrontal cortex; VAS: visual analogue scale; Electrode montage for tDCS: F3 (left DLPFC), F4 (right DLPFC), Fp2 (right supra-orbital); EEG: electroencephalography; N2, P3a: specific EEG electrophysiological measures.

valuable insights and open novel therapeutic avenues in this new scenario that places neurocognition as a central component of human eating behavior.

3.2.2. Summary of clinical studies to modify eating behavior and eating disorders

Eating behavior is a recent application in the field of non-invasive neuromodulation, with the earliest study dating back to 2005 (Uher et al., 2005). TMS and tDCS are the only techniques that have been used in this context. Table 4 provides a summary of randomized, controlled, proof-of-concept studies. To date, these studies have tested acute, single-session effects only, with two exceptions: one study with rTMS in bulimic patients (3 weeks), and a recent study with tDCS in healthy men (8 days). The targeted area, dorsolateral prefrontal cortex (dlPFC), is a complex brain region related to executive functions that supports cognitive control of food intake. Overall, the underlying hypothesis is that enhancing dlPFC activity may alter the reward–cognition balance towards facilitation of cognitive control and possibly suppression of reward-related mechanisms that drive food craving and overeating. The specific dlPFC-dependent cognitive processes being affected by rTMS or tDCS and mediating the observed behavioral effects remain largely unknown. Possibilities include changes in reward valuation mechanisms (Camus et al., 2009), attentional biases (Fregni et al., 2008), or inhibitory control (Lapenta et al., 2014). rTMS studies have targeted the left dlPFC only, via excitatory protocols (10 and 20 Hz). tDCS studies have targeted both the right and left dlPFC, with slightly different approaches/montages. The majority of studies — all with tDCS and one with rTMS — have evaluated effects on food craving, subjective appetite and food intake. Altogether, they have consistently found an acute suppression in the scores of self-reported food craving and appetite measured by ratings or visual analogue scales (VAS). There is some indication that the effect with tDCS may be more specific for craving of sweets. Changes in food intake have been rather inconsistent with a single session of rTMS or tDCS. In the longest study to date with tDCS (8 days), the authors found a 14% decrease in calorie consumption (Jauch-Chara et al., 2014). An important bias in some studies is the use of a sham procedure without any current flow as control, instead of sham stimulation in areas that are irrelevant to food intake for example. Since the stimulation is sometimes perceptible by the patient, we cannot exclude a placebo effect in some cases.

Studies with eating disorder patients so far have used only rTMS. Several case reports (Kamolz et al., 2008; McClelland et al., 2013b) and an open-label study (Van den Eynde et al., 2013) (not included in the table) suggest potential for rTMS in anorexia nervosa, but findings should be replicated in placebo-controlled trials. For the case of B N, an early case report suggested potential benefits with rTMS (Hausmann et al., 2004), but this was not confirmed in a subsequent clinical trial that used this technique over 3 weeks (Walpoth et al., 2008). A recent case study reported beneficial effects using 10 Hz rTMS applied over a different target, the dorsomedial prefrontal cortex, in a refractory patient with BN (20 sessions, 4 weeks) (Downar et al., 2012). This brain region represents a promising target given its general role in cognitive control, specifically performance monitoring and action selection (Bush et al., 2000; Krug and Carter, 2012), and its link with the clinical course of AN and BN (McCormick et al., 2008; Goddard et al., 2013; Lee et al., 2014).

3.2.3. Future needs: from empirically-driven studies to rational and mechanistic approaches

Results from these initial studies provide a good proof of concept for the translation of non-invasive neuromodulation into the field of eating behavior. Potential applications can be the enhancement of cognitive control and underlying brain regions to support successful weight loss maintenance in obesity (DelParigi et al., 2007; McCaffery et al., 2009; Hassenstab et al., 2012), or rebalancing ventral and dorsal brain systems in AN and B N (Kaye et al., 2010). While the overall rationale is quite clear, the specifics of using noninvasive neuromodulation in the

treatment of obesity and eating disorders are currently under investigation and the best approaches and protocols remain to be defined. Non-invasive neuromodulation could be used alone or in combination with other strategies such as behavioral therapy, cognitive training, physical fitness and nutrition, to create synergistic effects. Aside from therapeutic applications, neuromodulation techniques can be used to inform disease mechanisms, e.g. examining the causal involvement of a specific region in a given cognitive process or behavioral manifestation (Robertson et al., 2003). Recent studies have examined the potential of TMS to quantify reward responses (Robertson et al., 2003) and results from this line of work could eventually lead to the development of objective biomarkers that can help study eating phenotypes.

While there is a high potential for future uses of neuromodulation in the field of eating behavior, there are still many limitations and open questions. Blinding is a key issue, called into question by one rTMS study in food craving and a tDCS study where subjects were able to guess the condition they had received with 79% accuracy (Barth et al., 2011; Goldman et al., 2011). Future studies should consider parallel designs to overcome this problem, or at least rule out the possibility of incomplete blinding when crossover designs are used. Another need to address in future studies is the addition of more clinically meaningful outcomes. rTMS and tDCS have caused changes in measures that are sensitive and valid in an experimental setting, e.g. visual analogue scales, but their clinical relevance remains uncertain.

All studies to date have targeted the DLPFC, as in other applications of tDCS and rTMS in neuropsychiatry. There is need to explore additional targets; dorsomedial prefrontal cortex/dorsal anterior cingulate cortex (daCC), parietal regions and anterior insular cortex are particularly promising. Both rTMS and tDCS are currently optimized to target brain regions located on the surface. Reaching deeper brain structures may be more feasible with HD-tDCS, or with dTMS for the case of mid-depth areas such as insular cortex (Zangen et al., 2005). A recently described method for rTMS consists of guiding stimulation on the basis of intrinsic functional connectivity determined by resting-state fMRI (Fox et al., 2012a; Fox et al., 2012b). Aside from targeting brain regions alone, non-invasive neuromodulation can be administered with simultaneous cognitive training. This approach may lead to more functional effects (Martin et al., 2013; Martin et al., 2014) and is articularly suited for eating disorders and obesity, where there are impairments in specific neurocognitive domains, such as executive functions, even though the picture is complex (Alonso-Alonso, 2013; Balodis et al., 2013). The use of cognitive performance and/or ways of measuring brain activity can also facilitate target monitoring and overall contribute to optimize the delivery of neuromodulation. A recent tDCS study points in that direction, with a combination of EEG event-related potentials and behavioral measures of food craving and food intake (Lapenta et al., 2014).

