Neurobiological aspects of obesity: dopamine, serotonin, and Imaging

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WHAT DOES IMAGING TELL US ABOUT THE OBESE BRAIN? A REVIEW ON NEUROIMAGING IN OBESITY

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ABSTRACT

The brain is important in the regulation of eating behavior and satiety signaling. Consequently, it may play a role in the etiology and pathophysiology of obesity. In contrast, the obese state and its related metabolic changes may lead to neurobiological adaptations in the brain, which can impact on brain functions. The purpose of this review is to provide a detailed overview of neuroimaging studies in obesity to gain more insight in the role of the brain in obesity and the consequences of obesity for the brain.

The results of the reviewed studies show that molecular processes, brain function and structure are involved in the development of or are affected by obesity. Although preliminary, some results suggest that the molecular, functional and structural changes may be reversible by dieting or other weight loss procedures.

Integration of the results invites for comparison of obesity to substance use disorders and helps to identify the gaps in our knowledge. Finally, the potential clinical implications are discussed and a framework for future studies is suggested.
INTRODUCTION

Obesity is an increasing health problem worldwide (1). It is associated with serious health consequences including increased risk for cardiovascular diseases, diabetes mellitus, musculoskeletal disorders, cancer and psychosocial problems (2;3). The WHO estimates that currently 300 million people worldwide are clinically obese (body mass index (BMI) >30 kg/m²) and 2-6% of total the health-care costs in developed countries are obesity-related (WHO). As a result, the growing obesity epidemic has generated increased scientific attention, a better understanding of the underlying mechanisms, at better strategies to curb the epidemic spread and more effective treatments of patients with the disease. Part of this research is focused on the relationship between the brain and obesity. Basically, the two questions to be answered are: ‘what is the role of the brain in the development of obesity?’ and ‘what is the effect of obesity on the brain?’.

Regarding the first question, it has long been recognized that the brain plays a central role in the regulation of food intake (4). Therefore, it may be an important factor in the aetiology of obesity and a possible target for prevention and treatment. Many brain structures participate in food intake regulation (5;6): the caudal brainstem is directly involved in ingestion, digestion, and absorption of food and largely controls autonomic signaling related to the ingestive and digestive processes; the hypothalamus is a key structure in the homeostatic regulation of food intake, which integrates internal state signals and drives pituitary-endocrine and autonomic outputs; corticolimbic regions are important in learning and processing food-related reward and exerting control over food intake with integration of non-metabolic signals. One of the major causes of the current obesity epidemic is thought to be increasing overeating of high-caloric foods, which are presented and available in abundance in the present-day Western society. Overeating behavior can be considered a malfunction in the regulation of food intake with loss of control due to the combination of increased motivational salience and deficits in behavioral inhibition. In this respect, overeating and obesity have been compared with drug addiction and it has been hypothesized that similar mechanisms in the brain may be underlying both disorders (7).

Regarding the second question, obesity may affect the brain through interactions of the brain and homeostatic signaling by metabolic parameters. There are indications that metabolic parameters, such as glucose (8), leptin (9), and Peptide YY (PYY: 10)) can affect brain structures and functions in humans. The sensitivity for and levels of these metabolic parameters are often changed in obesity and brain functions may be affected by changes in these parameters in a high BMI state. Moreover, obesity is associated with an increased risk for developing brain disorders, such as Alzheimer’s disease and Parkinson’s disease (11-14). In addition, abdominal obesity in midlife increases the risk of dementia independent of the presence of comorbid diabetes mellitus and cardiovascular disorders (15). How the obese state leads to these increased susceptibilities and whether this is mediated by metabolic parameters is still unclear.

To better understand the interactions between obesity and the brain in humans, an increasing number of neuroimaging studies focusing on obesity have been performed in the last 15 years. This review aims to give an overview of results of neuroimaging studies that assessed the brain of obese people or examined the relationship between BMI and several brain characteristics. By providing this overview, we aim to integrate the current knowledge on the role of the brain in the regulation of food intake in obesity with the effects of the obese state on the brain. Thus, our review aims to increase the insight into the aetiology of obesity and into the mechanisms underlying the various consequences of obesity on brain.
The structure of the review is based on the different aspects the brain’s functioning that can be investigated with the current imaging techniques, i.e. molecular aspects (PET, SPECT), neurophysiological aspects (fMRI), and structural aspects (MRI). The studies for each aspect are described in separate sections, each ending with a discussion of the implications of the findings for the role of the brain in food regulation and the effects of obesity on the brain. The review ends with a general discussion of the reviewed studies, in which the results of the three sections are integrated, followed by some clinical implications and future directions for neuroimaging research in obesity.

METHODS
The search strategy to identify the relevant trials for this review included a search in PubMed and Embase with the following key search terms: “obesity, BMI, or body mass index” in combination with (AND) “neuroimaging, MRI, fMRI, PET, positron emission tomography, SPECT, or single photon emission computed tomography”. The search was limited to human studies. There were no language restrictions for either searching or trial inclusion. Cross-references were searched in the selected articles. The final search was conducted in July 2011.

Trials were selected for inclusion if they: 1) included obese people (BMI >30 kg/m²) in their subject sample; 2) imaged the brains of their participants using PET, SPECT or (f)MRI; and 3) conducted analyses of imaging data in relation to obesity or BMI. Articles focusing on rare forms of obesity, e.g. leptin deficiency or Prader-Willi syndrome were excluded.

The titles, abstracts, and keywords of all articles that were identified by this search strategy were scanned in an initial screening. Those articles, which did not meet the selection criteria, were rejected. Subsequently, all potentially relevant articles were investigated as a full text. The search initially yielded >1600 results, of which the greater part was rejected in the first screening. Finally, 70 studies were found eligible for this review (tables 1, 2, and 5). The findings of these studies are described below, organized in groups based on the different imaging techniques that were used, i.e. the molecular imaging (PET, SPECT), the functional imaging (fMRI), and structural imaging (MRI).

