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REVIEW

Inhibitory control as a potential treatment target for obesity

M. T. de Klerk[a,b], P. A. M. Smeets [a,c] and S. E. la Fleur [b]

[a]Image Sciences Institute, UMC Utrecht Brain Center, Utrecht University, Utrecht, The Netherlands; [b]Neurobiology of Energy Metabolism, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands; [c]Division of Human Nutrition and Health, Wageningen University, Wageningen, The Netherlands

ABSTRACT

Objectives: Strong reward responsiveness to food and insufficient inhibitory control are thought to be implicated in the development and maintenance of obesity. This narrative review addresses the role of inhibitory control in obesity and weight loss, and in how far inhibitory control is a promising target for weight loss interventions. Methods: PubMed, Web of Science, and Google Scholar were searched for papers up to May 2021. 41 papers were included. Results: Individuals with obesity have poorer food-specific inhibitory control, particularly when hungry, and less concurrent activation of inhibitory brain areas. Moreover, this was strongly predictive of future weight gain. More activation of inhibitory brain areas, on the other hand, was predictive of weight loss: individuals with successful weight loss initially show inhibitory brain activity comparable to that of normal weight individuals. When successful weight maintenance is achieved for at least 1 year, this inhibitory activity is further increased. Interventions targeting inhibitory control in obese individuals have divergent effects. Firstly, food-specific inhibitory control training is particularly effective for people with low inhibitory control and high BMI. Secondly, neuromodulation paradigms are rather heterogeneous: although rTMS to the left dorsolateral prefrontal cortex induced some weight-loss, multiple sessions of tDCS reduced food consumption (desire) and induced weight loss in two thirds of the papers. Thirdly, neurofeedback results in successful upregulation of brain activity and connectivity, but occasionally leads to increased food intake. In conclusion, inhibitory control is implicated in obesity. It can be targeted to promote weight loss although major weight losses have not been achieved.

KEYWORDS

Obesity; inhibitory control; weight loss; interventions; inhibitory brain areas

Introduction

Over the past four decennia, the number of people with obesity has nearly tripled. It was estimated that 650 million adults were obese in 2016, in addition to 1.9 billion overweight adults [1], and this problem is not restricted to the Western world [2]. Obesity is associated with many comorbidities, such as cardiovascular disease, type II diabetes mellitus, hypertension and various cancers [3–5]. Moreover, the risk for dementia and Alzheimer's disease is increased as well [6,7]. As such, obesity and being overweight are estimated to account for nearly 3.4 million deaths per year, which corresponds to the fifth leading cause of deaths worldwide [8]. In the current society, high-calorie palatable food is abundantly available, and most people have a largely sedentary lifestyle, often leading to an imbalance in energy intake and expenditure [9]. Excess energy is converted into fat, which results in weight gain and obesity [10].

Within the brain, several processes regulate eating behavior. Firstly, gastrointestinal appetite-related hormones signal to the brain stem and hypothalamus, which regulates food intake and energy homeostasis. Secondly, the reward value of food is encoded in dopaminergic brain areas such as the striatum and ventromedial prefrontal cortex. Thirdly, inhibitory control over eating behavior is subserved by the dorsolateral part of the prefrontal cortex [11,12]. It has been proposed that in obesity, the balance between these three processes is altered. There are two theories concerning the role of inhibitory control in obesity:

(1) Low inhibitory control may lead to short-term rewards not being inhibited, leading to overeating and consequently obesity [13]. Humans respond strongly to the external environment and have an innate preference for sweet foods [14,15]. The current

CONTACT P. A. M. Smeets p.smeets@umcutrecht.nl Image Sciences Institute, UMC Utrecht Brain Center, Heidelberglaan 100, Q02.4.45, Utrecht University, Utrecht 3584 CX, The Netherlands

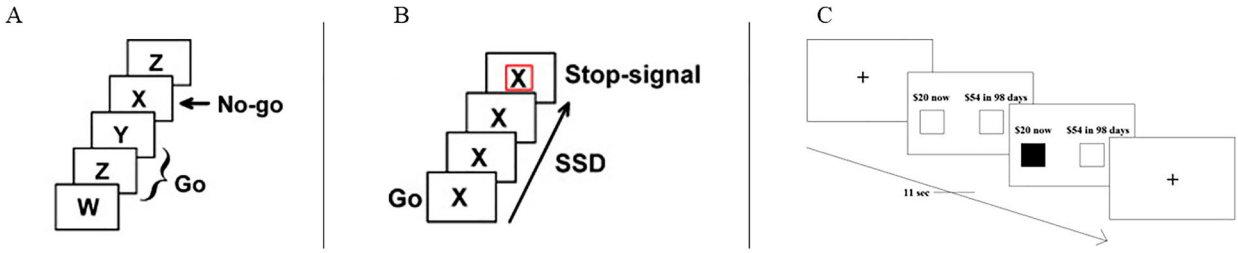

Figure 1. Paradigms that assess different aspects of inhibitory control. (A) Go/No-go task (response inhibition). (B) Stop-signal task (response inhibition). (C) Delay discounting task (future reward). Figures derived from Chambers et al. [19] and Kishinevsky et al. [68].

'obesogenic' environment, in which palatable high-calorie food is inexpensive and readily available, can thus promote overeating and weight gain.

(2) Increases in BMI could lead to metabolic changes in the brain, possibly due to inflammatory markers, which result in lower inhibitory control [16]. This theory is based on the association of insulin resistance (often observed in people with obesity) with decreased brain vascular reactivity. Moreover, the presence of inflammatory markers in people with obesity has been related to cognitive decline, as described by Maayan et al. [16].

Inhibitory control ability is defined as the capacity to inhibit a pre-potent response [17]. It can be assessed using several validated paradigms that measure different aspects of inhibitory control: A Go/No-go task, a stop-signal task, and a delay discounting task (see Figure 1) [18]. These tasks provide a measure of general inhibitory control ability, although also food-specific variants have been developed (see Figure 2). Both food-specific and non-food inhibitory control tasks typically activate parts of the dorsolateral prefrontal cortex (DLPFC) [19–23]. The DLPFC is involved in inhibitory control by suppression of reward values (e.g. reward associated with a certain action), which are represented in ventromedial prefrontal cortex (VMPFC) [24–26]. Therefore, connectivity between these brain areas is often observed in these tasks. The DLPFC is localized over 3 frontal gyri: the inferior frontal gyrus (IFG), the middle frontal gyrus (MFG), and the superior frontal gyrus (SFG) [27]. The left IFG and MFG are proposed to be responsible for response selection, whereas the right hemisphere parts of these regions are involved in suppression of motor responses [20,28]. The SFG is thought to be involved in general response inhibition [29]. With non-food inhibitory control tasks, it has been found that lower inhibitory control is related to higher energy intake and weight gain in normal-weight individuals [30,31]. It has even been suggested that poor inhibitory control *causes* overeating [13].