More work is needed to understand potential sources of variability in the response to neuromodulation. The majority of participants in these rTMS/tDCS studies have been young women, with variable BMI. Gender effects remain unaddressed, with no direct comparisons so far between women and men, but differences are likely based on the effect of gender on brain correlates of appetite (Del Parigi et al., 2002; Wang et al., 2009a). When studying food-related processes and mechanisms, it is also important to consider the underlying variability in brain activity related to metabolic state. As mentioned in Table 4, subjects have been stimulated typically in an intermediate state, i.e. about 2–4 h after a meal. It is unknown whether different conditions can cause better results. Another potential confounder that remains unaddressed is the role of dieting. Patients with eating disorders and obesity usually follow diets that can be quite restrictive and, more importantly, could have substantial effects on brain excitability and also in the sensitivity/response to neuromodulation (Alonso-Alonso, 2013). An additional factor is whether a person receives TMS or tDCS in a weight-reduced state or in a weight-stable state, which would also have consequences in the resting brain state and neuromodulatory response (Alonso-Alonso, 2013). Lastly, at a more technical level, individual head anatomy can

alter electric or electromagnetic transmission. This issue has been extensively addressed using computational models of tDCS (Bikson et al., 2013). A particular concern in this regard is whether head fat, a relatively resistive tissue, could affect current density distribution (Nitsche et al., 2008; Truong et al., 2013).

Regarding side effects, both TMS and tDCS are non-invasive, safe and rather painless techniques that are very well tolerated in the vast majority of cases (Nitsche et al., 2008; Rossi et al., 2009). The most common adverse effects with rTMS is headache, which occurs approximately in 25–35% of patients during dlPFC stimulation, followed by neck pain (12.4%) (Machii et al., 2006). With tDCS, a substantial proportion of people (>50%) report transient sensations under the electrode that can be defined as tingling, itching, burning or pain, and are usually mild or moderate (Brunoni et al., 2011). When designing a study it is important to exclude participants with contraindications to receive either TMS or tDCS, and collect adverse events in a systematic manner. There are standardized questionnaires available for that purpose (Rossi et al., 2009; Brunoni et al., 2011). The most worrisome adverse effect of non-invasive neuromodulation is the induction of seizure, which has been reported only a few times with rTMS (Rossi et al., 2009).

The field of neuromodulation is expanding very quickly and it has started to cross boundaries beyond the medical and research community to curious individual consumers and recreational users. It is important that we, the community of scientists working in neuromodulation, remain committed to guarantee research integrity and maintain high ethical standards in the use of these methods. The possibility of manipulating the human brain can be as fascinating and tempting as trying a new diet to curb appetite, but it is important to remind that the current state of science in this field is far from being conclusive. And, as importantly, transcranial devices are not playthings (Bikson et al., 2013).

4. Invasive neuromodulation strategies: recent developments and current challenges

4.1. Overview of the peripheral neuromodulation strategies in the context of food intake and weight control

4.1.1. Changes in vagal signaling during obesity

The homeostatic control of food intake involves a complex, bidirectional communication system between the periphery and the central nervous system that has been extensively reviewed (Williams and Elmquist, 2012). The vagus nerve, because it contains mainly afferents neurons that arise from the gut, the pancreas and the liver, plays a key role in this communication. In non-obese individuals, chemosensory (acid-sensing ion channels) and mechanosensory vagal receptors signal immediate availability of food (Page et al., 2012). Further, several hormones including ghrelin, cholecystokinin (CCK) and peptide tyrosine tyrosine (PYY) have the capability to activate vagal afferents (Blackshaw et al., 2007).

Aside from an excessive accumulation of fat, a substantial body of evidence suggests that obesity and/or high fat diet is associated with alteration of peripheral responses to nutrients. Studies in rodents subjected to a high-fat diet (HFD), or in diet-induced obesity consistently show reduced suppressive effects of intestinal nutrients on food intake compared to control animals (Covasa and Ritter, 2000; Little, 2010). This is associated with a reduced sensitivity of jejunal afferents (primarily vagal) to low-level distension and reduced excitability of identified jejunal vagal afferents within the nodose ganglion to CCK and 5-HT exposure (Daly et al., 2011). Corresponding reductions in vagal afferent expression of receptors for CCK, 5-HT and other anorexic GI peptides have been reported in the nodose ganglion (Donovan and Bohland, 2009). Additionally, HFD reduced the responses of gastric vagal tension receptors to distension and augmented the inhibitory effect of ghrelin on vagal afferents. Alternatively, while leptin potentiated vagal mucosal afferent responses, potentiation of mucosal afferents by leptin was lost after HFD (Kentish et al., 2012). The loss of vagal afferent signaling

together with the altered processing of vagal signals within the dorsal vagal complex suggest that resetting these sensitivities by chronic vagal stimulation (VNS) might reduce overeating.

4.1.2. Effects of vagal stimulation

Unilateral left cervical vagal stimulation is approved for treatment-resistant depression and intractable epilepsy in the European Union, the United States and Canada. Epileptic patients reported frequently changes in eating behavior with alteration in diet preferences (Abubakr and Wambacq, 2008). These reports generated further investigations, initially through pure serendipity, which subsequently used animal models to evaluate the effects of VNS on food intake and related weight control (for synthetic tables on VNS studies, please see Val-Laillet et al., 2010; McClelland et al., 2013a). The original studies in 2001 of Roslin and Kurian (2001) in dogs and the other from Krolczyk et al. (2001) in rats suggested a decrease in weight gain or a weight loss during chronic vagal stimulation. Surprisingly, despite different surgical approaches, the results demonstrated by these authors were identical. Indeed, Roslin and Kurian (2001) used a bilateral cuff placement within the thorax (hence stimulating both dorsal and ventral vagal trunks) while Krolczyk et al. (2001) used a cervical placement on the sole left vagus to be similar with the clinical setup for intractable epilepsy. Since these pioneering studies, several research groups, including us, have published positive results using various electrodes locations, electrodes set-up and stimulation parameters. The first attempt to evaluate the adequate location of the electrodes for food intake control was performed by Laskiewicz et al. (2003). They demonstrated that bilateral VNS is more effective than unilateral stimulation. Using a large animal pre-clinical model, we used juxta-abdominal bilateral vagal stimulation on the longest longitudinal study performed to date. We show that chronic vagus nerve stimulation decreased weight gain, food consumption and sweet craving in adult obese minipigs (Val-Laillet et al., 2010). Further, unlike others studies performed in smaller animal models, efficacy improves over time in a manner comparable that already exemplified in intractable epilepsy patients (Arle and Shils, 2011).

