Obesity linked to addiction, a new challenge for Deep Brain Stimulation

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Abstract

Obesity is a growing worldwide problem that is currently the leading risk of global death. It is also very difficult to treat. Long and short-term signals contribute to the regulation of food intake, but these complexes together do not prevent excessive energy intake. In this review, the interaction between reward mechanisms and homeostatic mechanisms of eating behavior are lined out and may provide us a new insight in the process of overeating in obese patients. If hedonic (reward) regulation is disrupted, it can be a sign of addictive like behavior. Prior attempts of pharmacological or neurological modulation (Deep Brain Stimulation) focused primarily on homeostatic mechanisms in the hypothalamus and had limited success. Some researchers now suggest that the reward circuitry underlies behaviors of overeating. If that is the case, it may be a new challenge to treat obese patients with Deep Brain Stimulation in reward associated brain regions.

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I Introduction

Obesity is a growing worldwide problem. Some people might even speak of an epidemic. For the first time in history, the number of overweight people in the world is bigger than the number of underweight people. According to the World Health Organisation (WHO) (Shah, 2010), approximately 11% of the current adult world population is obese, which means they have a BMI greater than or equal to 30 (kg/m^2). This BMI (Body Mass Index) provides an easy parameter of weight-for-height and it is often used to classify anorexic, overweight or obese adults. It's worldwide use is due to the fact that it is calculated easily and it can be used for both sexes. However, it may not correspond to the same degree of fat in different individuals (WHO, 2014).

The health impact of obesity is big, it is a leading risk to global death. Many lethal diseases like diabetes, cardiovascular diseases and some cancers can be the result of being obese. The WHO adds: "What is not widely known is that the risk of health problems starts when someone is only very slightly overweight, and that the likelihood of problems increases as someone becomes more and more overweight. Many of these conditions cause long-term suffering for individuals and families. In addition, the costs for the health care system can be extremely high." (WHO, 2014). In Europe for example, the WHO estimates that obesity is already responsible for 2-8% of health costs and 10-13% of deaths.

Although there are many different surgeries and diets available to help reduce the obesity problem, the number of obese people isn't decreasing. Scientist are now trying to develop different medicines and treatments. One of these attempted treatments is Deep Brain Stimulation (DBS), in which an electrode is placed in the brain region of interest. DBS is already proven to be effective in Parkinson Disease (Rezai, 2008). The first trials of DBS in obese patients modulated the homeostatic mechanisms of weight control (the satiety center of the ventromedial hypothalamus and the feeding center of the lateral hypothalamus) but gained limited success. Current investigation is proposing that maybe addiction to food has something to do with the limited success of previous treatments. It seems to be interesting, regarding the disappointing results of primary DBS treatments, to look at the brain's reward circuitry such as the Nucleus Accumbens. (Quaade, 1974)

So, if there is evidence that obesity is linked to addiction, is there is a chance deep brain stimulation might work in addiction associated brain regions?

II Shortcomings in previous obesity treatments

Exercise, diet and pharmacological treatments

The role of exercise, diet and pharmacological treatments have been studied intensively in people suffering from obesity. Exercise alone has shown a moderate weight loss, so generally no dramatic weight drops, in the range of 0.5 to 4 kg (in 1 year). Dietary alone typically leads to more weight loss, in the range of 2.8 to 13.6 kg (in 1 year). This seems like a lot, but the issue with dietary and exercise is that, on average, weight is regained after a certain period of lifestyle change. (Bethesda, 1998)

Pharmacotherapy is not a very successful way to lose weight. First, recombinant human leptin was used to target the homeostatic mechanisms of obesity. Leptin is an anorectic hormone that inhibits food intake . However somewhat contrary to this, in most obese individuals the leptin level is elevated. That might explain the fact that the trial with recombinant human leptin did not show positive results. Researchers now suggest that some obese individuals could be leptin resistant. (Oswal, 2010) Second, Silbutramine, a neurotransmitter reuptake inhibitor was designed. This drug inhibited the uptake of serotonin, norepinephrine and dopamine in the brain. Patients using Silbutramine experienced an average weight loss of 4.2 kg in 1 year. It was only a few years later that Silbutramine was pulled off from the market because of signs of increased risks of stroke and cardiovascular events. Another drug Rimonabant, a cannabinoid-1 receptor antagonist, reduces the feeling of craving for food in people suffering from obesity. Average weight loss was rather high: around 4.9 kg in 1 year. Unfortunately this drug was also removed from the market in 2007 because of reports from patients suffering from depression and suicidality while using Rimonabant. The only pharmacologic therapy that is still on the market and approved by Food and Drug Administration, is Orlistat. Orlistat inhibits pancreatic lipases that are responsible for breaking down fatty acids, and by this limiting the uptake of fat in the small intestines. Side effects are gastrointestinal intolerane, oily stools and fecal incontinence. Weight loss using Orlistat has an average of 2.9 kg in 1 year. (Rucker, 2007)

Although these treatments seem to be effectively, they failed to achieve any long term effects, or they received reports of serious side effects.