MOLECULAR IMAGING IN OBESITY

Introduction molecular imaging
Many neurotransmitters in the brain are involved in the regulation of food intake, including, dopamine, serotonin, noradrenaline, glutamate, gamma-aminobutyric acid (GABA), opioids and endocannabinoids (S). Anti-obesity drugs, e.g. sibutramine and rimonabant, show that manipulation of the serotonergic/noradrenergic or the cannabinoid system affects eating behavior and can induce weight loss. Drugs that increase dopamine levels, such as methylphenidate and amphetamines, also have an anorexigenic effect, whereas dopamine D₂ receptor blockers (neuroleptics) can lead to weight gain. In addition, it has been shown that food can induce a dopamine release in the striatum (16;17), therewith modulating the situational reward value of food (18). Finally, in the key regulatory center for food intake, the
hypothalamus, dopamine and serotonin also play an important role (19). In short, it is plausible to think that neurotransmitter systems play a role in the development of and are affected by obesity. Using advanced imaging techniques it is possible to visualize and measure some of these molecular brain processes in-vivo. In the following section we review studies that focus on molecular changes in the brain of obese people. An overview of all the publications on molecular imaging in obesity reviewed in this section can be found in table 1.

The dopaminergic system

The majority of the neuroimaging studies on the neurotransmitter systems in obese subjects focus on the dopaminergic system. The earliest imaging study demonstrating abnormalities in the dopaminergic system in obese humans was a study by Wang et al. (20). They conducted $^{[11C]}$raclopride PET scans in 10 morbidly obese subjects ($\text{BMI} > 40 \text{ kg/m}^2$) and 10 controls ($\text{BMI} < 30$) and showed that dopamine D2 receptor (DRD2) binding was lower in the striatum of obese participants, but also that there was a negative correlation between BMI and DRD2 availability in the obese subjects. The finding of decreased striatal DRD2 availability in obese subjects was confirmed by the same research group in a subject sample that partly overlapped with the previous one (21). Another research team (22) conducted $^{[11C]}$raclopride PET scans in a sample of normal weight, overweight and obese subjects. However in this study, the overweight and obese subjects had substantially lower BMIs than the subjects of the two previously described studies. In a voxel-based analysis Haltia et al. (22) showed that the overweight/obese participants had significantly lower DRD2 binding in left and right striatal and thalamic sub regions, although this difference was not significant in the region of interest analysis. In a more recent publication, Steele et al. (23) report a comparison of $^{[11C]}$raclopride PET scans in five morbidly obese subjects ($\text{BMI} > 40 \text{ kg/m}^2$) to an historical control sample of five females and also did not find a significant difference in DRD2 availability between the groups. However, this is limited by several factors, such as its small sample size, the ten-year difference in average age between groups and by the use of a historical control sample. Overall, the four studies reviewed here provide a strong indication that the striatal level of free synaptic DRD2 is decreased in obesity. Further work investigating the dopaminergic system was undertaken by Haltia et al. (22). Based on the hypothesis that the dopaminergic system in obese people is hypo-reactive, as suggested by the reward deficiency syndrome theory (24), this group attempted to demonstrate a blunted dopamine release in overweight and obese people after intravenous glucose administration that serves to mimic recent food intake. To test this hypothesis the researchers conducted a post-placebo injection and a post-glucose injection $^{[11C]}$raclopride PET scan in overweight/obese and normal weight subjects after an overnight fasting period. Any difference measured in DRD2 levels between the baseline and post-glucose injection scan could reflect a change in the intrasynaptic dopamine level and thus indicate dopamine release. However, Haltia et al. (22) could not find a significantly different dopamine release between the normal weight and overweight/obese group. What they did find was a significant gender effect in the response to the intravenous glucose injection: While men showed a decrease in DRD2 levels after intravenous glucose injection, reflecting dopamine release, women showed an increase in DRD2 levels. This suggests that increasing glucose levels can have a different effect on the brain depending on the sex. Haltia et al. also demonstrated the importance of expectancy for the effect, at least in male participants (25). Using the same subject sample as before, the team compared two $^{[11C]}$raclopride PET scans
Table 1. Studies on molecular imaging in obesity