In this narrative review, we first compare inhibitory control ability between people with obesity (OB) and with normal weight (NW). We then explore whether inhibitory control is also a key factor in weight loss (maintenance), and whether neural mechanisms of inhibitory control play a role. Finally, we discuss in how far inhibitory control is an effective target for weight loss interventions.

Methods

Search strategy

The databases of PubMed, Web of Science, and Google Scholar were searched for papers; relevant papers were considered for inclusion in this narrative review up to May 2021. Experimental studies were sought that examined inhibitory control in OB, as well as the relevance of inhibitory control for weight loss and interventions that target inhibitory control. Therefore, the following search terms were used consecutively: *obes*, impuls*, impulse control, inhibit*, inhibitory control, cognitive control, weight loss, successful dieters, intervention, treatment.* Moreover, the tasks used to measure inhibitory control were searched to ensure that articles that measured inhibitory control without naming the above-mentioned terms were included: *go/no-go, stop-signal, delay discounting,* and *delayed gratification.* Subsequently, the 'snowball' method was used, i.e. references from the papers found using the search terms were also screened to find eligible papers.

Inclusion criteria

Prospective and cross-sectional studies were included when an adult or adolescent population with obesity was examined. Obesity is characterized by body mass index (BMI) ≥ 30, which is a widely used and useful measure, although body composition and adipose tissue distribution are not taken into account [32]. Importantly, papers that used validated behavioral paradigms to measure inhibitory control were included, as opposed

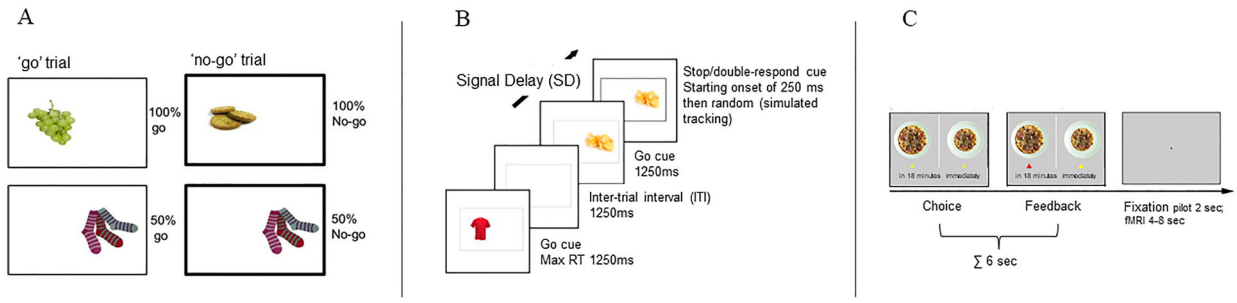

Figure 2. Food-specific paradigms that assess different aspects of inhibitory control. (A) Go/No-go task (response inhibition). (B) Stop-signal task (response inhibition). (C) Delay discounting task (future reward). Figures derived from Lawrence et al. [103], Lawrence et al. [104] and Weygandt et al. [87].

to papers that used only self-report measures of inhibitory control, which may be prone to memory biases and overestimation [33]. One author did the paper selection and another author reviewed the identified papers for eligibility. In case of doubt inclusion was discussed. Both agreed on the final selection of papers.

Exclusion criteria

There were three major reasons for exclusion. Firstly, papers examining binge-eating disorder (BED) were excluded. Although some evidence supports that BED is a subtype of obesity, it has also been suggested that individuals with BED show elevated food-related impulsivity or lessened inhibitory control compared to OB, which might indicate it is a different subpopulation [34]. In this review, we focus on common obesity. Secondly, papers that included populations with disorders that could potentially influence weight and/or eating behavior, such as Prader-Willi syndrome, were excluded. Thirdly, cross-sectional research examining children was excluded, because their prefrontal cortex is still developing [35]. Notwithstanding, as a considerable amount of prospective research has included children, predicting BMI up to adulthood, these papers were included. Following the eligibility criteria, papers were assessed by screening the title and abstract. This resulted in 41 articles.

Results

Inhibitory control and obesity

Although previous reviews have been written about inhibitory control and obesity [36–38], this section is unique in that it discusses papers that used several tasks for measuring inhibitory control. Moreover, not all previous reviews included neuroimaging findings. It was observed that low inhibitory control causes overeating and weight gain in NW, accompanied by reduced activation of inhibitory control areas in the brain (parts of the DLPFC) [13,30,31]. Here, we discuss inhibitory control ability in *obesity*; see Table 1 for an overview of the 11 papers discussed. First, 9 papers using a response inhibition task are reviewed, followed by 2 papers that on valuing future reward.

Response inhibition

General response inhibition has been measured in several studies to compare individuals with obesity (OB) with normal-weight individuals (NW). For example, it has been shown that OB perform worse on general response inhibition tasks than lean individuals; they have longer reaction times (RTs) on a stop-signal task [39,40]. Moreover, OB make more errors, in addition to having longer RTs, in a Go/No-go task [41,42]. In contrast, however, three other studies reported no differences in general inhibitory control ability between adult OB and NW. Lawyer et al. found that BMI was unrelated to inhibitory control in a stop-signal task [43]. However, underweight, NW, and overweight individuals were grouped together into a non-obese group and compared to the obese group. This could bias the results, since participants with overweight might shift the results of the non-obese group in the direction of the obese group. A correlational analysis would have yielded more robust results. Hendrick et al. also found no differences between OB and NW with regard to performance on a stop-signal task [44]. Moreover, a moderate negative correlation was observed between BMI and activation of the right IFG, although this effect did not survive proper correction for multiple comparisons.