Bariatric Surgeries

Given the high relapse rate of the previous mentioned interventions, bariatric surgery is used to treat people suffering from morbid obesity, which is typically for obese patients with a BMI of 35kg/m^2 or higher. Often, this surgery is their last chance to lose weight, and these surgeries are experienced quite radically. Three common used interventions are: the adjustable gastric band, the laparoscopic (Roux-en-Y) gastric bypass and the laparoscopic sleeve gastrectomy.

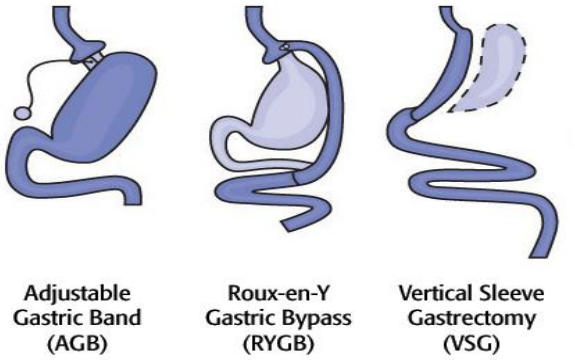


Figure 1. *Three ways of bariatric surgery (Source: weight control information network)*

The first results of bariatric surgery were excellent. A large study of 10.000 patients suffering from obesity indicated a weight loss of around 39.7 kg and an average BMI reduction of 14.2 kg/m^2. Although the results were good, complications happened in the range of 20% to 30% in gastric banding and gastric bypass. Complications consisted of wound leakage, feelings of nauseous and infections. Besides these complications, gastric bypass caused micronutrient deficiencies including thiamine deficiency and deficiencies in different important vitamins and minerals like calcium, vitamin D and B12, iron, zinc and selenium. (Bal, 2010) A second difficulty in bariatric surgery was that there were no positive long-term effects and high rates of relapse. One study evaluated 228 patients during 10 years of living with a gastric bypass. They identified two groups, the obese (BMI 40kg/m^2) and the "superobese" (BMI 50kg/m^2) at the time of initial surgery. They found a relapse of 20.4% after 10 years in the obese individuals and the "superobese" patients relapsed 34.9%. Satiety is a prominent feature of weight loss after gastric bypass and persists in those patients with an excellent result. Patients who regain large amounts of weight say they are eating almost as much as before the operation. This increase in intake takes place over several years and does not occur suddenly as with staple line dehiscence. (Christou, 2006)

Binge Eating Disorder

Looking at the lack of effectiveness of the treatments currently available may be explained by the fact that wrong mechanisms are targeted. Almost all of the previous mentioned treatments are unsuccessful in the so called 'superobese' patients. These patients often experience episodes of binge eating. Binge eating disorder (BED) is a relatively new established diagnosis in the fourth edition of the DSM-IV. The definition of BED states: "Recurrent episodes of binge eating in the absence of the regular use of inappropriate compensatory behaviors". The BED requirement is that binge episodes occur at least 2 times a week. Eating habits of patients with BED are not that distinctive and sometimes difficult to separate intro episodes. That is the reason why eating unusually large amounts of food is measured instead of the number of days in a week on which it happens. Patients with BED also show a lack of dietary control during their episodes. (Grilo, 2002) Recent findings suggest that the prevalence of BED in the general population is about 1-3%. In patients with obesity, and in patients desperately seeking help for weight loss, a much higher prevalence has been reported (25% or more), possibly reflecting both the association between severity of binge eating and obesity. (Pull, 2004)