<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>Imaging method</th>
<th>Subjects</th>
<th>Primary outcome measures</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dopaminergic system</strong></td>
<td></td>
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<tr>
<td>Wang et al. (20)</td>
<td>2001</td>
<td>[C-11]raclopride PET + [F-18]FDG PET</td>
<td>10 morbidly OB, 10 NW/OW</td>
<td>DRD2 availability</td>
</tr>
<tr>
<td>Volkow et al. (21)*</td>
<td>2008</td>
<td>[C]raclopride PET + [F-18]FDG PET</td>
<td>10 morbidly OB, 12 NW/OW</td>
<td>DRD2 availability and metabolism</td>
</tr>
<tr>
<td>Haltia et al. (22)</td>
<td>2008</td>
<td>[C]raclopride PET</td>
<td>12 OW/OB, 12 NW</td>
<td>DA release after glucose injection</td>
</tr>
<tr>
<td>Steele et al. (23)</td>
<td>2010</td>
<td>[C]raclopride PET</td>
<td>5 morbidly OBwomen</td>
<td>DRD2 availability after bariatric surgery</td>
</tr>
<tr>
<td>Haltia et al. (25)</td>
<td>2007</td>
<td>[C]raclopride PET</td>
<td>12 OW/OB, 12 NW</td>
<td>DA release after glucose expectancy</td>
</tr>
<tr>
<td>Wang et al. (26)</td>
<td>2011</td>
<td>[C]raclopride PET</td>
<td>8 OB, 10 OB with BED</td>
<td>Dopamine release after food stimulation</td>
</tr>
<tr>
<td>Dunn et al. (27)</td>
<td>2010</td>
<td>[C]raclopride PET</td>
<td>5 morbidly OBwomen</td>
<td>DRD2 availability after bariatric surgery</td>
</tr>
<tr>
<td>Chen et al. (28)</td>
<td>2008</td>
<td>[Tc-99m]TRODAT-1 SPECT</td>
<td>50 subjects, BMI 18.7 – 30.6</td>
<td>DAT availability</td>
</tr>
<tr>
<td>Wilcox et al. (30)</td>
<td>2010</td>
<td>6-[18F]-DPA PET</td>
<td>3 OB, 3 OW, 9 NW</td>
<td>DA synthesis capacity</td>
</tr>
<tr>
<td><strong>Serotonergic system</strong></td>
<td></td>
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<tr>
<td>Adams et al. (31)</td>
<td>2004</td>
<td>[F]altanserin PET</td>
<td>52 subjects, BMI 24.8 +/- 3.7</td>
<td>5HT₁a receptor availability</td>
</tr>
<tr>
<td>Erritzoe et al. (32)</td>
<td>2009</td>
<td>[F]altanserin PET</td>
<td>136 subjects, BMI 18.4 – 42.8</td>
<td>5HT₁a receptor availability</td>
</tr>
<tr>
<td>Erritzoe et al. (33)</td>
<td>2010</td>
<td>[I]DaSB PET</td>
<td>7 OB, 36 OW, 17 NW</td>
<td>Cerebral SERT binding</td>
</tr>
<tr>
<td>Kuikka et al. (34)</td>
<td>2001</td>
<td>[I]nor-β-CIT SPECT</td>
<td>7 OB women, 11 OB women with BED</td>
<td>SERT availability</td>
</tr>
<tr>
<td>Tammela et al. (35)**</td>
<td>2003</td>
<td>[I]nor-β-CIT SPECT</td>
<td>6 OB women, 6 OB women with BED</td>
<td>SERT availability</td>
</tr>
<tr>
<td>Koskela et al. (29)</td>
<td>2008</td>
<td>[I]nor-β-CIT SPECT</td>
<td>16 monozygotic twin pairs, BMI 19±1.31.9</td>
<td>DAT and SERT availability</td>
</tr>
</tbody>
</table>

* sample overlap with Wang et al. (20)
** sample overlap with Kuikka et al. (34)

PET = positron emission tomography, SPECT = single photon emission computed tomography, OB = obese (BMI > 30), NW = normal weight (BMI < 25), OW = overweight (BMI 25-30), BMI = body mass index, BED = binge eating disorder, DA = dopamine, DRD2 = Dopamine D2 receptor, DAT = dopamine transporter, SERT = serotonin transporter
after placebo injection, one in which the subject was expecting glucose or placebo injection and one with an open placebo expectation. Men showed higher dopamine levels after the placebo injection with glucose expectancy compared to the open placebo injection, revealing an effect of glucose expectancy that seems to facilitate dopamine release. Again, however, there was no difference between the normal weight and overweight/obese participants. Within obese subjects, those with binge eating disorder actually show increased striatal dopamine release after food stimulation. Wang et al. (26) showed that in obese binge eaters, dopamine release in the caudate nucleus in response to a food cue correlates with binge eating severity scores. The researchers found no relationship between BMI and dopamine release.

It has been questioned whether weight loss in obese people can lead to a normalization (i.e. increase) of striatal DRD2 levels. An often-effective procedure to induce weight reduction is bariatric surgery. Bariatric surgery can lead to serious weight loss and influences eating behavior and, thus, may affect dopaminergic neurotransmission in the brain. Two studies have focused on answering the question whether dopaminergic neurotransmission and DRD2 availability might change after bariatric surgery in morbidly obese subjects (23,27). Both publications report preliminary findings in small samples. Steele et al. (23) performed [11C]raclopride PET scans in five female subjects (preoperative BMI >40 kg/m²) before and six weeks after laparoscopic Roux-en Y gastric bypass. This team of researchers found that DRD2 availability increased in four out of five subjects after bariatric surgery, although no statistical test was performed to test significance and the subject with the highest BMI actually showed a strong post-operative decrease in DRD2 availability. In a similar study, Dunn et al. (27) also compared DRD2 availability pre- and post-operatively (7 weeks after bypass operation) in 5 female subjects (BMI >40kg/m²). However, they found that in those subjects there was a significant decrease of DRD2 availability and of DA binding potential in several areas of interest (caudate, hypothalamus, medial thalamus and amygdala). The result of Steele et al. (23) and Dunn et al. (27) clearly contradict each other. It is possible that this is partly due to the use of different tracers, i.e. [18F]fallypride in Dunn’s study, compared to [11C]raclopride in Steele’s research. The small sample size of both studies makes it difficult to make any firm statements. In short, a conclusion of the effect of weight loss on DRD2 availability cannot yet be drawn.

So far, most imaging studies on the dopaminergic system in obesity have concentrated their attention on the DRD2, which are located postsynaptically. However, the presynaptic dopamine transporter (DAT) could be equally important for the regulation of the synaptic dopamine levels, in particular for the tonic dopamine levels. Therefore, also DAT may potentially play a role in reward processing of food. Two studies have investigated DAT availability in relation to BMI: Chen et al. reported a negative correlation between BMI and striatal DAT level, as measured with [99mTc]-TRODAT-1 SPECT, in healthy subjects (BMI range 18.7 – 30.6) (28). However, a monozygotic twin study by Koskela et al. (29) could not demonstrate a difference in striatal DAT levels, measured with the more specific ligand [123I]-nor-b-CIT SPECT, between the heavier twin (BMI mean ± SD: 26.8±3.6) and it’s leaner twin sibling (BMI mean ± SD: 24.5±3.1). Both studies included only a limited range of BMIs and neither included severely obese subjects. A study assessing morbidly obese subjects may provide a more conclusive answer to the question whether striatal DAT levels are decreased in obesity or not.