It has also been examined whether people with obesity display a food-specific impairment in inhibitory control. In a Go/No-go paradigm, Batterink et al. assessed whether BMI was related to response inhibition in hungry adolescent girls, ranging from NW to OB [45]. The

Table 1. Summary of studies examining inhibitory control ability in obese and overweight individuals.[a]

Ref.	Study	Subjects	Task	Outcome measure	Results
[36]	Nederkoorn et al. (2006)	OB and NW women, $N = 59$	Stop-signal (non-food)	RT	OB had longer RT than NW
[37]	Chamberlain et al. (2015)	Young OB, OW, and NW adults, $N = 511$	Stop-signal (non-food)	RT	OB had slower RT compared to NW
[38]	Calvo et al. (2014)	Young OB, OW, and NW adults, $N = 62$	Go/No-go (non-food)	RT and accuracy	OB had slower RT compared to NW, accuracy did not differ between groups
[39]	Mobbs et al. (2011)	OB and NW adults, $N = 32$	Go/No-go (food and non-food)	RT, accuracy, and number of omissions	OB and NW responded faster to food-related targets and OB were more likely to make errors on all types of stimuli. There were no differences with regard to omissions
[40]	Lawyer et al. (2015)	Non-OB (UW, NW, and OW) and OB, $N = 296$	Stop-signal (non-food)	RT	BMI was unrelated to RT
[41]	Hendrick et al. (2012)	OB and NW women, $N = 43$	Stop-signal (non-food)	RT and accuracy, brain activity (fMRI)	OB and NW had similar RT and accuracy. BMI correlated with lower brain activity in the right IFG
[42]	Batterink et al. (2010)	Hungry adolescent girls ranging from NW to OB, $N = 29$	Go/No-go (food-specific)	RT and accuracy, brain activity (fMRI)	Individuals with high BMI had shorter RT but made more errors during no-go trials. They had lower activity in bilateral SFG and MFG during response inhibition
[43]	Loeber et al. (2012)	OB and NW adults, restrained from eating > 3 h, $N = 32$	Go/No-go (food-specific)	RT and accuracy	OB and NW were faster to respond to food-specific stimuli and made more errors during the non-food stimuli. For OB, the time since the last meal correlated with the number of errors in food-specific trials
[45]	Aiello et al. (2018)	Older OB and NW adults in sated state, $N = 30$	Go/No-go (food-specific)	RT and accuracy	RT was larger for food-related words (compared to utensils) for both OB and NW, no group differences were observed. There were no differences for accuracy
[51]	Kishinevsky et al. (2012)	OB women, $N = 24$	Delay discounting (monetary)	Brain activity (fMRI)	Difficult compared to easy trials resulted in greater activity in the left IFG, and bilateral MFG and SFG
[52]	Stoeckel et al. (2013)	OB women, $N = 24$	Delay discounting (monetary)	Brain activity (fMRI)	Women who chose more immediate rewards had less activation in the left IFG, and bilateral MFG and SFG, which was unrelated to BMI

[a]OB = obese, OW = overweight, NW = normal weight, UW = underweight, BMI = body mass index (kg/m^2), RT = reaction time, fMRI = functional magnetic resonance imaging, IFG = inferior frontal gyrus, MFG = middle frontal gyrus, SFG = superior frontal gyrus.

go-trials were low-calorie vegetables, whereas the no-go trials were high-calorie desserts. Individuals with higher BMI had shorter RTs but made more errors during no-go trials (high-calorie desserts). Moreover, these individuals had lower activation of the bilateral SFG and MFG during response inhibition. These moderate effects were replicated by Loeber et al.: when the time since their last meal was included, OB men and women made more errors than NW when food stimuli were go-trials in a Go/No-go task [46]. Consistent with findings in NW [47], they found that both OB and NW responded faster to and made fewer errors during food-specific stimuli, irrespective of the time since their last meal. These findings suggest that both OB and NW have a bias towards food stimuli when they are not hungry.

In relatively older (aged 42–70) OB and NW, a Go/No-go task revealed that RTs were larger for food-related images compared to utensils in both OB and NW, which is opposing the previous two studies [48]. Additionally, no differences between groups were observed. Because the individuals were tested in a sated state, this may be indicative of a role of hunger in food-specific response inhibition in OB. Indeed, in the two studies discussed before, the OB only performed worse compared to NW when they were hungry.

These three food-specific studies indicate that people with obesity display a food-specific reduction in inhibitory control, at least in hungry participants. Therefore, hunger state is an important factor to consider. This has also been concluded by Bartholdy et al. (2016), be it only for the stop signal task [36]. One of those studies found concurrent reduced activation of the SFG and MFG during response inhibition [45], which needs replication. Findings regarding general inhibitory control are more mixed. When the results of Lawyer et al. [43] are disregarded, because of inconvenient grouping, only one study disputes the general inhibitory control reduction in obesity [44]. The four other studies point towards a general inhibitory control impairment [39–42]. These results are similar to findings in NW with low inhibitory control [11,22,23,30]. However, most of the aforementioned studies did not control for IQ or income, which are confounding factors with regard to inhibitory control [49]. At the same time, a disproportional percentage of people with obesity has a low IQ and is of low SES [50–52].

Valuing future reward

In a comprehensive meta-analysis on behavioral findings of delay discounting tasks, consisting of 29

case–control and 30 continuous comparison studies, it was established that steep discounting of both food and money are robust aspects of obesity, indicating diminished inhibitory control in obesity with a medium effect size (ES) [53]. The effect did not differ with regard to study design (case–control or continuous), reward type (food or monetary), or sex (female or mixed sample).

To date, only two neuroimaging studies used a delay discounting task to examine inhibitory control in obesity. The first study tested women with obesity in a monetary delay discounting paradigm. Difficult compared to easy trials were associated with greater activation of the left IFG, and bilateral MFG and SFG [54]. Difficult trials were trials where the subjective value was relatively similar between the immediate and the delayed reward. The second study examined the same sample of participants as the first study. They found that women who chose more immediate rewards rather than delayed rewards, had less activation of the same brain areas [55]. BMI did not modulate this strong association, but this may be a ceiling effect since all participants had obesity.

Together, these findings indicate that the necessity to execute more inhibitory control is accompanied by stronger activation of the left IFG, and bilateral MFG and SFG, and less inhibitory control is accompanied by weaker activation of these regions in women with obesity. Less inhibitory control may lead to short-term rewards not being inhibited. This is a similar finding as in healthy-weight controls [21]. However, because no control group was included, we cannot deduce any differences between those groups from these studies. Moreover, studies including women should take the phase of the menstrual cycle in account since this affects food craving and intake, as well as performance on response inhibition tasks, including activation of the DLPFC [56–58].

Inhibitory control and weight loss

The evidence discussed suggests that OB have diminished inhibitory control. Here, first potential predictors of weight loss will be reviewed (14 papers), and subsequently characteristics of individuals with successful weight loss (SWL) will be discussed (5 papers; see Table 2).

Predictors of weight loss

Prospective research with children has assessed their performance on response inhibition tasks and BMI or weight-change on short and long-term. Shorter RTs on a stop-signal task predicted greater reduction in body-weight up to 12 months thereafter in children with obesity [59]. Moreover, performance in a non-food Go/No-go task predicted successful weight loss in a weight-reduction program, particularly among adolescents, although the criterion for success was a mere 5% reduction in BMI [60]. Furthermore, low food-specific and monetary discounting at a young age is associated with lower BMI, up to 30 years later [61–65].