III Obesity and addiction

Differences between and exogenous and endogenous addictive substances

Besides the context of substance addiction, involving exogenous compounds with rewarding properties like endorphins and cannabinoids, changes in endogenous signals can also be associated with addiction. This means that chemical addiction does not require a exogenous substance but can also be endogenous. If those endogenous substances can be rewarding in certain brain regions, it can show a link between stimuli and behavioral addiction. Next, the link of appetite and satiety with the reward system can be the first step in the development of addictive like eating behavior. Some psychological or environmental cues like boredom, stress or a negative mood might trigger overeating in the absence of hunger. This would lead to changes in the regulatory system of the brain related to addictive behaviors. During normal physical and psychological activities, endogenous chemicals similar to neurotransmitters are released in the brain with various concentrations depending on the type of activity. Just as the effect of exogenous drugs, this can lead to behavioral adaptation and signs of tolerance and

withdrawal, but are a fraction of the signs we see in exogenous drug responses. (Hedebrand, 2014)

Rewarding properties of food and their ability to activate the reward system might lead to the idea that some components of our food have addictive properties. But just because eating stimulates these reward systems, doesn't mean that specific nutrients, like sugar or fat, are able to evoke a substance addiction. Ending in the fact that food-addiction can be viewed as being addicted to eating palatable (pleasant to taste) food and not nutrient specific. (Hedebrand, 2014)

Interaction of the homeostatic and reward pathways of eating and satiety

Many neural circuits in the brain are part of the feeding behavior system in the body including the hypothalamus, the dorsolateral prefrontal cortex (DLPFC), amygdala, striatum and the midbrain. These neural systems are regulators in both homeostatic food control and hedonic food control. They do not work independent, but are in constant interaction with each other and both respond to metabolic signals. (Berthoud, 2011)

In this part the framework for understanding the neurobiological systems of motivation for food and the possible routes by which feeding can be linked to addiction are lined out.

To survive, animals show a motivation to find and consume food. Not only reinforcing because of the food itself, but also toward environmental stimuli. Behaviors related to these environmental stimuli can become more important in addictive behavior than the primary stimulus itself. In people, high calorie (palatable) foods or the environmental cues associated with them become more important as the pleasure associated with their consumption is noticed. If this cue is present over a long period of time, their prominence as a stimulus to drive behavior becomes more and more distinctive. This may eventually lead to overeating when there is no metabolic need. This pathway of stimulus and drive has already been linked to drug abuse, because of the dominant role of the mesolimbic dopamine system in both drug abuse and overeating. (Volkow, 2013)

The hypothalamic (homeostatic) approach of reducing food intake focusses on two key mediators: leptin and insulin. These are both produced peripherally and act centrally (brain). Leptin is an hormone that is produced by adipocytes (fat tissue) and has the ability to pass through the blood-brain barrier and effects the ventromedial portion of the hypothalamus. It inhibits orexigenic (pro-feeding) and excites anorexigenic (anti-feeding) neurons, to down regulate neuropeptide Y (NPY) which is a pro-feeding peptide. Insulin is a peptide that is

secreted by the pancreas in response to plasma glucose levels after a meal and also acts on neurons to suppress feeding behavior. The lateral hypothalamus, or the feeding center, on the other hand produces pro-feeding hormones like melanin-concentrating hormone and orexins. mRNA levels of these peptides increase in starvation processes and decrease in the presence of leptin. These feeding and satiety systems are found in the lateral hypothalamus. In the case of addiction, the lateral hypothalamus (but also other hypothalamic nuclei) is connected to the arcuate nucleus. The neurons in the arcuate nucleus are kept informed of whether or not the body has sufficient calories and nutrients so that it can adjust feeding accordingly. For example, neurons expressing NPY are found in the arcuate nucleus and these project to neurons of the hypothalamus to promote feeding. The arcuate nucleus is also partly responsible for the release of dopamine. This suggests an overlap between homeostatic and reward mechanisms. (Rezai, 2012)

The main evidence that homeostatic and reward mechanisms are influenced by each other comes from the action of leptin and insulin on the ventral tegmental area (VTA). The VTA provides the dopamine release into the limbic frontostriatal circuitry (the reward centre). (Könner, 2009) These dopaminergic neurons express both a receptor for leptin and insulin. Leptin causes a reduction in firing of the neurons in the VTA. (Hommel, 2006)) That means that leptin that is secreted by adipocytes causes a decrease in the actual reward the food is associated with. So patients suffering from obesity, generally with high adipocytes rate and high levels of leptin, are trying to get the same reward from the food and the only way they can achieve this is by overeating. Besides the biochemical part, neuronal projections also exist that connect the reward