Looking at the dopamine system from a slightly different angle, Wilcox et al. (30) conducted a PET study using the ligand 6-[18F]-fluoro-L-m-tyrosine (FMT) as a tracer to analyze the
capacity of striatal neurons to convert levodopa (L-Dopa) to dopamine. The results of this study showed that in obese and overweight subjects the capacity for synthesis of dopamine was compromised compared to lean controls. Also, the researchers found that the more frequent past, unsuccessful attempts of dieting and weight loss were, the lower the synthesis of dopamine in the dorsal putamen was. This finding points towards a down-regulation mechanism that limits the available striatal dopamine in response to overeating.

The serotonergic system
Apart from the dopaminergic system, only the serotonergic system has been studied in obese humans using molecular imaging methods. First of all, 5-HT2A receptor availability has been assessed in relation to BMI. Adams et al. (31) found a positive correlation between BMI and 5-HT2A receptor binding in cortical regions, measured with [18F]-altanserin PET, in healthy subjects (mean BMI 24.8 ± 3.7). They found this correlation in all cortical regions except the occipital cortex. The same group replicated this finding in a larger sample (n = 136) of healthy subjects, BMI range 18.2 – 42.8 (14 obese), and again found a positive correlation between BMI and 5-HT2A receptor availability in cortical regions (32). This time the correlation was found for the complete neocortex, including the occipital cortex. The authors interpreted this finding as a compensatory upregulation of the cortical 5-HT2A receptor availability due to lower serotonin levels in the overweight and obese subjects.

Also the pre-synaptic side of the serotonergic system has been assessed. The largest study on serotonin transporter (SERT) availability and BMI was performed by Erritzoe et al. (33). They showed in a [11C]DASB PET study with 60 healthy volunteers ranging in BMI from 20.6 to 32.4 (7 obese) that BMI correlated negatively with SERT binding in the global neocortex and in sub-cortical regions (caudate, putamen, thalamus, and midbrain). This finding contrasts with results reported by Koskela et al. (29). In this previously mentioned monozygotic twin study DAT levels were measured and the serotonin transporter (SERT) levels were investigated. Although SERT-binding did not correlate with BMI on an individual level, the heavier twins overall showed higher SERT binding in the hypothalamus/thalamus region than their leaner twin siblings. The significance of this finding appeared to be based on differences within the female twin pairs, while there was no significant difference in SERT binding within the male twin pairs between the heavier and the leaner twin. Another study showed that obese women with binge-eating disorder have decreased SERT availability in the midbrain compared to obese non-binge eating women (34). In a subsample of these women, successful treatment of the binge eating disorder went together with an upregulation of SERT availability in the midbrain (35). This suggests that obese women with a comorbid psychiatric disorder, such as binge eating disorder, have lower midbrain SERT availability than obese subjects without psychiatric comorbidity. Together, the reviewed studies on SERT binding indicate that a dysregulation of subcortical and cortical SERT levels is associated with a high BMI, but it will require further work to elucidate the exact direction of the associations and to find out how it is regulated in obesity.

Discussion of molecular imaging
Several independent research groups have shown that the dopaminergic and serotonergic systems are affected by obesity, highlighting the importance of the molecular processes in the brain. The two major findings are that the striatal DRD2 availability is lower in obese subjects
compared to lean controls, whereas 5-HT\textsubscript{2A} receptor binding in cortical regions correlates positively with BMI.

The lower striatal DRD2 availability in obesity is supported by animal research: decreased DRD2 levels were found in the nucleus accumbens (NAc) and striatum of genetically obese rodent models and in diet induced obese rodent models (36-41), although one study reported an increase in DRD2 levels in the dorsal striatum of diet-induced obese mice (42;42). The lower striatal DRD2 availability has been linked to reward deficiency. It has been postulated that a decrease in DRD2 availability results in a decreased sensitivity of the reward circuit to food, which subsequently leads to increased food intake to temporarily reach the desired reward level (18;18). The role of this system in the underlying pathologic mechanism has been compared to the role in substance abuse. In this respect, it is worth to notice that the studies with morbidly obese subjects were able to detect a lower striatal DRD2 binding (17.4\% (20) and 13.4\% (21)) that is comparable to the decrease observed in drug abusers, such as alcohol (43), methamphetamine (44) and opiate abusers (45). However, in obese subjects the lower DRD2 availability has not yet been linked to eating behavior or other behavioral parameters. To confirm the postulated role of low striatal DRD2 in overeating, it is important to assess the relation with behavior in obesity. Apart from that, there is increasing evidence that glucose homeostasis can directly affect the striatal dopaminergic system (46). The obese state might therefore affect striatal DRD2 availability via imbalances in metabolic systems and a focus on eating behavior alone would be too narrow.

Whether a lower striatal DRD2 availability in obesity is a predisposing condition or a result of the obese state has not been determined. It has been found that carriers of the Taq1A allele in the gene encoding DRD2 show decreased DRD2 expression (47) and have a higher chance of being obese than non-carriers (48-50). This suggests that a lower DRD2 expression is a pre-existing and predisposing condition that increases the risk of developing obesity. However, in a recent animal study, Johnson & Kenney (41) demonstrated that a down-regulation of striatal DRD2 can be induced by a cafeteria-style diet and that a DRD2 down-regulation increases the susceptibility for reward deficits and compulsive eating behavior in rats. A combination of both, i.e. cause and consequence, is also a possibility: a predisposing low level of striatal DRD2, which is then further decreased by the obese state. The studies on striatal DRD2 availability after acute weight loss by bariatric surgery do not yet answer the question in how far a change in body weight or eating behavior is linked to DRD2 levels. There is no evidence yet that the striatal DRD2 availability increases by significant weight loss, which would suggest some form of reversibility. The results of the available studies are conflicting and the samples too small. However, more information on these effects would help to better understand the link between body weight or eating behaviour and DRD2 availability and the flexibility of the system.