Similar findings have been observed in prospective research in adults. Using a monetary delay discounting task, it was found that less activation in the right IFG, bilateral MFG, and left SFG during difficult monetary trials predicted a greater rate of weight gain 1–3 years later in women with obesity [54]. Because this study was not longitudinal, it remains unclear what causes the altered functioning of these inhibitory control regions. For example, it is possible that low functioning leads to overeating and subsequently to obesity, but also that obesity induces changes in these brain areas.

Reversely, these findings suggest that greater inhibition-related activation in these brain areas could be protective against weight gain or promote weight loss. Accordingly, Weygandt et al. reported that greater brain activity in and stronger connectivity between the VMPFC and DLPFC during a food-specific delay discounting paradigm correlated strongly with subsequent dieting-induced weight loss in men and women with obesity [66]. In addition, participants with greater behavioral inhibitory control lost more weight. In a follow-up experiment with similar experimental settings, weight loss maintenance after the diet was predicted by activation in the right SFG, and inhibitory control was inversely related to successful weight maintenance [67]. Similarly, Kulendran et al. investigated whether impulsivity *improved* with weight loss during a weight loss intervention [68]. This intervention lasted 2–8 weeks and focused on behavioral change. The average BMI reduction was 8.4%, ranging from 2.54 to 3.12 kg/m^2. Indeed, those who improved their performance on a stop-signal task the most also achieved the greatest BMI reduction. This was not the case for a monetary delay discounting task. The results of [69] are in line with these findings. Although performance on a non-food Go/No-go task and a monetary delay discounting task improved after an internet-based 3-month weight loss program, this was unrelated to weight changes.

On the contrary, Batterink et al. found that behavioral inhibitory control on a food-specific Go/No-go task and inhibition-related brain activation were not related to BMI change 1 year later [45]. The authors explain these null findings by their modest sample size

Table 2. Summary of studies examining the role of inhibitory control for weight loss (maintenance).[a]

Ref.	Study	Subjects	Task	Outcome measure	Results
[42]	Batterink et al. (2010)	Hungry adolescent girls ranging from NW to OB, $N = 29$	Go/No-go (food-specific)	BMI change in 12 mo	Performance on the Go/No-go task could not be related to BMI change, nor could brain areas involved in inhibitory control
[51]	Kishinevsky et al. (2012)	OB women, $N = 24$	Delay discounting (monetary)	Weight-gain in 3 yr	Less activation of the right IFG, bilateral MFG, and left SFG on difficult monetary trials could predict greater rate of weight-gain
[56]	Nederkoorn et al. (2007)	OB children aged 8–12, $N = 18$	Stop-signal (non-food)	Change in body weight at 6 and 12 mo follow-up	Shorter RT predicted greater reduction in body-weight
[57]	Pauli-Pott et al. (2010)	Children and adolescents aged 7.5–15 in a weight-reduction program, $N = 111$	Go/No-go (non-food)	BMI change in 1 yr	Short RT and fewer errors predicted successful (>5%) weight loss, particularly in adolescents
[58]	Anzman & Birch (2009)	Girls aged 5–15, $N = 197$	The Child Behavior Questionnaire for parents	BMI and weight-gain at age 15	Girls with lower inhibitory control at age 7 had higher BMI and greater weight gain. They were almost 2 times more likely to be overweight
[59]	Francis & Susman (2009)	Children aged 3–5, $N = 1061$	Video-records, delay discounting (food-specific)	BMI change at age 12	Children with low self-regulation had higher BMI at follow-up measurements. They also had a higher increase in BMI
[60]	Duckworth et al. (2010)	Children aged 11, $N = 105$	Delay discounting (monetary)	Weight-gain in 3 yr	Steep discounting predicted weight-gain
[61]	Schlam et al. (2013)	Children aged 4, $N = 164$	Delay discounting (food-specific)	BMI change after 30 yr	Longer delay of gratification at age 4 was associated with lower BMI
[62]	Tsukayama et al. (2010)	Children aged 9, $N = 844$	Social Skills Rating System questionnaire	Chance of being overweight at age 15	Children with more self-control had a lower chance of being overweight (RR = 0.74)
[63]	Weygandt et al. (2013)	OB adults, before the onset of a diet, $N = 16$	Delay discounting (food-specific)	Weight loss after 12 wk	Greater brain activity in and stronger connectivity between the VMPFC and DLPFC correlated with subsequent weight loss. Adults with low discounting lost more weight
[64]	Weygandt et al. (2015)	OB adults on a diet, $N = 19$	Delay discounting (food-specific)	Weight loss maintenance 12 mo later	Activity in the right SFG predicted weight loss maintenance, and inhibitory control was inversely related to successful weight-maintenance
[65]	Kulendran et al. (2014)	Adolescent OB and OW in a weight-reduction program, $N = 53$	Delay discounting (monetary), stop-signal (non-food)	BMI change in 8 wk	BMI was reduced with 8.4% on average. Performance on a monetary delay-discounting and a non-food stop-signal task also improved over the course of the intervention, with 23.6% and 22.9%, respectively, which in the case of the stop-signal predicted the reduction in BMI
[66]	Ross et al. (2020)	OB and NW adults in a weight-reduction program, $N = 75$	Delay discounting (monetary), Go/No-go (non-food)	Weigth loss and inhibitory control change at 3, 6, 9, and 12 mo follow-up	Improvement of performance on non-food inhibitory control tasks was unrelated to weight changes
[67]	Brockmeyer et al. (2016)	OB adults, prior to a weight-reduction program, $N = 13$	Go/No-go (food-specific)	Weight loss in 12 mo	Performance on the GO/No-go task only predicted weight loss in combination with food liking
[69]	DelParigi et al. (2007)	Adult SWL (>3 mo) and non-dieters (OB and NW), $N = 29$	Meal consumption	Brain activity (PET)	SWL had increased activation in the DLPFC compared to non-dieters, which was associated with dietary restraint
[70]	Le et al. (2007)	Adult OB, NW, and SWL (>3 mo), $N = 30$	Meal consumption	Brain activity (PET)	SWL had greater activity in the left IFG compared to OB, but no differences could be observed between SWL and NW
[72]	Sweet et al. (2011)	OB, NW, and SWL (>3 yr), $N = 49$	Orosensory stimulation with a lemon lollipop	Brain activity (fMRI)	SWL maintainers displayed greater activity in the left IFG compared to both OB and NW
[73]	McCaffery et al. (2009)	Adult OB, NW and SWL (>12 mo), $N = 51$	Viewing images of food	Brain activity (fMRI)	SWL had increased activation in the left SFG for both high- and low-caloric food images compared to OB and NW. Compared to OB only, SWL had greater activation in the bilateral SFG and MFG
[74]	Jensen & Kirwan (2015)	Adolescent OB, NW, and SWL (>12 mo), $N = 34$	Viewing images of food	Brain activity (fMRI)	SWL displayed increased right DLPFC and right SFG activation compared to both OB and NW when viewing high-caloric food images compared to non-food images only, not when viewing low-caloric food images compared to non-food images

[a]OB = obese, OW = overweight, NW = normal weight, SWL = successful weight loser, BMI = body mass index (kg/m^2), RT = reaction time, RR = relative risk, GM = gray matter, fMRI = functional magnetic resonance imaging, PET = positron emission tomography, DLPFC = dorsolateral prefrontal cortex, VMPFC = ventrolateral prefrontal cortex, IFG = inferior frontal gyrus, MFG = middle frontal gyrus, SFG = superior frontal gyrus.