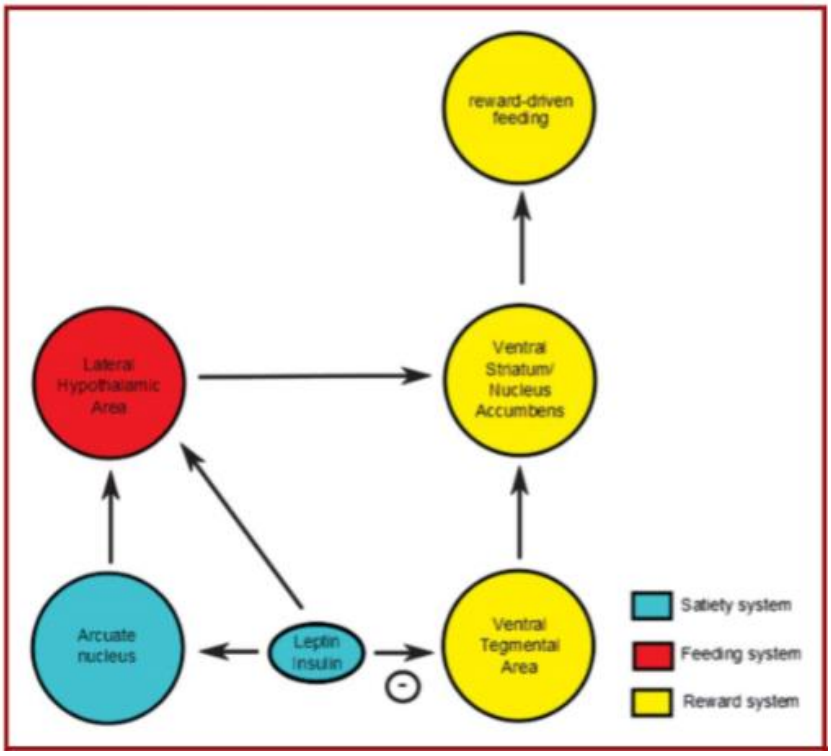


Figure 2. *Showing the overlap between homeostatic and reward mechanisms present in feeding (Rezai, 2012)*

to the feeding circuits. For example, the lateral hypothalamic area (that regulates food intake) is connected to the limbic circuitry, the emotional area of the brain. Orexin neurons (pro-feeding) from the lateral hypothalamus have a connection with the Nucleus Accumbens (NA). That means that signals that begin in the hypothalamus can increase or decrease the relative reward of food by releasing more or less dopamine. There is also a reversed way, from the amygdala (i.e. emotional reactions) to the ventromedial nucleus of the hypothalamus, providing a link between the reward that is given to food and the homeostatic values. So there is evidence that this circuitry is shared by people suffering from addiction. (Peyron, 1998) A study with rats revealed the same symptoms during food restriction as it is after a period of drug abuse. (Olds, 1958) In people dopaminergic pathways have been implicated as a common link to obesity and drug abuse. This will be reviewed next in this article. (Rezai, 2012)

Dopamine

As implicated before, dopamine plays a crucial role in the process of addiction. A study by Johnson and Kenny investigated the link between eating and the dopaminergic pathway. They studied whether extended access to a palatable high fat cafeteria diet had any effect on the sensitivity of brain reward systems in rats and the role of striatal dopamine 2 receptors (D2R) in these addiction-like responses. Brain reward systems were assessed by a Brain Stimulation Reward (BSR) procedure. In this procedure, rats responded to get rewarding electrical self-stimulation through the electrode that was placed in the brain of the rat. The minimal stimulation that it took to get self-stimulation behavior, was called the reward threshold. Three different groups were given different access to the 'cafeteria diet'. Rats had 0h (chow-only rats), 1h (restricted-access rats) or 18-23h (extended access rats) access to the diet per day for a period of 40 days. They also had unlimited access to chow. Weight increased significantly in the extended access rats compared with the restricted and chow only rats. Besides that, it was closely associated with a worsening in brain reward function