Apart from the lower striatal DRD2 availability, it has also been hypothesized that obese people have a blunted reactivity of the dopaminergic system, similar to what has been shown in cases of addiction (51;52). A blunted dopamine release in obesity would also fit in the reward deficiency theory. To date, a dopamine release after food intake in healthy humans has been demonstrated only once after a meal (17) and once after amplification of the dopamine release by methylphenidate (53). Interestingly, the studies using glucose injection to mimic high energy intake could not find any differences in dopamine release between lean and obese subjects. This might be explained by the fact that the intravenous glucose injection did not activate all
the same processes that are involved in eating, because it lacks important aspects like the sight, taste, texture and smell of food, as well as the actual action of eating (chewing, swallowing, etc). Therefore, the reward experience after glucose injection might have been incomplete and too small to detect. A difference in the level of dopamine release between obese and lean subjects after real food intake might be very difficult to detect with the currently available techniques because of the naturally limited size of the dopamine release and a ceiling effect. Nevertheless, in one animal study researchers managed to show that obese rats release less dopamine the nucleus accumbens after food intake and after amphetamine stimulation (54). In addition, it was shown that an amphetamine-induced striatal dopamine release is lower in obese subjects without binge eating disorder compared to obese subjects with binge eating disorder. As the authors did not find a correlation between BMI and dopamine release, this study shows that it is the (pathologic) eating behavior pattern that is related to the dopamine release, whereas there is not yet evidence for a direct relation with the obese status. The question still remains whether the responsiveness of the striatal dopaminergic system is different between obese and lean humans.

On the pre-synaptic side of the dopaminergic system, results so far points towards a reduced DAT availability in obesity and to a reduced dopamine synthesis. This points to an overall hypodopaminergic system in obesity, i.e. both pre- and post-synaptically. Whereas the reduced dopamine synthesis may indeed lead to reward deficits, the lower DAT availability may represent a compensation mechanism aimed at keeping the dopamine levels sufficiently high. Animal studies demonstrate that rodents on a high-fat diet for obesity induction also show a significant decrease in DAT density on the cell surface in the striatum (42;55), although one animal study shows that this effect only occurs in obesity-resistant mice on a high-fat diet and not in the obesity-prone mice on the same high-fat diet (56). The literature on addiction shows variable results regarding DAT levels in drug abusers, but overall these studies rather suggest decreased levels of DAT in drugs abusers: lower DAT levels for methamphetamine (57;58) and nicotine users (59;60), lower levels or no change for alcohol users (43;61), and no change or an increase in DAT levels for users of cocaine (62;63). Taken together, these findings constitute a further similarity between the effects of obesity and addiction on the dopaminergic system.

Concerning the role of dopamine in obesity many important questions have been addressed. Apart from the finding of lower striatal DRD2 availability, most of them are not yet conclusively answered and need further evidence. One aspect that has not been studied yet is whether the baseline synaptic dopamine levels are also lower in obesity. The indications for a general hypodopaminergia in striatum in obesity make it plausible that these dopamine levels may also be lower, similar to what has been shown in cocaine addiction (64). A dopamine depletion study (e.g., using alfa-methyl-para-tyrosine to decrease the synthesis of dopamine) comparing obese and control subjects would be necessary to assess this hypothesis.

Regarding the serotonergic system, the positive correlation of BMI and cortical 5-HT\textsubscript{2A} receptor binding in humans has been replicated (although by the same group) and seems a robust finding (31;32). It is (partly) supported by animal work, which also shows that there are significantly higher 5-HT2A levels in the anterior olfactory nucleus and ventromedial hypothalamic nucleus (VMH) in obesity prone mice compared to the obesity resistant and control mice (65;66). The positive association suggests that there is an up-regulation of cortical 5-HT\textsubscript{2A} receptors, which might be compensatory to decreased serotonin levels. In a SPECT study comparing 10 bulimia nervosa patients to 11 healthy controls, all within a normal BMI
range, no difference was found in cortical 5-HT\textsubscript{2A} binding between the groups (67). This might indicate that it is not necessarily pathologic eating behavior, but possibly the obese state that affects the 5-HT\textsubscript{2A} availability.

Research on SERT in obesity however shows still inconclusive results. An inverse correlation of SERT binding with BMI has been found in both cortical and subcortical regions (33), which opposed the finding in female twins that SERT availability was higher in the heavier twin (29). There is one study in patients with Parkinson’s disease (PD), which shows that patients, who have a large change in BMI in the past year, have higher SERT availability (in rostral raphe nuclei, hypothalamus, caudate nucleus and ventral striatum) than PD patients with stable BMI (68). However, it is difficult to directly apply this finding to obesity, in particular because PD itself has an effect on SERT levels, i.e. lower binding compared to controls (68). A negative correlation between SERT and BMI is not directly confirmed by animal studies, which found that only mice that were resistant to diet-induced obesity had decreased SERT binding in the nucleus accumbens, amygdaloid nucleus, and olfactory tubercle and not the obesity prone mice (66). On the other hand, female SERT knock-out mice have increased abdominal fat, although the males have not (69). Also the role of SERT in (pathologic) eating behavior still remains unclear. Whereas obese subjects with binge eating had lower midbrain SERT than obese subjects without binge eating (34), a study in a subject sample with night eating syndrome found increased SERT availability in the midbrain (70;71). On the other hand, in bulimia nervosa patients SERT availability was decreased in thalamus and hypothalamus (72). So, binge eating might well lead to lower SERT availability, but the relation between SERT and eating behaviour is complex and not yet disentangled. To better understand the relation between brain SERT and BMI, replications of the studies of Erritzoe et al. (33) or Koskela et al. (29) are necessary.