(29 hungry adolescent girls, ranging from lean to obese). Nevertheless, Brockmeyer et al. found that inhibitory control, as measured by a food-specific Go/No-go paradigm, only predicted weight loss in combination with low food liking when measured prior to a weight-reduction program (28% of unique variance in % weight loss explained) [70]. Hence, it is also conceivable that the null findings of Batterink et al. [45] are due to the fact that food liking was not taken into account.

In sum, seven studies examining children confirm that weight loss can be predicted by high inhibitory control ability. In adults, four of the seven studies were in accordance with the findings in children, because in one study the effect of inhibitory control was not strong enough by itself. Additionally, it seems as if it is important to distinguish food-specific and non-food tasks; food-specific tasks appear to be a more robust predictor of weight-loss in adults. Moreover, high inhibitory brain activation in and high connectivity between the DLPFC and the VMPFC were strongly correlated with reductions in body weight and weight loss maintenance in three studies.

An important caveat in the aforementioned papers is that the weight loss programs highly differed in approach and length, which makes comparison of weight loss success difficult. For example, Pauli-Pott et al. [60] included physical exercise and dietary courses, which endured for 12 months, whereas Weygandt et al. [66] used a program of 12 weeks, in which caloric restriction was administered in addition to physical exercise.

Characteristics of successful weight loss

In order to identify the characteristics of SWL, it is informative to compare this group to OB as well as to NW, as this would show whether inhibitory control-related brain activation returns to levels of NW. No study directly measured inhibitory control, but many neuroimaging studies compared SWL with OB and NW on test meal intake and on food-cue viewing paradigms. Successful weight loss is defined as intentionally losing at least 10% of body weight, maintained for at least 12 months, according to Wing & Hill [71].

In a positron emission tomography (PET) study in women, SWL were compared to non-dieters (OB and NW grouped together). SWL had increased activity in the DLPFC in response to meal *consumption* compared to non-dieters, which was moderately associated with dietary restraint [72]. However, grouping OB and NW together eliminates some of the information the study could have provided with regards to the mechanism of weight loss in the brain. In an identical study, also using PET but not grouping OB and NW together, SWL had greater activation of the left IFG in response to receiving a liquid meal compared to OB, but no differences were observed between SWL and NW [73]. Hence, SWL either have their inhibitory control responses in the brain normalized, or individuals with increased activation in these brain areas are better able to lose weight. An important side note of both studies is that SWL had only been successful for 3 months. Even 12 months after weight loss, hormones that regulate appetite do not diverge from levels from before the onset of a diet, which may make individuals prone to relapse [74]. Findings from Sweet et al. are, therefore, more informative: SWL that were successful for at least 3 years displayed greater activity in the left IFG compared to both OB and NW, during orosensory stimulation with a lemon lollipop [75]. This may suggest that SWL make greater effort to inhibit responsiveness to desired food cues.

When adult OB, NW, and SWL – who maintained their weight loss for at least 12 months –*view* images of low-calorie and high-calorie food while undergoing fMRI scanning, SWL have increased activation in the left SFG for both high- and low-calorie food images compared to OB and NW [76]. Moreover, compared to OB only, SWL had greater activation of the bilateral SFG and MFG. In an adolescent sample, SWL displayed increased right DLPFC and right SFG activation compared to both OB and NW when viewing high-calorie food images compared to non-food images only, not when viewing low-calorie food images compared to non-food images [77]. The latter indicates that SWL have a bias for high-calorie food and increased activation in comparison to OB in the left IFG. This may reflect the greater (successful) effort SWL make to inhibit responsiveness to desired food cues.

Together, these results might reflect initial normalization and subsequent compensation of inhibitory brain areas. SWL first show brain activity comparable to that of NW, hence normalization during food consumption [73]. When successful weight maintenance is achieved for at least 1 year, inhibitory activity in the left IFG and bilateral SFG is further increased compared to NW, hence compensation during food consumption and viewing [75–77]. Nevertheless, studies monitoring different time points after weight loss using both food consumption and viewing paradigms are necessary to verify this hypothesis.

Regardless of these affirmative findings, a major limitation is the lack of focus on inhibitory control. In none of the aforementioned studies inhibitory control was assessed behaviorally, preventing inference of whether initial normalization and subsequent

compensation in brain activity coincided with increases in inhibitory control ability. In addition, inclusion criteria for SWL differed enormously, ranging from having lost a certain amount of weight to having lost a certain percentage, and from a certain current weight to weight-change. Thus, it is necessary to replicate the aforementioned findings using behavioral inhibitory control paradigms.

Interventions

A variety of weight loss treatments and interventions have been developed, ranging from behavioral weight-control (a simple diet) to surgery. However, these interventions are often not effective or preferred [78]. Treatment outcomes of these interventions are variable: one-third to two-thirds of patients with obesity who initially succeed to lose weight, gain it back or even exceed their initial weight [71,79]. Therefore, the need for novel techniques seems evident. Inhibitory control has been clearly implicated in obesity and weight loss, although interventions exclusively targeting inhibitory control would presumably not treat morbid obesity. In this section, interventions targeting inhibitory control and implicated brain areas will be discussed per intervention, see also Table 3 for an overview of the findings (a total of 14 papers).

Behavioral inhibitory control training

Better performance on inhibitory control tasks is associated with and predictive of lower BMI and better results regarding weight loss. This raises the possibility that when inhibitory control is trained, more weight loss can be achieved, or weight gain can be prevented. Inhibitory control training (ICT) has been examined extensively in NW. For such training, a modified version of a response inhibition task is typically used, where inhibition is required for unhealthy foods. The effectiveness depends on the task: Go/No-go tasks are generally more effective than stop-signal tasks, with a reduction in calorie consumption of 32% and 18%, respectively after ICT [80]. Two meta-analyses affirm that a Go/No-go paradigm is more successful than a stop-signal paradigm to promote healthy eating behavior (medium versus small ES [81]) and reduce food consumption (medium versus small ES [82]). The effectiveness of ICT also depends on BMI: particularly individuals with a relatively high BMI benefit from training [83]. This could be due to their lower performance, leaving more room for improvement.