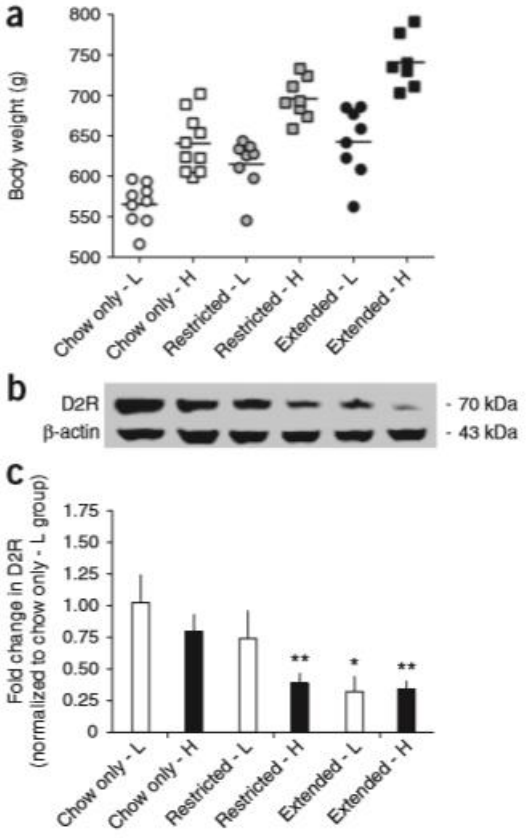


Figure 3. *After administration of lentiviral D2R RNA (Johnson and Kenny, 2010)*

(addiction-like), what caused an elevated BSR response. The restricted-access rats created a binge-eating like pattern, in which they only obtained around 33% of their daily calories from chow and 66% in their daily 1 h access session to the cafeteria diet.

Next, they tested the amount of D2R receptors in the striatum after a period of eating the cafeteria diet for 40 days. Contributing to the addiction-like reward hyposensitivity of dopamine. Two conclusions were formed: the striatal expression of the membrane bound form of D2R was lower in extended-access rats than in the restricted and chow-only rats. And they found a clear inverse relationship between body weight and striatal D2R expression. *(Figure 3)* Johnson and Kenny also investigated the functional relevance of diet-induced reductions in striatal D2R to brain reward function. They designed a lentiviral vector in a short hairpin interfering RNA form in order to knock down D2R. Lentiviral vectors are a kind of gene delivery vehicles (vectors) with the ability to integrate into the genome of both dividing and non-dividing cell. Almost immediately after the intervention reward thresholds were increasing in extended access rats compared to an extended access rats control group with an empty lentivirus vector. Also in chow-only rats treated with both Lenti-D2R and Lenti-control, effects were unaltered. So knockdown of striatal D2R caused a reward hypofunction in the striatal area of the brain, but after a certain period of abstinence with only standard chow, the baseline activity of the brain reward system did not change. (Johnson and Kenny, 2010)

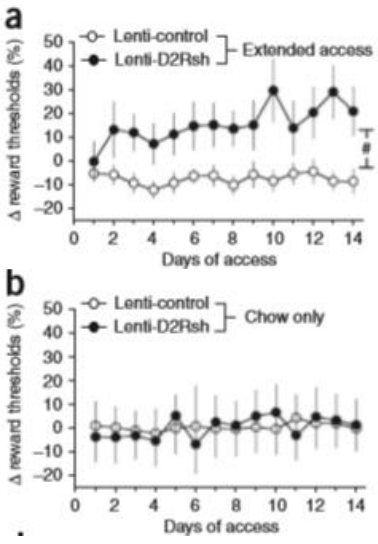


Figure 4. *Reward thresholds (Johnson and Kenny, 2010)*

Besides the D2R dysfunction theory, there is also the suggestion that dopamine levels in the brain have an effect on eating behavior. The so called "sweet spot", which is a narrow range of dopamine levels for normal reward processing, seems to be a risk for dysfunction. Too much dopamine release after eating causes addictive like behavior (wanting the same reward again). But also too little dopamine, which can cause overeating because of the little reward they get from eating normal amounts of food. (Volkow, 2007)

IV Deep Brain Stimulation

Deep Brain Stimulation

The first experiments that confirmed the ability of electrical impulses to modify the function of certain brain regions were performed around 200 years ago, in 1809, by a researcher named Rolando. (Rolando, 1809) After that, the amount of experiments that involved electrical stimulation to map the function of the human brain raised. The first DBS experiments done by Hassler et al. revealed that acute low-frequency stimulation could reduce tremor in patients. They also found that high-frequency stimulation (25 to 100 Hz) of the brain had an opposite effect. (Hassler, 1950) Lesions at various brain regions had the same effects, but the impact and safety of the operation showed a superior profile for DBS. Since the discovery of DBS, 40,000 successful implants have been performed in patients with various diseases such as Parkinson Disease (PD), dystonia and essential tremor. The placement of the electrodes causes different targets of neuromodulation. DBS causes a reversible electrical field on the surrounding neurons. The exact effect of this electrical field remains unclear and is a popular subject in today's research. It appears to inhibit neuronal activity, modulate abnormal patterns of activity and activate axons. Studies show that DBS induces a decrease in cellular activity by either activating neural transmission through stimulated nuclei or by direct inhibition of neurotransmitter release in the synaptic cleft. (Rezai, 2007).