**FUNCTIONAL IMAGING IN OBESITY**

**Introduction to functional imaging**

Techniques that image brain activation make it possible to demonstrate differences in brain functioning between obese and control subjects. It has been shown that the visual presentation of food is able to produce activation of specific brain areas in healthy, normal weight people (73) and subsequently it has been questioned whether this activation pattern would be different in obese people. The notion that regulation of eating behavior requires considerable self-control has raised the interest in the functioning of frontal brain regions involved in the control of behavior. In the following section we begin by describing the results of studies investigating basal brain activity levels in obese people not using stimuli to induce specific brain activation patterns. In a second part of the section, we review the findings of studies on brain activation changes in response to various kinds of food-related stimuli. There are several studies that focus on the reaction of the brain to a variety external and internal food stimuli: visual, i.e. food pictures, olfactory, i.e. food odors, gustatory, i.e. tasting food, or eating a meal to induce satiation. An overview of the publications included in this review focusing on functional imaging in obesity can be found in table 2.
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<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>Imaging method</th>
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<tr>
<td>Wang et al. (20)</td>
<td>2001</td>
<td>$[^{18}F]FDG$ PET + $[^{11}C]raclopride$ PET</td>
<td>10 OB, mean BMI 31.2, 10 NW, mean BMI 24.7</td>
<td>Brain metabolism and DRD2 availability</td>
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<td>Volkow et al. (21)</td>
<td>2008</td>
<td>$[^{11}C]raclopride$ PET + $[^{18}F]FDG$ PET</td>
<td>10 morbidly OB, 12 NW</td>
<td>Brain metabolism and DRD2 availability</td>
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<tr>
<td>Wang et al. (74)</td>
<td>2002</td>
<td>$[^{18}F]FDG$ PET</td>
<td>10 morbidly OB, 20 NW</td>
<td>Brain metabolism at rest</td>
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<td>Volkow et al. (75)</td>
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<td>$[^{18}F]FDG$ PET</td>
<td>21 BMI 19 – 37</td>
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<td>Wang et al. (78)</td>
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<td>Schmoller et al. (79)</td>
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<td>45 male, BMI 17 – 44</td>
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<td>Karhunen et al. (80)</td>
<td>1997</td>
<td>$[^{99m}Tc]$- ECD-SPECT</td>
<td>11 OB, 12 NW (all women)</td>
<td>Brain activation by visual food stimuli</td>
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<td>Karhunen et al. (81)</td>
<td>2000</td>
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<td>Rothemund et al. (82)</td>
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<td>Stoeckel et al. (83)</td>
<td>2008</td>
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<td>13 OB, 13 NW (all women)</td>
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<tr>
<td>Stoeckel et al. (84)</td>
<td>2009</td>
<td>fMRI</td>
<td>12 OB BMI 30.8–41.2, 12 NW women BMI 19.7–24.5</td>
<td>Brain activation by visual food stimuli</td>
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<td>Stoeckel et al. (85)*</td>
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<td>fMRI</td>
<td>44 adolescent girls, BMI 17.3–38.9</td>
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<td>Martin et al. (86)</td>
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<td>10 OB (5 men), BMI 30.2–38.1 \ 10 NW (5 men), BMI 19.5–24.7</td>
<td>Brain activation by visual food stimuli pre- vs post-meal</td>
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<td>Cormier et al. (89)</td>
<td>2009</td>
<td>fMRI</td>
<td>19 reduced OB, BMI 27–32, 22 NW, BMI 19–23</td>
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<tr>
<td>McCaffery et al. (90)</td>
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<td>Rosenbaum et al. (94)</td>
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<td>6 OB (2 male, 4 female), BMI 30.3-59.6</td>
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<td>Gellner et al. (95)</td>
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<td>Killgore et al. (96)</td>
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<td>Wallner-Liebermann et al. (97)</td>
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<td>12 OB, mean BMI 34.1 ± 5.6, \ 12 NW, mean BMI 20.9 ± 1.6</td>
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<tr>
<td>Bruce et al. (98)</td>
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<td>Type</td>
<td>Sample Description</td>
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<td>Davids et al. (99)</td>
<td>2009</td>
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<td>22 OW/OB, mean BMI 31.38</td>
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<td>22 NW children, mean BMI 19.7</td>
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<td>Stice et al. (100)</td>
<td>2008</td>
<td>fMRI</td>
<td>33 adolescent girls, BMI 17.3 – 38.9</td>
<td>Brain activation by tasting milkshake</td>
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<tr>
<td>Stice et al. (101)*</td>
<td>2008</td>
<td>fMRI</td>
<td>43 women, BMI 23.8 – 33.2,33 girls, BMI 17.3 – 38.9</td>
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<td>Stice et al. (102)*</td>
<td>2010</td>
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<td>23 OB, 21 NW, 11 postobese</td>
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<td>Delparigi et al. (104)</td>
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<td>21 OB, 20 NW</td>
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<td>Le et al. (105)</td>
<td>2006</td>
<td>[15O]water PET</td>
<td>9 OB, 9 NW (all men)</td>
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<td>Gautier et al. (106)</td>
<td>2000</td>
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<td>11 OB, 11 NW (all men)</td>
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<tr>
<td>Le et al. (107)**</td>
<td>2007</td>
<td>[15O]water PET</td>
<td>9 OB, 10 NW, 8 postobese (all women)</td>
<td>Brain activation by satiation</td>
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<tr>
<td>Gautier et al. (108)</td>
<td>2001</td>
<td>[15O]water PET</td>
<td>12 OB, 10 NW (all women)</td>
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<td>2009</td>
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<td>Brain activation by satiation, GLP-1 plasma</td>
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<td>DelParigi et al. (111)</td>
<td>2007</td>
<td>[15O]water PET</td>
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<td><strong>Other food stimuli</strong></td>
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<tr>
<td>Bragulat et al. (113)</td>
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<td>fMRI</td>
<td>5 OB mean BMI 41.6 ± 5.0, 5 NW mean BMI 22.0 ± 2.9</td>
<td>Brain activation to food related odors after</td>
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</table>