When considering this intervention in a sample ranging from lean to obese, Houben found that participants with low inhibitory control benefit the most from ICT, possibly due to leaving more room for improvement, but promising for individuals with obesity nonetheless [84]. A stop-signal task was used with food-related and non-food pictures. There were three types of foods (counterbalanced): either always paired with the stop signal (inhibition food), never paired with the stop signal (impulsivity food), or paired with the stop signal on 50% of the trials (control food). As a result of the ICT (inhibition food), food consumption of participants with low inhibitory control was effectively reduced to levels of individuals with high inhibitory control for the control food. Lawrence et al. extended these findings by demonstrating that only ICT with food-specific targets are moderately effective in reducing subsequent food intake, as opposed to ICT with general non-food targets [85]. The same authors investigated the effect of an online ICT in a Go/No-go task [86]. The active group trained on a food-specific paradigm, where low-calorie foods were the targets and high-calorie foods were the non-targets. The control group performed a general Go/No-go task. Participants ranged from lean to obese, but the sample consisted predominantly of overweight and OB (mean BMI 28.5). The active group reduced their caloric intake during the intervention week of 4 sessions, as assessed with a personal diary, although on a taste test no differences were found between the intervention groups. In this test, participants could consume two high-calorie foods, of which one was associated with the non-target. However, the taste test was performed at home, thus without the time of the day or hunger levels taken into account. Moreover, the active group showed a small weight reduction of 2.21 kg on average compared to their baseline weight up to 6 months later.

Delay discounting tasks have also been used in ICT. Women that were overweight or had obesity were asked to perform a monetary delay discounting task, while prospectively experiencing events in the future (episodic future thinking, EFT). EFT is known to reduce discounting. EFT indeed resulted in less discounting compared to the control condition, and caloric intake from an ad libitum buffet meal was reduced by ~30% with 315 calories [87]. However, participants may have thought specifically about future food events. In another study, women ranging from lean to obese were asked to perform a written assignment of EFT or episodic past thinking (EPT, as a control measure). Subsequently, participants completed a discount rate questionnaire. Both food-related EFT and general EFT resulted in reduced discounting on the questionnaire, but only food-related EFT reduced actual food intake when snacks were provided at the testing location

Table 3. Intervention studies targeting inhibitory control in obese and overweight individuals.[a]

Ref.	Study	Subjects	Task	Outcome measure	Results
[81]	Houben (2011)	Young women ranging from NW to OB, $N = 29$	ICT stop-signal (food and non-food)	Food consumption	Food consumption of participants with low inhibitory control was reduced to levels of individuals with high inhibitory control
[82]	Lawrence et al. (2015)	Adults ranging from NW to OB, $N = 65$	ICT stop-signal (food and non-food)	Food consumption	Only food-specific targets were effective in reducing subsequent food intake, as opposed to non-food targets
[83]	Lawrence et al. (2015)	OB and OW adults, $N = 83$	Online ICT Go/No-go, intervention week of 4 sessions	Caloric intake (assessed with a personal diary), food consumption (taste test), weight-change	The active group reduced their caloric intake, although no differences were found between the intervention groups with regards to food consumption. The active group showed a weight reduction of 2.21 kg on average up to 6 months later
[84]	Daniel et al. (2013)	OB and OW women, $N = 26$	EFT	Discounting rate on delay discounting (monetary), caloric intake	EFT resulted in less discounting compared to the control condition, and caloric intake was reduced
[85]	Dassen et al. (2016)	Young women ranging from NW to OB, $N = 94$	EFT (food and non-food)	Discounting rate on delay discounting (monetary)	Both food-related EFT and general EFT resulted in reduced discounting on the questionnaire, but only food-related EFT reduced actual food intake
[86]	Yokum & Stice (2013)	Adolescents ranging from NW to OB, $N = 21$	EFT	Brain activity (fMRI)	Thinking of future benefits of not eating certain foods activated the left medial SFG and left MFG, whereas thinking of future costs of eating certain foods activated the left medial SFG only. No differences between NW, OW, and OB individuals were found
[91]	Kim et al. (2018)	OB and OW adults, $N = 60$	rTMS on left DLPFC, 4 sessions for 2 weeks	Food consumption, weight-change after 2 wk	rTMS resulted in reduced food intake and weight-loss
[92]	Kim et al. (2019)	OB and OW adults, $N = 36$	rTMS on left DLPFC, 8 sessions for 4 weeks	Food consumption, weight-change, functional connectivity (fMRI)	rTMS resulted in reduced food intake and weight-loss. Functional connectivity in the right frontoparietal network was increased
[95]	Ray et al. (2017)	OB adults, $N = 18$	tDCS for 20 min: anode on right DLPFC and cathode on left DLPFC, 1 session	Food craving and consumption	tDCS decreased food craving and consumption, but only when controlling for individual differences in impulsivity: the higher the impulsivity the more effect
[96]	Gluck et al. (2015)	OB adults, $N = 9$	tDCS for 40 min on left DLPFC, 3 sessions	Food consumption, weight-change after 9 days	Food consumption was reduced during anodal stimulation, particularly regarding fat and soda (on average −23% of their weight-maintenance needs). More importantly, weight-loss was induced (−0.4%)
[97]	Montenegro et al. (2012)	OW adults, $N = 9$	tDCS for 20 min on left DLPFC, 3 sessions, physical exercise	Food consumption desire	Food consumption desire was reduced with 20%, up to 30 min after stimulation. Moreover, when tDCS was paired with physical exercise, these effects were doubled
[98]	Heinitz et al. (2017)	OB adults, $N = 31$	tDCS for 40 min on left DLPFC, 3 sessions	Food intake, weight-change after 6 wk	Food intake and weight-change were not changed
[103]	Kohl et al. (2019)	OB and OW adults, $N = 35$	1 session neurofeedback to the DLPFC while passively viewing high-caloric food	Brain activity and functional connectivity (fMRI), caloric intake, weight-change	Activity in the left DLPFC and functional connectivity with the VMPFC increased. There was no change in caloric intake or weight-change immediately after the training nor 4 weeks later
[104]	Spetter et al. (2017)	OB and OW men, $N = 8$	4 sessions neurofeedback spread out over 4 weeks, to DLPFC and VMPFC	Functional connectivity (fMRI), food choice, caloric intake	Compared to passively viewing high-caloric food images, upregulating functional connectivity led to activation in the IFG and DLPFC. Less high-caloric food was chosen (11% reduction), although actual food intake was increased

[a]OB = obese, OW = overweight, NW = normal weight, BMI = body mass index (kg/m^2), RT = reaction time, fMRI = functional magnetic resonance imaging, ICT = inhibitory control training, EFT = episodic future thinking, EPT = episodic past thinking, tDCS = transcranial direct current stimulation, rTMS = repetitive transcranial magnetic stimulation, DLPFC = dorsolateral prefrontal cortex, VMPFC = ventrolateral prefrontal cortex, IFG = inferior frontal gyrus, MFG = middle frontal gyrus, SFG = superior frontal gyrus.