Placing of the electrodes and limbic CSPTC loop

In the case of influencing the hedonic aspect of eating, targeting the correct brain areas is important and these neuronal pathways have to be lined out. An important circuit is called the cortico-striato-pallido-thalamo-cortical (CSPTC) circuit. *(Figure 5&6)* These exist for limbic, associative and motor function. (Alexander, 1986) Only limbic and associative circuits are explained because they are important in addictive-like pathways. The main source of dopaminergic input in the brain is the VTA. In terms of feeding behavior this means that if high calorie food is presented, a response of the ventromedial circuitry is activated. Neurons from the limbic circuitry are connected to the lateral prefrontal cortex, which is the association center of the brain. This acts as a gateway of translating emotional drive into an expected reward associated with the cue. So an obese patient with an imbalanced circuitry may decide to overrate

the immediate pleasure of eating unhealthy food above the long-term health consequences associated with the food. (Koechlin, 2007) Obese women had significantly greater activation of brain structures associated with the limbic (ventromedial) CSPT loop including the NA, ventral striatum, amygdala and insula. Also, structures in the associative loop were highly activated compared with non-obese women. (Stoeckel, 2009) Studies showed that pictures of high calorie foods caused more activation of hedonic circuitries in obese patients than low calorie foods compared to participants in the healthy-weight group who showed no difference. However, in healthy-weight group elevated levels of activation were seen in the associative circuitry, which may suggest that hyperactivation of this circuitry (compared to the limbic loop) may prevent healthy-weight individuals to overindulge. According to this, placing the electrode can be difficult because of the amount of brain areas involved in the process of eating behavior. (Rothemund, 2007)