Unfortunately, the positive results observed in almost all animal pre-clinical studies have not been confirmed in humans. Because of regulatory restraints, all human studies have been performed using left cervical vagal cuff only with stimulation settings similar or closely identical to those used for depression or epilepsy. Despite using long-term stimulation, weight loss was found in about half of the subjects (Burneo et al., 2002; Pardo et al., 2007; Verdam et al., 2012). At present, no clear explanation for these non-responsive subjects can be offered. A recent study by Bodenlos et al. (2014) suggests that large BMI individuals are less responsive to VNS than lean people. Indeed, in their study, VNS suppressed food intake in lean patients only.

Several authors have investigated the physiological basis of VNS with specific reference to the left cervical placement of the electrode. Vijgen et al. (2013) have demonstrated in an elegant study combining PET imaging of the brown adipose tissue (BAT) and a cohort of VNS epileptic patients that VNS significantly increases energy expenditure. Moreover, the change in energy expenditure was related to the change in BAT activity suggesting a role for BAT in the VNS increase in energy expenditure. VNS has been demonstrated to change brain activity throughout the entire cerebrum (Conway et al., 2012) and modulate the monoaminergic systems (Manta et al., 2013). In humans, left VNS induced rCBF (regional cerebral brain flow) decreases in the left and right lateral OFC and left inferior temporal lobe. Significant increases were found also in the right dorsal anterior cingulate, left posterior limb of the internal capsule/medial putamen, the right superior temporal gyrus. Despite the critical importance of these areas towards control of food intake and depression, no correlation was found between brain activation and the outcome of depression score after 12 months of VNS therapy. Therefore, it remains to be demonstrated that the observed brain activity changes are causative factors to explain VNS effects. The demonstration in rats that VNS modulates visceral pain-related affective

memory (Zhang et al., 2013) might represent an alternative pathway that could explain the beneficial effects observed on about half of the patients. Our early studies on brain activation after juxta-abdominal bilateral VNS performed in growing pigs (Biraben et al., 2008) using single photon gamma scintigraphy was the first to evaluate VNS effects on the non-pathological brain. We showed the activation of two networks. The first one is associated with the olfactory bulb and primary olfactory projections areas. The second one involves areas that are essential to integrate gastro-duodenal mechanosensory information (hippocampus, pallidum) so to give a hedonic value to these. Similar results have been reported in rats either using PET (Dedeurwaerdere et al., 2005) or MRI (Reyt et al., 2010). Unlike behavioral effects that take several weeks to be identified, alterations in brain metabolism identified by PET imaging were present 1 week only after the onset of VNS therapy. In our porcine model of juxta-abdominal VNS, the cingulate cortex, putamen, caudate nucleus and substantia nigra/tegmental ventral area, i.e. the main reward meso-limbic dopaminergic network, presented changes in brain metabolism (Malbert, 2013; Divoux et al., 2014) (Fig. 4). The massive activation of the reward network at an early stage of the chronic stimulation suggests that brain imaging might be used as a tool to optimize the vagal stimulation parameters.

As with several others therapies, the relatively poor success of VNS in obese humans could be explained by an insufficient understanding of the action of VNS on the brain networks controlling food intake. Translation of animal models into clinical practice was (too) quick without experimental clues towards a normalized procedure for stimulation. For instance, as mentioned above, early human studies were performed with unilateral cervical vagal stimulation whereas all animal studies suggested that bilateral juxta-abdominal location for the stimulating cuffs was more appropriate. Furthermore, we are still in need for early clues to refine stimulation parameters without having to wait for changes in body weight. It can be speculated that brain-imaging methods together with computational model of VNS (Helmers et al., 2012) might be of significant help towards this clinical requirement.

4.1.3. Effects of vagal blockade

Several patients after vagotomy performed as a cure for ulcer disease report short-term loss of appetite; less commonly, prolonged loss of appetite and furthe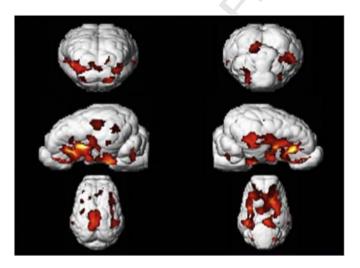r weight loss or failure to regain weight have been noted (Gortz et al., 1990). Bilateral truncal vagotomy has been used historically as a treatment for obesity refractory to other therapies, and has been associated with satiety and weight loss (Kral et al., 2009). Based upon this observation and although that it has been reported that the effects on body weight are lost over time (Camilleri et al., 2008) and that truncal vagotomy was virtually ineffective to reduce solid food intake (Gortz et al., 1990), vagal blockade therapy was tested in humans with the primary objective to reduce weight of morbid obese individuals. Vagal blockade was performed bilaterally at the abdominal level using high frequency (5 kHz) current pulses. The large scale, long lasting study called EMPOWER (Sarr et al., 2012) demonstrated that weight loss was not greater in treated compared to control. Despite this therapeutic failure, Vbloc therapy in type 2 diabetic patients (DM2) reduces the level of HbA$_{1c}$ and hypertension shortly after activation of the device (Shikora et al., 2013). This benefit and the stability of the improvement over time suggest that the mechanisms of action may be, at least in part, independent from weight loss. Since these parameters are entirely related to fat deposition and truncal vagotomy led to significant reductions in diet-induced visceral abdominal fat deposition (Stearns et al., 2012), it is quite possible that the efferent neurons blocked by the therapy might be responsible for the improvements observed in DM2 patients.

4.2. State of the art of deep brain stimulation (DBS) and its potential for tackling obesity and eating disorders

4.2.1. Overview on the state of the art in DBS

4.2.1.1. Current therapeutic applications of DBS.
Deep brain stimulation (DBS) is a technique based on implanted electrodes for treating neuromotor disorders such as Parkinson's disease (PD), as well as epilepsy, while showing promise for psychological disorders like treatment-resistant depression (TRD) and obsessive–compulsive disorders (OCD) (Perlmutter and Mink, 2006).