[88]. EFT also resulted in activation of inhibitory regions: thinking of future benefits of not eating certain foods activated the left medial SFG and left MFG, whereas thinking of future costs of eating certain foods only activated the left medial SFG [89].

Considering the findings above, particularly people with low inhibitory control and high BMI may benefit from ICT. Importantly, ICT was only effective when food-specific stimuli were used. Thus, repeatedly pairing food stimuli with stop or no-go signals facilitates the formation of an association, eventually resulting in response inhibition to these foods [90]. Consequently, this leads to a reduction of caloric intake and subsequent weight loss, as endorsed by all 5 papers. Effect sizes were overall medium, but large for EFT.

Transcranial magnetic stimulation

Transcranial magnetic stimulation (TMS) is a non-invasive technique that induces an electrical current in the targeted cortical brain area [91]. Electrical pulses are usually set at 110% of the motor threshold (MT) for each individual: 10% more than the amount needed to let the thumb contract. TMS, in contrast to transcranial direct current stimulation (see 5.3), can elicit action potentials and cause brain activity. Particularly repetitive TMS (rTMS) can cause longer-lasting effects of up to several hours: when > 1 Hz is applied excitatory effects emerge, and when < 1 Hz is applied the brain is inhibited.

With regard to inhibitory control, many studies have started examining the effects of TMS in NW. Meta-analyses show moderate effects of TMS on the DLPFC on food craving and consumption, although major differences between studies existed (ES −0.43 and −0.47, respectively [92]; ES 0.46 and 0.66, respectively [93]). However, as we have seen in section 3.1, improving inhibitory control is particularly effective in people with higher BMI and low inhibitory control, suggesting that improving inhibitory control through brain modulation would likely yield similar results.

Only one group has investigated the effectiveness of rTMS in adults with obesity. They conducted a randomized, sham-controlled (10% MT) study in order to examine the effectiveness of rTMS on the left DLPFC on food intake and weight loss [94]. rTMS was applied in 4 sessions for 2 weeks, and resulted in reduced food intake (201.22 ± 265.18 fewer kcal/day), a BMI reduction (–0.43 ± 0.79 kg/m^2) and weight loss (−1.35 ± 2.31 kg) with a large effect size, already after the first 2 weeks. In a follow-up trial of 8 sessions for 4 weeks, an even greater reduction in food intake (246.98 ± 168.48 fewer kcal/day), BMI (–1.06 ± 0.77 kg/m^2), and greater weight loss (−2.53 ± 2.41 kg) was observed [95]. In addition to these changes, functional connectivity in the right frontoparietal network was increased in response to rTMS of the left DLPFC. This network includes the DLPFC and inferior parietal cortex and is involved in top-down inhibitory control.

In conclusion, rTMS to the left DLPFC seems to induce weight loss in people with obesity, probably by increasing inhibitory control ability. However, this was not examined using a behavioral measure of inhibitory control. The inclusion of such measures would elucidate whether altered activity in inhibitory areas is directly related to improvement of inhibitory control. Additionally, although both hemispheres have been reported to be involved in inhibitory control, these studies have focused exclusively on stimulation of the left DLPFC, preventing direct comparison of the left and right hemisphere.

Transcranial direct current stimulation

Transcranial direct current stimulation (tDCS) is another mildly invasive technique, but more tolerable and low cost [96]. Analogous to TMS, an electrical current is applied to the brain. This current runs between two electrodes: an anode, where it enters the brain, and a cathode, where it leaves the brain. When the anode is placed on a cortical region of interest (ROI), the excitability of that part of the cortex is increased, whereas the cathode decreases the excitability of the ROI, leading to facilitation or inhibition of neuronal firing, respectively [91]. In contrast to TMS, the current applied is relatively small (usually between 0.5 and 2.0 mA), merely modifying cortical excitability, rather than eliciting action potentials. Repeated sessions of tDCS have been thought to induce synaptic plasticity, thereby exerting longer-lasting effects on cognitive functioning [97].

Similar to TMS interventions, the target-ROI is most often the DLPFC (left F3 and right F4 of the 10–20 EEG system), applying anodal stimulation to this area. A meta-analysis in NW found that tDCS is not as effective as TMS in reducing food craving and consumption (ES −0.26 and −0.47, respectively [92]). However, another meta-analysis found comparable reductions in food craving (ES 0.46) and consumption (ES 0.66) for TMS and tDCS in studies on NW and OB [93]. Therefore, similar to behavioral ICT and TMS, only tDCS studies that included OB will be discussed.

A single 20-minute session of tDCS on the DLPFC in men and women with obesity decreased food craving and consumption, but only when controlling for individual differences in impulsivity: the higher the impulsivity the greater the effect [98]. 2 mA was applied, with

the anode on the right DLPFC and the cathode on the left DLPFC. Gluck et al. applied 2 mA to the left DLPFC in a sham-controlled study [99]. There were 3 consecutive sessions of cathodal (inhibitory) stimulation, which were repeated after approximately 3 years with anodal (excitatory) stimulation. Hence, in total there were 6 sessions of two different 3-day periods and all participants received cathodal stimulation first. Sessions lasted for 40 min. Food consumption was reduced with 23% of the weight maintenance needs immediately after anodal stimulation compared to cathodal stimulation, particularly regarding fat and soda. As a consequence, some minor weight loss was also induced (–0.9%). These promising results were already achieved after the 3 days of treatment. In a similar 3-day anodal tDCS intervention, where sessions lasted 20 min, stimulation of the left DLPFC decreased food consumption desire with 26% immediately after stimulation; compared to 14% during sham stimulation [100]. Moreover, when tDCS was paired with physical exercise, food consumption desire was reduced even more with 39% immediately after stimulation (compared to 27% during sham stimulation paired with physical exercise). This reduction lasted up to 30 min after stimulation, when the *increase* in desire to eat (due to the physical exercise) was 48% lower than after sham.

Contrary to these findings but with a similar intervention, Heinitz et al. found that food intake and weight remained unchanged after a period of 6 weeks after anodal DLPFC stimulation [101].