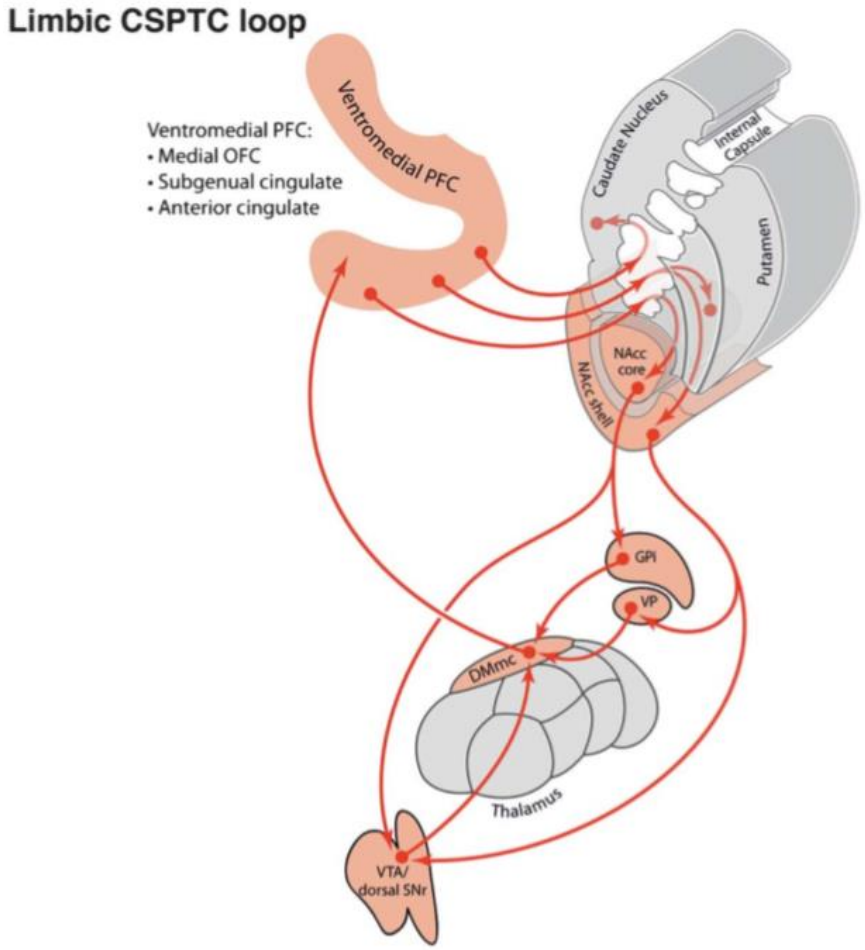


Figure 5. *Limbic CSPTC loop of the brain (Rezai, 2012)*

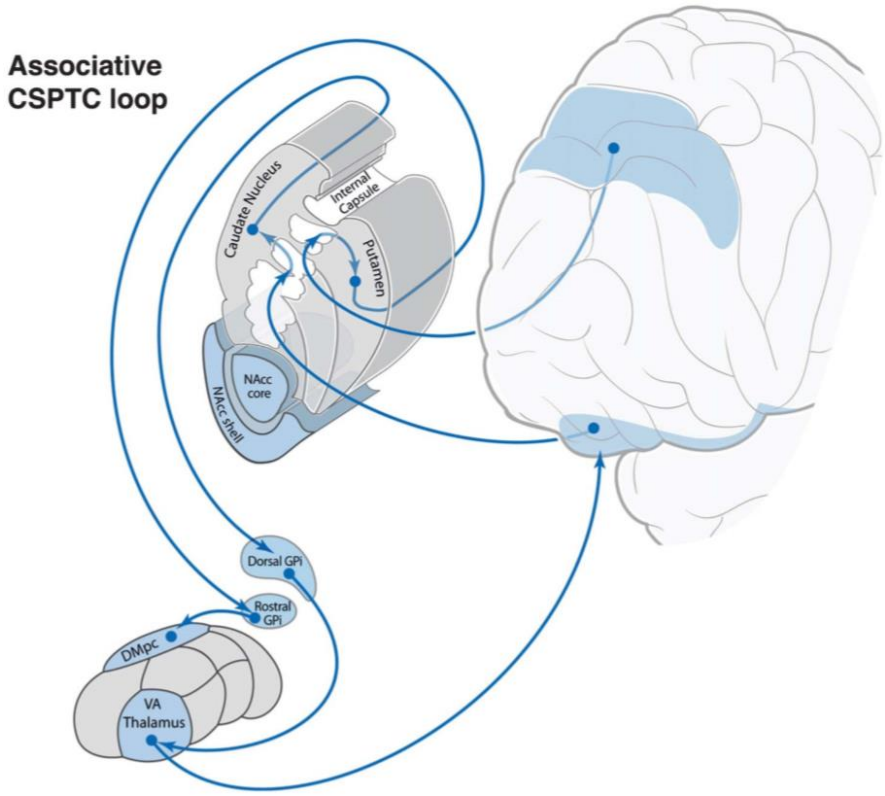


Figure 6. *Associative CSPTC loop of the brain (Rezai, 2012)*

Deep Brain stimulation and obesity

More concrete research about DBS treatment in obese mice has been done by Halpern et al. They investigated whether targeting de NAS (nucleus accumbens shell) by DBS would change the reward mechanisms in diet-induced obese mice. Three experiments were performed: first c-Fos immunoreactivity in the NAS was measured, which is a marker of neuronal activity. Also involvement of both dopamine receptors, D1R and D2R, were examined by administration of an antagonist, respectively SCH-23390 and raclopride. Finally chronic treatment with DBS was measured in diet-induced obese mice, with a binge-eating disorder, meaning they consume >25% calories a day from the high-fat diet. The output of the DBS electrode was set at 150mA for 4 days, after the intervention they were allowed to recover for a week. NAS stimulation by DBS revealed a significant decrease in high fat kilocalories consumed with DBS-on compared to DBS-off. *(Figure 7)* Despite this, total daily intake and chow intake didn't change after DBS

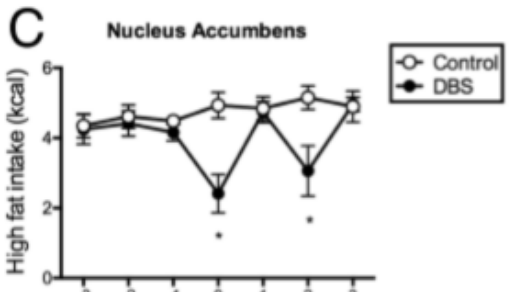


Figure 7. *Decrease in high fat intake after DBS in NAS (Halpern, 2013)*

treatment. Also, there was no interaction detected between body weight and NAS DBS. (Halpern, 2013)