The subthalamic nucleus (STN) is commonly targeted for PD, while the anterior nucleus of the thalamus (ANT), subgenual cingulate (Cg25), and nucleus accumbens (Nac) are respectively targeted for epilepsy, TRD and OCD (Fig. 5). The penetration of DBS, roughly **Q5** 10,000 patients per year worldwide, is minuscule compared to the prevalence of treatment-resistant PD, epilepsy, and psychiatric disorders (see allcountries.org; TRD: Fava, 2003; PD: Tanner et al., 2008; OCD: Denys et al., 2010). This section is aimed at identifying these technological developments and their potential to combat obesity and eating disorders.

4.2.1.2. Traditional surgery planning in DBS.
In the traditional deep-brain therapy (DBT) framework, preoperative brain MRI is acquired, a stereotactic frame is affixed to the patient, who then undergoes a CT scan, and the insertion trajectory is set based on the registered modalities and a deep brain atlas in printed form (Sierens et al., 2008). This framework places restrictions on the choice of approach, and surgical planning involves considerable mental computation by the surgeon. Modern DBS practice relies on intra-operative microelectrode recordings (MER) for confirmation comes at the cost of extended operating times and greater potential for complications (Lyons et al., 2004). While MER use is common in PD, feedback on targeting success is not possible for many non-motor disorders.

4.2.1.3. Potential complications of DBS.
In traditional and image-guided approaches, targeting does not account for brain shift, and this neglect leads to a heightened risk of complications. While brain shift may be negligible under some conditions (Petersen et al., 2010), other studies suggest that shifts up to 4 mm can occur (Miyagi et al., 2007; Khan et al., 2008). The worst case is a cerebrovascular complication, especially when multiple trajectories are used during exploration (Hariz, 2002).

Fig. 4. Changes in glucose metabolism observed via positron emission tomography (PET) imaging after injection of ^{18}FDG (fluorodeoxyglucose), between vagal stimulated vs. sham animals. $N = 8$ Yucatán minipigs in both groups. VNS (vagus nerve stimulation) therapy was applied during 8 days on ventral and dorsal vagal trunks at the level of the abdomen. The cuff electrodes were placed surgically using a coelioscopic approach. $p < 0.0001$ with FDR (false discovery rate correction) (see text for details).
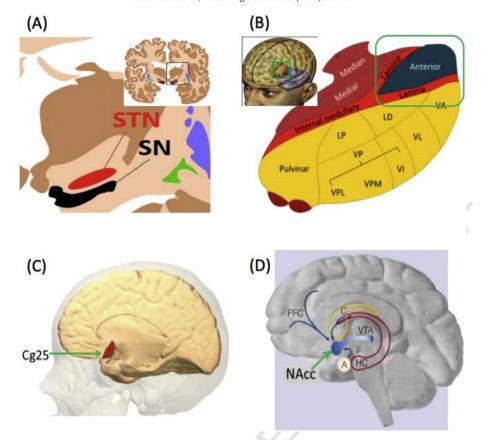
Fig. 5. DBT targets: (A) subthalamic nucleus (coronal view, yellow, labeled "STN"); (B) anterior nucleus of thalamus (3D rendering, dark blue, labeled "anterior"); (C) subgenual anterior cingulate (medial view, region high-lighted in red); (D) nucleus accumbens (medial view, blue circle) (Wiki).

Moreover, the risk of penetration of a ventricular wall is an important consideration (Gologorsky et al., 2011), which correlates strongly with neurological sequelae. Despite the foregoing, DBS still has a relatively low complication rate compared to bariatric surgery (Gorgulho et al., 2014) and recent DBS innovations will considerably improve the safety and accuracy of this surgery.

4.2.2. Recent DBS innovations and emerging DBS therapies

A number of innovative techniques have been proposed in image-guided DBS, improving the functionally descriptive aspects of surgery planning. Most groups emphasize only a small number of these techniques at once, which include 1) a digital deep-brain atlas depicting deep-brain structures in humans (D'Haese et al., 2005; Chakravarty et al., 2006) and animal models such as the pig (Saikali et al., 2010; Saikali et al., in revision); 2) a surface model, featuring shape statistics, for registering an atlas to patient data (Patenaude et al., 2011); 3) an electrophysiological database with successful target coordinates (Guo et al., 2006); 4) a model of venous and arterial structures, identified from the combination of Susceptibility Weighted Imaging and Time-Of-Flight angiographic magnetic resonance imaging (Bériault et al., 2011); 5) multi-contrast MRI that directly delineates the basal ganglia structures through coregistered images weighted on T1, R2* (1/T2*), and susceptibility phase/magnitude (Xiao et al., 2012); 6) validation of deep brain therapy through animal trials, mostly confined to rodents (Bove and Perier, 2012) but also applied to (mini)pigs (Sauleau et al., 2009a; Knight et al., 2013); 7) computer simulation of DBS (McNeal, 1976; Miocinovic et al., 2006), using a finite element model of voltage distribution of the stimulating electrode as well as an anatomical model of the stimulated neural tissue; and 8) connectomic surgery planning for DBS (Henderson, 2012; Lambert et al., 2012), where patient-specific white matter tracts identified from diffusion tensor/spectrum imaging (DTI/DSI) are exploited for effective targeting.

The above technologies relate to preoperative planning; Meanwhile, very little effort has been devoted to intraoperative accuracy. The main exception is intraoperative MRI (ioMRI)-guided DBS, which was proposed in Starr et al. (2010), using an MRI-compatible frame. Another recent intraoperative development is *closed-loop deep-brain therapy delivery*, based on electrical or neurochemical feedback (Rosin et al., 2011; Chang et al., 2013).

Last, highly selective therapies have been proposed for the treatment of epilepsy, which target mutated genes that modulate ion channels (Pathan et al., 2010).

Therapies that address molecular pathways specific to PD (LeWitt et al., 2011), and TRD (Alexander et al., 2010) are also being developed. In this kind of deep-brain therapy, the electrical stimulation is replaced by the infusion of substances that modulate the neurotransmission locally.