**Other studies on functional imaging in obesity**

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Type</th>
<th>Sample Description</th>
<th>Brain Activation Remarks</th>
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<td>Batterink et al. (114)*</td>
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<td>18 lean (BMI&lt;22), 12 intermediate (BMI 22-30) 12 OB (BMI&gt;30) (all women)</td>
<td>Brain activation on stop signal task</td>
</tr>
<tr>
<td>Jastreboff et al. (116)</td>
<td>2011</td>
<td>fMRI</td>
<td>21 OB/OI, BMI 28.98 ± 3.29, 27 NW, mean BMI 22.28 ± 1.70</td>
<td>Brain activation to mental imagery (relaxation, stress, alcohol cue)</td>
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<tr>
<td>Matsuda et al. (117)</td>
<td>1999</td>
<td>fMRI</td>
<td>10 OB, 10 NW</td>
<td>Hypothalamic brain activation by oral glucose intake</td>
</tr>
<tr>
<td>Gonzales et al. (118)</td>
<td>2010</td>
<td>fMRI</td>
<td>12 OB, mean BMI 34.3 ± 3.5, 11 OW, mean BMI 27.4 ± 1.4, 9 NW mean BMI 22.4 ± 2.2</td>
<td>Cognitive task-related brain activation and insulin sensitivity</td>
</tr>
</tbody>
</table>

*Sample overlap with Stice et al. (100).
**Sample overlap with Gautier et al. (108).
OB = obese (BMI > 30), NW = normal weight (BMI < 25), OW = overweight (BMI 25-30), DRD2 = dopamine D2 receptor, IGS = implantable gastric stimulator, ECD-SPECT= ethylcysteine-dimer SPECT, fMRI= functional magnetic resonance imaging, GLP-1 = glucagon-like peptide-1.
Basal brain metabolism level

Most of the studies that focus on baseline brain activity levels in obesity mainly measure glucose metabolism as an indicator of brain activation using $[^{18}F]FDG$ PET. When comparing the baseline glucose metabolism levels between obese and normal weight subjects in a state of hunger, increased metabolism is found in the somatosensory brain regions of severely obese subjects and in the precuneus and cerebellum (74). On the other hand, Wang et al. also reported one year before that they found no differences in glucose metabolism levels in a very similar subject sample (20). This inconsistency may be explained by the fact that the subjects in the 2001 study were not necessarily in a state of hunger at the time of measurement. Interestingly, a later study showed that the level of glucose metabolism in the somatosensory cortex positively correlated with striatal DRD2 levels in both obese and normal weight subjects (21), suggesting a direct link between the somatosensory cortex and the mesolimbic dopaminergic system. The higher metabolism of the somatosensory cortex in obese subjects during hunger may be related to stronger sensitivity to food intake in these people. In addition, the glucose metabolism in the dorsolateral prefrontal (DLPFC), medial orbitofrontal, and anterior cingulate cortex (ACC) correlated positively with striatal DRD2 levels in the obese subjects.

There are other brain areas whose glucose metabolism appears to be associated with the subject’s BMI: in the prefrontal cortex (PFC), cingulate cortex (CC), left temporal cortex, left striatum, and right hippocampus glucose metabolism has been shown to be negatively correlated with BMI in healthy subjects (BMI range 19-37) (75). The first two regions relate to the previously mentioned positive correlation between glucose metabolism and DLPFC/ACC and DRD2 levels in obese subjects (21). The PFC and the CC are brain regions involved in inhibitory control, among others. These correlations can therefore be interpreted in the way that people with a higher BMI have a reduced ability to inhibit their drives, including their urges to consume food. The lower glucose metabolism in the PFC and the CC might also be affecting the cognitive abilities of people with a high BMI. It was shown that both glucose metabolism in PFC and CC, and BMI are negatively correlated with the performance scores on cognitive tasks on memory and executive function (75). The correlation between striatal DRD2 levels and glucose metabolism in PFC, CC might point towards a modulatory effect of the dopamine system on the frontal cortex activation. Already some years before, Volkow et al. observed a correlation between striatal DRD2 levels and prefrontal metabolism in drug users (cocaine: (76); methamphetamine: (44); alcohol: (77)). These findings support the hypothesis that similar mechanisms may play a major role both in obesity and addiction. The reported studies show that regional baseline brain activity differs between normal weight and obese people, although the results do not show a clearly consistent pattern yet (table 3).

Interestingly, Wang et al. have shown that it is possible to influence and change the basal brain metabolism level in obese people (78). They studied the effect of an implantable gastric stimulator in severely obese people. This implant acts on the vagus nerve and induces stomach expansion. When the stimulator was switched on, the glucose metabolism decreased by 18% in the right hippocampus, and to a lesser, but significant extent in the right striatum, right orbitofrontal cortex, and right anterior cerebellum. One might wonder whether this is an advantageous outcome, as Volkow et al. (75) had shown that glucose metabolism in left striatum and right hippocampus were negatively correlated with BMI. However, these are areas that are involved in motivation and reward processing, but from the observed activation
change it appears that stimulating the vagus nerve may reduce motivation to eat and reward expectancy from food. It should be noted that all the studies reporting effects of basal brain metabolism levels have been performed by the same research group, hence an independent replication would clearly strengthen these findings.