Next, they investigated the amount of c-Fos-IR cells in both the NAS and the infralimbic cortex ILC (control group) to look at neuronal activation effects from NAS DBS. C-Fos levels were significantly elevated in the ipsilateral side of the electrode compared to the samples of ILC. Which indicates increased neuronal activity in de NAS directly after DBS. (*Figure 8)*

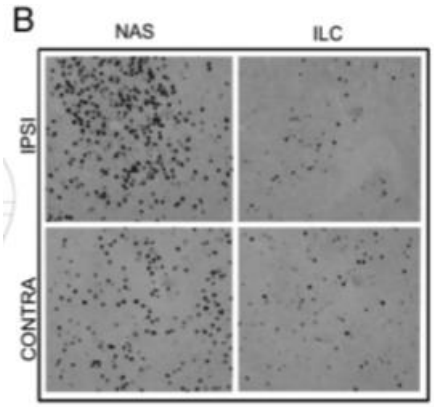
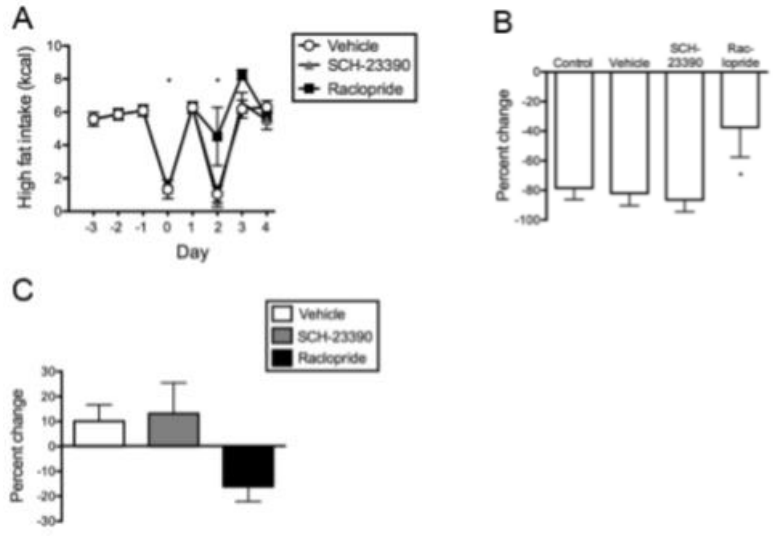


Figure 8. *Amount of c-Fos in the NAS compared to the ILC (Halpern, 2013)*

Halpern did also investigate the effect of the D1R and D2R antagonism. DBS mediated decrease of binge eating was nog changed by administration of SCH-23390 (the D1R antagonist). However, raclopride significantly lowered the effect of DBS, what caused an increase in high fat intake. *(Figure 9 A,B)* This seems consistent with the outcomes of the study performed by Johnson and Kenny. What they also found is that neither SCH-23390 and raclopride affected binge eating in the absence of DBS. (*Figure 9 C).* (Halpern, 2013)



Figuur 9. *Effects of SCH-23390 and reclopride (Halpern, 2013)*

Halpern et al. indicate that acute administration of NAS DBS may provide a new treatment for obese patients suffering from binge eating disorder. DBS is already proven to be effective in Parkinson's disease and positively changes lifestyle in these patients. Besides the promising results of this study, the researchers underline the need for more animal studies examining the acute effects of DBS. (Halpern, 2013)

V Conclusion

In attempting to find an effective treatment in patients suffering from obesity, a variety of diets, pharmacotherapy and surgeries have been tried. Some of them successful, but most of the time causing a lot of complications, side effects and lack of long-term effects. In figuring out the process that causes overeating in obese patients, signs of active brain circuitries also involved in addiction were discovered. Homeostatic food control mechanisms were the first targets of Deep Brain Stimulation but no significant positive results came out. So a new approach could be the hedonic circuit of the brain and especially the dopamine producing part of the brain: the Nucleus Accumbens (NA). Johnson and Kenny did a promising experiment with the dopamine 2 receptor in which they show an increase in eating behavior in D2R knockdown mice. The study by Halpern et al. confirmed this D2R role and also tried DBS in the NA shell (NAS). Results were not totally convincing, but Halpern et al. underlined the need for more animal studies. Possibly, targeting other parts of the limbic (hedonic) brain circuitry can be examined in order get the desirable results.

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