4.2.3. Applicability of DBS in the context of obesity and eating disorders

4.2.3.1. The effects of DBS on eating behavior and body weight. In a comprehensive review, McClelland et al. (2013a) presented evidence from human and animal studies on the effects of neuromodulation on eating behavior and body weight. Four studies observed clinical improvements and weight gain in patients with anorexia nervosa (AN) treated with DBS (in the Cg25, Nac, or ventral capsule/striatum – VC/VS) (Israel et al., 2010; Lipsman et al., 2013; McLaughlin et al., 2013; Wu et al., 2013); a single case report showed a significant weight loss in a DBS-treated patient suffering from obsessive–compulsive disorders (Mantione et al., 2010); and eleven studies reported either over-eating and/or increases in

cravings, weight gain and BMI following DBS of the STN and/or globus pallidus — GP (Macia et al., 2004; Tuite et al., 2005; Montaurier et al., 2007; Novakova et al., 2007; Bannier et al., 2009; Sauleau et al., 2009b; Walker et al., 2009; Strowd et al., 2010; Locke et al., 2011; Novakova et al., 2011; Zahodne et al., 2011). In patients treated for PD, we can assume that the decrease in motor activity, and thus in energy expenditure, might explain part of the increased weight gain, even though Amami et al. (2014) recently suggested that compulsive eating may be specifically related to STN stimulation.

Amongst the 18 animal studies (mainly rats) assessing food intake and weight further DBS (McClelland et al., 2013a), only two stimulated the Nac or dorsal striatum, while the others focused on the lateral (LHA) or ventromedial (vmH) hypothalamus. Halpern et al. (2013) showed that DBS of Nac can reduce binge eating, while van der Plasse et al. (2012) interestingly revealed different effects on sugar motivation and food intake according to the sub-area of Nac stimulated (core, lateral or medial shell). LHA stimulation mostly induced food intake and weight gain (Delgado and Anand, 1953; Mogenson, 1971; Stephan et al., 1971; Schallert, 1977; Halperin et al., 1983), even though Sani et al. (2007) showed a decreased weight gain in rats. vmH stimulation decreased food intake and/or weight gain in most cases (Brown et al., 1984; Stenger et al., 1991; Bielajew et al., 1994; Ruffin and Nicolaidis, 1999; Lehmkuhle et al., 2010), but two studies showed increased food intake (Lacan et al., 2008; Torres et al., 2011).

Tomycz et al. (2012) published the theoretical foundations and design of the first human pilot study aimed at using DBS to combat obesity specifically. Preliminary results from this study (Whiting et al., 2013) indicate that DBS of the LHA may be applied safely to humans with intractable obesity, and induce some weight loss under metabolically optimized settings. Two clinical trials on DBS for AN are also in progress according to Gorgulho et al. (2014), which demonstrate that DBS is a hot topic and promising alternative strategy to combat obesity and eating disorders.

4.2.3.2. What the future has to offer. Most of the DBS studies aimed at modifying eating behavior or body weight in animal models were performed one to several decades ago, and almost exclusively focused on the hypothalamus, which plays a pivotal role in homeostatic regulations. The explosion of functional brain imaging studies and the description of brain anomalies in the reward and dopaminergic circuits of subjects suffering from obesity or eating disorders show that hedonic regulations are of the utmost importance for food intake control.

The most effective treatment against obesity remains bariatric surgery, and especially the gastric bypass surgery. We have a lot to learn from the effectiveness of this treatment in terms of brain mechanisms and potential targets for DBS, and recent studies managed to describe the surgery-induced remodeling of brain responses to food reward, hunger or satiety (Geliebter, 2013; Frank et al., 2014; Scholtz et al., 2014). The Nac and PFC are part of the brain areas impacted. Knight et al. (2013) showed in pigs that DBS of the Nac can modulate the activity of psychiatrically important brain areas, such as the PFC, for which anomalies were described in obese humans (Le et al., 2006; Volkow et al., 2008) and minipigs (Val-Laillet et al., 2011). All the DBS improvements described beforehand will help targeting the best structures and coping with brain shift, and large animal models such as the minipig are an asset in perfecting surgical strategies.

Basal nuclei have a complex 'somatotopy' (Choi et al., 2012), and DA spatial and temporal release involves distinct neural microcircuits within subregions of these nuclei (Besson et al., 2010; Bassareo et al., 2011; Saddoris et al., 2013), which means that small errors in terms of targeting can have dramatic consequences in terms of neural networks and neurotransmission processes impacted. Once this challenge will be achieved, highly innovative deep-brain therapies could target some functions of the dopaminergic system for example, which is altered in patients suffering from obesity (Wang et al., 2002; Volkow et al., 2008) and animal models of addictive-like cravings or bingeing (Avena et al., 2006; Avena et al., 2008), with the aim of normalizing the functional processes of the DA system (as in Parkinson's for the motor disorders). Even though findings relating obesity and DA abnormalities appear sometimes inconsistent, it is probably because incorrect interpretations or comparisons have been done. Most of the discrepancies in the DA literature arose because different pathological stages (different degrees of obesity with different comorbidities, reward deficit vs. surfeit phenotypes), brain processes (basal activity vs. response to food stimuli), or cognitive processes (liking vs. wanting, occasional vs. habitual consumption) were compared. Before proposing a DBS strategy, there is a need for phenotyping patients in terms of neural circuits/functions impacted. For example, the individual reward sensitivity phenotype may determine the treatment target in terms of goal brain change (i.e. increased/decreased DA regions responsivity for deficit vs. surfeit phenotypes, respectively). In other patients for whom there is no alteration of the reward circuit but rather neural abnormalities in metabolic centers (such as the hypothalamus), the DBS strategy might be completely different (e.g. modulate the LHA or vMH activity in AN or obese patients to stimulate or decrease food intake, respectively).

Real-time fMRI neurofeedback combined with cognitive therapy (cf. Section 3.1) might also be used for closed-loop DBS therapy. Even though it has never been tested in our knowledge, the efficacy of targeting specific nuclei for DBS might be validated through its ability to improve real-time brain and cognitive processes related to self-control over highly palatable food stimuli (Mantione et al., 2014). This approach might be used to finely tune the DBS parameters and location to maximize its impact on specific cognitive tasks or processes (e.g. self-control over palatable foods).

Overall, these data offer a large field of research and developments to improve DBS surgery and make it, one day, a safer, flexible and reversible alternative to classical bariatric surgery.