Most of the aforementioned studies applied anodal tDCS to the left DLPFC, aiming to increase cortical excitability and facilitating neuronal firing in this brain area. All but one found decreases in food craving, consumption desire, and actual consumption. Individual differences in susceptibility to tDCS treatment have been reported [102,103], which may explain why the number of sessions differed between studies and to what extent they achieved changes in eating behavior. Nevertheless, the findings indicate that more frequent, repeated stimulation is necessary. It is important to note that blinding was successful in all mentioned studies: participants did not guess whether they received active or sham stimulation.

Future interventions could use a combination of tDCS with ICT. In NW, modulation of cortical excitability with tDCS over the right IFG was more effective when activity in the ROI was promoted by the stop-signal task, which engages that specific brain region [104]. In addition to proving effective, these findings also demonstrate that the right hemisphere should not be neglected and research on neuromodulation should extend to the right hemisphere.

Neurofeedback

Real-time fMRI (rt-fMRI) neurofeedback provides feedback on brain activity levels in specific brain areas. With that information, a participant can learn to voluntarily regulate that activity in order to achieve behavioral change [105].

Two studies have tested the efficacy of neurofeedback in a sample of overweight and OB. Participants were asked to upregulate DLPFC activity during passive viewing of high-calorie food. One session of rt-fMRI neurofeedback was already effective in increasing activity of the left DLPFC and functional connectivity with the VMPFC. However, there was no change in caloric intake or weight-change immediately after the training nor 4 weeks later [106]. Nevertheless, only one session was carried out. In a study with 4 sessions spread out over 4 weeks, men were asked to upregulate the functional connectivity between the DLPFC and VMPFC. Compared to passively viewing high-calorie food images, upregulating functional connectivity led to increased activity in the IFG and DLPFC [107]. Moreover, 11% less high-calorie food was chosen in a food-choice task two days after the final session compared to before the first session, but when presented with actual snacks the participants ate more.

These two studies indicate that activity in and functional connectivity with the DLPFC can be upregulated effectively. However, the lack of behavioral findings or weight-change urge for more research on this topic. Only three years ago, researchers have begun assessing the effectiveness of neurofeedback in obesity, affirming it is still in its infancy. Importantly, neither of the studies included a control condition, for example upregulating another brain area or without providing feedback. Therefore, it is difficult to deduce the effectiveness of this training, and future studies are warranted including a control condition. It would be beneficial to report whether participants are in a hungry or sated state when they receive an intervention, as OB have particularly poorer food-specific inhibitory control when they are hungry and this might influence the effectiveness of the intervention. This is applicable to all interventions discussed.

Conclusion

We addressed the role of inhibitory control in obesity and weight loss, and in how far inhibitory control is a promising target for interventions in the interest of weight reduction. Based on our literature review, we conclude that OB have poorer food-specific inhibitory control, at least when they are hungry, and most studies

also endorsed poorer general inhibitory control in obesity, as assessed with a variety of tasks. Although replication is needed, concurrent reduced activation of inhibitory control areas (e.g. SFG, MFG, IFG, DLPFC) was observed. Moreover, high food-specific inhibitory control and activity in inhibitory control areas relative to NW are predictive of weight loss (maintenance). This is also endorsed by a recent paper where involvement of inhibitory control areas correlated with weight loss (maintenance) in OB [12]. The interventions targeting inhibitory control are still in their childhood, but are promising to improve inhibitory control and to reduce food craving, desire, and consumption. Inhibitory control may be targeted to promote weight-loss maintenance or to prevent the onset of obesity in an early stage.

Two theories concerning the role of inhibitory control in obesity have been mentioned in the introduction:

- Low inhibitory control may lead to short-term rewards not being inhibited, leading to overeating and consequently obesity [13].
- Increases in BMI could lead to metabolic changes in the brain, possibly due to inflammatory markers, which results in low inhibitory control [16].

The first theory is strengthened by our findings that low inhibitory control is predictive of weight gain and high inhibitory control is predictive of weight loss. The second theory, however, is not directly supported by the results, although it can also not be rejected based on the current evidence; it is merely a possible explanation. There is currently no literature that links increases in BMI to inflammatory markers, but it would be a valuable addition to the literature. In order to find a direction or causality, longitudinal research must be performed, in addition to behavioral measures that assess whether inhibitory control is normalized or further improved analogous to inhibitory brain activity. Neuromodulation studies provide another opportunity for causal research, as cortical excitability can be manipulated. Predominantly TMS would be a suitable technique for causal inference, as it has higher spatial and temporal resolution than tDCS [96]. However, in the studies discussed, targeting of the individual gyri or of a subregion of the DLPFC was not yet possible. Therefore, more research is warranted that includes TMS coupled with neuroimaging, in order to be able to target these areas more precisely and to be able to infer what exactly takes place in the specific subregions during stimulation.

All in all, OB have poorer food-specific inhibitory control when hungry and reduced activation in inhibitory brain regions. These features are predictive of future weight-gain. Interventions targeting inhibitory control are not very effective in inducing weight loss, but promising to improve inhibitory control and to reduce food craving, desire, and consumption.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Notes on contributors

Merel de Klerk recently graduated from the interdisciplinary research master Brain & Cognitive Sciences at the University of Amsterdam. During her studies, the majority of her work was related to well-being; both psychological and physical. More specifically, the central theme across her studies was how to live a brain-healthy lifestyle. In this regard a healthy relationship with food is indispensable, which is largely regulated by the brain or – in the case of obesity – dysregulated by the brain.

Paul Smeets is associate professor at the University Medical Center (UMC) Utrecht and has a background in Behavioral Biology. His PhD work, at the Image Sciences Institute (ISI), aimed at finding biomarkers of satiety in the human brain, using functional MRI. Currently, he works at ISI/UMC and at the Division of Human Nutrition and Health of Wageningen University. The central theme in his research is the decision to eat, which is taken in the brain on the basis of multiple neural as well as hormonal signals. Research topics include the neural correlates of taste, satiety and (un)healthy food choice, gut-brain interactions, effects of personality characteristics on food-induced brain responses and functional neuroimaging in anorexia nervosa. In recent years he has been using MRI techniques to study (gastric) digestion.

Susanne la Fleur has been working as a neuroendocrinologist and principal investigator at the Department of Endocrinology and Energy Metabolism at the Amsterdam University Medical Center since 2008. In addition, she has been leading a pre-clinical research group at the Netherlands Institute for Neuroscience since 2016. Susanne la Fleur investigates the link between diet composition and the development of obesity and diabetes, focusing on the role of the brain. As a professor, she focuses on understanding how (poor) diet composition and deviant eating patterns affect different parts of the brain, and how found changes contribute to disruption of energy metabolism. She further intensifies translational research in the field of nutrition, brain and metabolism in order to translate clinical problems into basic research questions and vice versa.

ORCID

P. A. M. Smeets http://orcid.org/0000-0002-8695-9612
Susanne la Fleur http://orcid.org/0000-0002-4298-7451

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