5. General discussion and conclusions: the brain at the core of research, prevention and therapy in the context of obesity and eating disorders

As described in this review, neuroimaging and neuromodulation approaches are emergent and promising tools to explore the neural vulnerability factors and obesity-related brain anomalies, and eventually to provide innovative therapeutic strategies to combat obesity and ED. The different sections of this review article can raise several questions in terms of implementation of these tools in fundamental research, prevention programs and therapeutic plans. How can these new technologies and exploratory approaches find a place within the current medical workflow, from prevention to treatment? What are the requisites for their implementation, for which added value in comparison to existing solutions, and where could they slot into the current therapeutic plan? To answer these questions, we propose to initiate three debates that will inevitably need further work and reflection. First, we will discuss the possibility to identify new biological markers of key brain functions. Second, we will highlight the potential role of neuroimaging and neuromodulation in individualized medicine to improve the clinical pathways and strategies. Third, we will introduce the ethical questions that are unavoidably concomitant to the emergence of new neuromodulation therapies in humans.

5.1. Towards new biological markers?

"It is far more important to know what person the disease has than what disease the person has." This quote from Hippocrates bears the quintessence of preventive medicine. Indeed, reliable prediction and efficient prevention are the ultimate objective in public health. Similarly, accurate diagnosis, prognosis and treatment are mandatory for a good medical practice. But all of these cannot be reached without a good knowledge of the healthy and ill (or at risk) individual phenotypes,

which can be achieved through the description and validation of consistent biological markers.

Psychiatric studies extensively described the symptomology as well as the environmental and behavioral risk factors underlying ED, while obesity has been described through the lenses of multiple disciplines as a multifactorial disease with a complex etiology. Despite all of this knowledge, accurate biomarkers or clinical criteria are still lacking and obsolete indices (such as BMI) are still used all over the world to define and categorize patients. Yet, as reminded by Denis and Hamilton (2013), many persons classified as obese (BMI > 30) are healthy and should not be treated and categorized as diseased. On the contrary, subjects that are not considered at risk with classical clinical criteria might show a real vulnerability with more accurate markers, as described for the TOFI sub-phenotype (i.e. thin-on-the-outside, fat-on-the-inside), characterizing individuals at increased metabolic risk with normal body mass, BMI and waist circumference, but with abdominal adiposity and ectopic fat that MRI and MRS phenotyping can help to diagnose (Thomas et al., 2012). In the context of neuroimaging, neural vulnerability factors could help predicting a risk for further weight gain or susceptibility to contract a contentious relationship with food, as described in Burger and Stice (2014). For obvious practical and economical reasons, this approach could not be used for a systematic screening, but might be proposed to subjects that are particularly at risk, because of an unfavorable genetic or environmental ground. Since plasmatic gut-brain obesity-associated biomarkers were found to be associated with neurocognitive skills (Miller et al., 2015), their detection could advocate the collection of further functional biomarkers at the brain level and contribute to a step-by-step diagnosis. Identifying neural risk factors in people at risk, preferably in the young age, might guide further interventions (e.g. cognitive therapy) for pre-symptomatic treatment of obesity or eating disorders. For example, reward sensitivity phenotype may dictate the treatment target in terms of goal brain change (i.e. increased/decreased reward regions responsivity for deficit vs. surfeit phenotypes, respectively). Another example is the case of patients presenting symptoms that are common to different diseases and for which specific explorations are required. Some gastrointestinal diseases commonly mimic the presentation of eating disorders, which incites the clinician to consider a broad differential diagnosis when evaluating a patient for an eating disorder (Bern and O'Brien, 2013). New neuropsychiatric markers would consequently help diagnosis and should be added to the battery of decision criteria available.

Omics approaches, referring to innovative technology platforms such as genetics, genomics, proteomics, and metabolomics, can provide extensive data of which the computation might lead to the formulation of new biomarkers for prediction and diagnosis (Katsareli and Dedoussis, 2014; Cox et al., 2015; van Dijk et al., 2015). But the integration between omics and imaging technologies should potentiate the definition of these biomarkers, through the identification of organ-specific (notably brain-specific) metabolisms and culprits associated with diseases (Hannukainen et al., 2014). As described in the first section of this review, neural vulnerability factors could appear before the onset of ED or weight problems, highlighting the possible existence of subliminal predictors that brain imaging only might reveal.

Radiomics is a new discipline referring to the extraction and analysis of large amounts of advanced quantitative imaging features with high throughput from medical images obtained with computed tomography, PET, or structural and functional MRI (Kumar et al., 2012; Lambin et al., 2012). Radiomics has been initially developed to decode tumor phenotypes (Aerts et al., 2014), including brain tumors (Coquery et al., 2014), but could be applied to other medical fields than oncology, such as eating disorders and obesity. As reminded in Section 2.2, the combination of imaging modalities holds potential for future studies to decipher the neuropathological mechanisms of a disease or disorder. Radiomics (or *neuromics* when applied to brain imaging) could merge in the same individual some information about brain activity and cognitive processes (via fMRI, fNIRS, PET or SPECT) (see Section 2.1), availability

of neurotransmitters, transporters or receptors (via PET or SPECT) (see Section 2.2), focal differences in brain anatomy (via voxel-based morphometry − VBM) or connectivity (via diffusor tensor imaging – DTI) (Karlsson et al., 2013; Shott et al., 2015), brain inflammatory status (via PET or MRI) (Cazettes et al., 2011; Amhaoul et al., 2014), etc., and generate synthetic brain mapping to provide an integrative/holistic insight on brain anomalies associated with loss of food intake control or ED. Moreover, this combination of neurological information might help clarifying some discrepancies between studies, or apparent inconsistent findings such as those highlighted in the literature relating BMI and DA signaling for example. Indeed, these discrepancies might depend on the interpretation of studies that have looked at different aspects of dopamine signaling, or that compared processes (associated to cognitive functions) that were not comparable.

These biomarkers could be used to phenotype patients with a diagnosis of obesity and/or ED, as well as establish prognosis further specific interventions. They could also be used in prevention programs to identify subjects with neural vulnerability factors and provide some recommendations to prevent the onset of behavioral and health problems. In terms of therapy, radiomics/neuromics might also be used before selecting brain target(s) for neuromodulation, because the information gathered through this method might help predicting the consequences of neurostimulation on the activation of neural networks or the modulation of neurotransmission.

5.2. Neuroimaging and neuromodulation in the scope of personalized medicine

Personalized (or individualized) medicine is a medical model that proposes the customization of healthcare using all clinical, genetic and environmental information available, with medical decisions, practices, and/or products being tailored to the individual patient. As reminded by Cortese (2007), individualized medicine is in a pivotal position in the evolution of national and global health care in the 21st century, and this assertion is particularly true for nutritional disorders and diseases, given the societal and economical burden that obesity represents in the world for example, as well as the complexity and diversity of obese phenotypes (Blundell and Cooling, 2000; Pajunen et al., 2011). Advances in computational power and medical imaging are paving the way for personalized medical treatments that consider a patient's genetic, anatomical, and physiological characteristics. In addition to these criteria, cognitive measurements related to eating behavior (see Gibbons et al., 2014 for a review) should be used in conjunction with brain imaging because linking imaging data with cognitive processes (or biological measures) can potentiate the analysis and discrimination power.

Once the patient and the disease are well portrayed, the question of the best suitable therapy arises. Of course, individual history (and notably, previously unsuccessful therapeutic attempts) is particularly important. There is a graduation in both the severity of the disease and the degree of invasiveness of treatments available (Fig. 6A). Obviously, basic requirements for a healthy lifestyle (i.e. balanced diet, minimal physical activity, good sleep and social life, etc.) are sometimes difficult to achieve for many people, and never sufficient for those who went beyond a particular threshold in the disease progression. The classical therapeutic treatment plan then includes psychological and nutritional interventions, pharmacological treatments and, in pharmacorefractory patients, the logical next step is bariatric surgery (for morbid obesity) or hospitalization (for severe eating disorders). All the neuroimaging and neuromodulation strategies presented in this review can slot into the possible therapeutic plan at different levels, therefore at different stages of a disease, from identification of neural vulnerability traits to treatment of severe forms of the disease (Fig. 6A). Moreover, as illustrated in Fig. 6B, all the neuromodulation approaches presented do not target the same brain structures or networks. The PFC, which is the
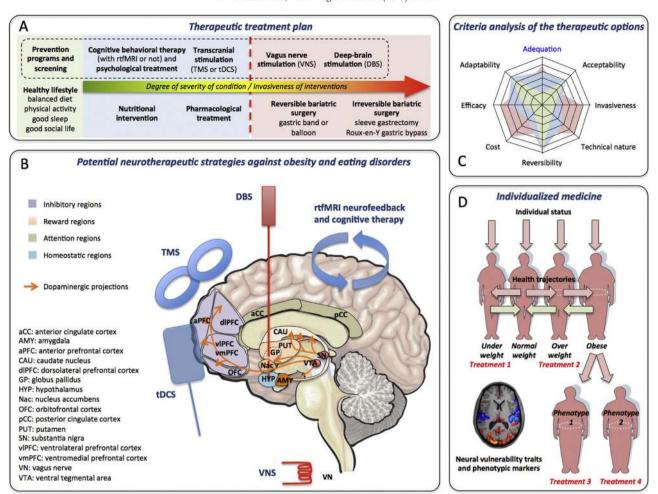
Fig. 6. Schematic representation showing how potential neurotherapeutic strategies could be included in the therapeutic treatment plan for patients suffering from obesity and/or eating disorders. (A) Simplified therapeutic treatment plan categorizing the different options according to the degree of severity of the patient's condition (BMI, comorbidities, etc.) and/or the degree of invasiveness of the interventions (in green: prevention programs and basic behavioral requirements for a healthy lifestyle; in blue: minimally invasive interventions; in red: invasive interventions requiring surgery/anesthesia). In the dotted box are indicated the therapeutic options discussed in the review. (B) Potential neurotherapeutic strategies against obesity and/or eating disorders, which target specific brain areas or complete neural networks regulating food intake, reward, attention, and homeostasis. (C) Examples of criteria analysis for the assessment of therapeutic options for an individual patient. Acceptability (pre- or post-intervention) of the therapy is patient-dependent. Some criteria are therapy-dependent, such as the invasiveness, technical nature, reversibility, and cost. The efficacy and adaptability of the therapy depend on the interaction between patient and therapy, and can be estimated upon data from a characterized clinical population. Adequation between therapy and patient is conditioned by all the aforementioned criteria, but also by external factors such as the social environment, the geographical/temporal availability of therapy, and the healthcare system the patient depends on. On the schematic three hypothetical intervention strategies to treat obesity in a lambda patient, e.g. a diet (in green), a minimally invasive therapy (in blue), and an invasive therapy (red) are represented. (D) In the context of individualized medicine, the absolute requirement is a good phenotyping of the clinical populations and individual patients, but also a good knowledge of the population/individual health trajectories. According to the type of disease/disorder, the individual history, and the degree of severity of the patient's condition, different therapeutic options can be considered. But within a given clinical population (e.g. morbidly obese), different phenotypes can exist and condition the choice of the treatment. Neuroimaging can help identifying neural vulnerability factors and markers, selecting the best treatment option, and shaping therapeutic strategies (e.g. rtfMRI neurofeedback or brain target identification for neuromodulation protocols).

primary target for transcranial neuromodulation strategies (e.g. TMS and tDCS), sends inhibitory projections to the orexigenic network but also has a major role in mood, food stimuli valuation, decision-making processes, etc. While rtfMRI neurofeedback could target virtually any moderate-sized brain region, existing studies mainly focused on the PFC, the ventral striatum, but also the cingulate cortex, which is very important for attentional processes. Lastly, in the context of nutritional disorders, DBS itself can target very different deep-brain structures, such as reward or homeostatic regions (Fig. 6B). As a consequence, the choice of a neuromodulation strategy cannot rest on a single criterion (e.g. balance between the severity of disease — e.g. high BMI with comorbidities — and the invasiveness of therapy), but on multiple assessment criteria, of which some of these are directly related to the patient's phenotype and some others to the interaction between patient and therapeutic option (Fig. 6C). For some obese patients, stimulating the hypothalamus via DBS for example might be ineffective or counterproductive if their condition takes its roots in anomalies of the brain reward circuit. There is consequently a great danger (the least being wasting time and money, the worst being worsening the patient's condition) in testing neuromodulation in patients before knowing which regulation process to target — and if the patient indeed develops iatrogenic neurobehavioral anomalies related to this process.

In the future, computational brain network models should play a major role in integrating, reconstructing, computing, simulating and predicting structural and functional brain data from various imaging modalities, from individual subjects to entire clinical populations. Such models could integrate functionalities for the reconstruction of structural connectivity from tractographic data, the simulation of neural mass models connected by realistic parameters, the computation of individualized measurements used in human brain imaging and their web-based 3D scientific visualization (e.g. The Virtual Brain, Jirsa et al., 2010), leading eventually to pre-operative modeling and predictions in the field of therapeutic neuromodulation.

5.3. Ethics related to novel diagnostic and therapeutic tools

As described in this paper, the battle against obesity and eating disorders has given rise to many new interdisciplinary developments. Novel less invasive treatments (in comparison to classical bariatric surgery for example) are within scrutiny in research and clinics. However, a sound critical attitude towards these novel techniques should be maintained especially before their clinical application. As reminded in Section 3.2, even minimally invasive neuromodulation techniques are not playthings (Bikson et al., 2013), and can have neuropsychological consequences that are not anodyne. Due to our current inability to understand the intricacies of brain modulations and their consequences on cognitive processes, eating behavior and body functions, it is crucial to remember another Hippocrates' aphorism: "first do no harm". Further preclinical studies in relevant animal models (e.g. pig models, Sauleau et al., 2009a; Clouard et al., 2012; Ochoa et al., 2015; Roura et al., submitted) are thus mandatory, along with extensive brain imaging programs to reveal the individual phenotypes and histories (Fig. 6D) that could shape prevention programs and possibly justify the use of neuromodulation therapy.

To be implemented in the therapeutic treatment plan against obesity and eating disorders, neuromodulation strategies must have higher assessment scores than classical options, and this assessment must integrate various criteria such as acceptability, invasiveness, technical nature (i.e. technologies and skills required), reversibility, cost, efficacy, adaptability and finally, adequation with the patient (Fig. 6C). The main advantages of neuromodulation approaches in comparison to classical bariatric surgery are: minimal invasiveness (e.g. DBS does not systematically require general anesthesia and leads to less comorbidities than a gastric by-pass), high reversibility (neuromodulation can be stopped immediately if problematic — even though insertion of deep-brain electrodes can induce residual lesions throughout the descent), adaptability/flexibility (brain target and/or stimulation parameters can be easily and quickly modified). But these advantages are not sufficient. The cost/advantage balance of each approach must be studied accurately, and the efficiency (cross between efficacy and level of investment, i.e. time, money, energy) of the alternative technique in improving life expectancy must compete with that of classical techniques. Minimally invasive and less costly neuroimaging and neuromodulation methods must receive a particular interest because they will permit a more important and widespread penetration in healthcare systems and populations. We gave the example of fNIRS and tDCS as non-invasive, relatively cheap and portable technologies, in comparison to other imaging and neuromodulation modalities that are costly, dependent on high-tech infrastructures, and consequently not readily available. Also, it is important to remind that, in the case of bariatric surgery, the aim is not to lose the most weight possible but to limit mortality and comorbidities associated with obesity. Some therapeutic options might be less effective than classical bariatric surgery to lose weight quickly but could be as efficient (or even better) to improve health on the long term, which means that the success criteria of (pre)-clinical trials should sometimes be revised or augmented with criteria related to the improvement of neurocognitive processes and control behavior, rather than mere weight loss (which is very often the case).

Once again, a lot of obese people are satisfied with their own lives/conditions (sometimes wrongfully) and some obese are indeed completely healthy. As a matter of fact, recent sociological phenomena, especially in North America, led for example to the emergence of *fat acceptance movements* (Kirkland, 2008). Such a phenomenon is far from being anecdotic or minor in terms of sociological impact on politics and healthcare systems, because it focuses on civil rights consciousness, freewill and discrimination, i.e. questions that affect directly a lot of people (in the USA, two thirds of the population is overweight, one third is obese). First, some people might perceive neuroimaging-based prevention and diagnosis as stigmatizing tools, which necessitates to focus scientific communication on the main objectives of this approach, i.e. improving vulnerability detection and healthcare solutions. Second, whatever the method employed, artificially modifying brain activity is not trivial, because the intervention can modify conscious and unconscious functions, self-control, and decision-making processes, which is very different than aiming at correcting motor functions such as for DBS and Parkinson's disease. Soda taxes and other dissuasive measures to fight obesity are usually unpopular and reproved, because it is sometimes perceived as paternalism and an affront against freewill (Parmet, 2014). But let's think about neuromodulation: Instead of increasing the monetary value of palatable foods, the aim is to decrease the hedonic value people attribute to these foods, *within* their brain. We must foresee that a technology that could change or correct mental processes will inexorably hatch a serious debate on bioethics, similarly to cloning, stem cells, genetically modified organisms, and gene therapy. Scientists, sociologists and bioethicists must be ready to address these questions because new exploratory tools and therapies cannot find their place without being accepted at every level of the society, i.e. individual patient, medical authorities, politics, and public opinion. Even if the decision to be subjected to a particular therapy belongs to the patient, individual decisions are always influenced by ideas that are conveyed at all levels of society, and medical authorities must approve all therapies. In a recent paper, Petersen (2013) stated that the rapid development of the life sciences and related technologies (including neuroimaging) has underlined the limitations of bioethics' perspectives and reasoning for addressing emergent normative questions. The author pleads in favor of a normative sociology of bio-knowledge that could benefit from the principles of *justice*, *beneficence* and *nonmaleficence*, as well as on the concept of human rights (Petersen, 2013). Even if some approaches are not biologically invasive, they can be psychologically and philosophically invasive.

5.4. Conclusion

The technologies and ideas presented in this paper rejoin the statement and conclusions of Schmidt and Campbell (2013), i.e. treatment of eating disorders and obesity cannot remain 'brainless'. A biomarker approach combining genetic, neuroimaging, cognitive and other biological measures will facilitate development of early effective precision treatments (Insel, 2009; Insel et al., 2013), and serve individualized prevention and medicine. Even though recent scientific discoveries and innovative technology breakthrough pave the way to new medical applications, our knowledge of the neuropsychological mechanisms governing eating behavior and favoring the emergence of a disease is still embryonic. Fundamental research in animal models and rigorous bioethics approach are consequently mandatory for a good translational science in this field.

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