A study that stands out from the previous ones investigated the relationship between energy metabolism in the brain and BMI using phosphor magnetic resonance spectroscopy (31P-MRS) (79). They found that subjects with higher BMI (including 15 obese subjects) have lower adenosine triphosphate (ATP) metabolism in the occipital cortex and that there is a direct inverse correlation between cortical energy metabolism and BMI. This suggests that there might be a relationship between the brain metabolism and body weight regulation, although the mechanism still remains unclear. Possibly it is related to impaired cellular glucose uptake. The effects of lower cortical energy metabolism on brain function and ageing are also not yet elucidated.

### Brain activity in response to food stimuli

**Food images**

Many studies of brain activation in obese people have focused on specific brain responses to various types of food stimuli. To our knowledge, the very first study to investigate differences in brain response to a food stimulus between obese and lean people was conducted by Karhunen et al. (80). They found that obese women showed an increase in cerebral blood flow (measured with [99mTc]ethyl-cysteine-dimer SPECT) in the temporal and parietal cortices when looking at a plate with food compared to a control condition, while normal weight women did not show this significant change in local brain activity. Moreover, the increased activation in parietal cortex correlated with the subjective feeling of hunger reported by the subject. Karhunen and his group also showed that obese women with binge eating disorder had an increase in regional cerebral blood flow of the left frontal and pre-frontal cortices in response to a food stimulus, whereas obese women without binge eating disorder and normal weight women did not show this (81). These studies were the first to demonstrate that obese subjects have different brain responses to food stimuli than lean people do.

Since 1997, several more research teams have chosen food pictures as their experimental stimuli and functional MRI (fMRI) as a means to measure brain activation. In the design of these studies a clear distinction is often made between pictures of high-caloric and low-caloric

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### Table 3. Basal brain metabolism studies

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<tr>
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<th>PFC</th>
<th>SSC</th>
<th>TC</th>
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<th>OC</th>
<th>HC</th>
<th>Strtm</th>
<th>CC</th>
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<td>Wang et al. (20)</td>
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*While hungry*

OFC = orbitofrontal cortex, PFC = prefrontal cortex, SSC = somatosensory cortex, PMC = premotor cortex, TC = temporal cortex, PC = parietal cortex, OC = occipital cortex, HC = hippocampus, Amyg = amygdala, Strtm = striatum, CC = cingulate cortex, Insl = insula, Thlms = thalamus, Cereb = cerebellum
foods, and people ranging from a lean, healthy BMI to obese were recruited to participate. As expected, the largest differences in brain activation between obese and normal weight subjects have been found when images of high-caloric food served as stimuli. Both Rothenmund and Stoeckel reported that, in their respective study, obese women had significantly more activation in the caudate, putamen, hippocampus and insula in response to high-caloric food pictures (82;83). Additionally, Stoeckel et al. (83), who were using a scanner with higher magnetic field strength and whose subjects had fasted longer than the subjects in the study of Rothenmund et al.(82), found increased activation in the OFC, PFC, ACC, NAc, amygdala and ventral pallidum of the obese women. Rothenmund et al. also reported an increased activation in the parietal cortex. Taken together, both studies demonstrate that obese women show an increased responsiveness to high caloric food stimuli in several brain regions that are either related to processing of reward (caudate, putamen, OFC), memory (hippocampus) or gustatory functioning (insula). Other regions involved in reward processing (such as NAc, amygdala, ventral pallidum), executive functioning and inhibitory control (PFC, ACC) are also more responsive to food stimuli in obese women than in lean controls. The general increase in activation of the reward system most likely reveals a larger reward expectation from food or increased motivation in obese women. In frontal brain areas the heightened activation can be interpreted as a preparation for action to obtain food and at the same time, an increased need to control and inhibit the action.

Stoeckel et al. conducted further analysis in the same sample as described above, only this time they focused their analyses on the functional connectivity of reward network areas during the processing of high or low caloric food and control images (84). Their main finding was an increased OFC→NAc connectivity in obesity and a deficient connectivity between amygdala and NAc, as well as between amygdala and OFC. The authors suggest the strong OFC→NAc link may partly explain the increased drive to consume foods in obese people, and the lacking connectivity of the amygdala could hamper the normal modulation of reward value attribution to food (or food stimuli).

Apart from the dissociation between obese versus lean subject’s brain activation to food stimuli, it is interesting to take a closer look at the differences that emerge during the processing in response to high versus low-caloric food stimuli. For instance, Rothenmund et al. (82) found an increased activation in the putamen to high caloric food images, when analyzing activation discrepancies by high-caloric versus low-caloric food pictures between obese and normal weight women and Stoeckel et al. (83) found increased activation in the OFC, PFC, ACC, insula, NAc, amygdala, ventral pallidum, hippocampus, and caudate. This shows that, in particular, high caloric food can trigger a strong brain response in obese women, and it is in line with the idea that specifically high-caloric food could lead to a food addiction.

A hypoactive reward circuitry with subdued levels of dopamine receptors (DRD2), or a particular brain response patterns to food cues could be partly due to a specific genotype. To address this hypothesis Stice et al. (85) genotyped and weighed 44 female students ranging from lean to obese and recorded their brain activity while exposing them to pictures of tasty food, unpalatable food, or glasses of water (neural control) following a 4-6 hrs fast. Six and 12 months after these initial measurements the team of researchers reassessed subjects’ BMI. The results of the study were that those women with either the DRD2 TaqIA A1 allele or the DRD4–7R allele, who showed decreased activation in frontal operculum, lateral orbitofrontal cortex, and
striatum, were significantly more likely to have increased their BMI during the following 6-12 months. For those girls who did not have these allele variants, a greater activation of frontal operculum, lateral orbitofrontal cortex, and striatum correlated with future weight gain. These results suggest that genes coding for specific variants of the dopamine receptors may moderate the effect of brain activation in response to food cues. This would mean that when a particular brain response to food stimuli occurs in carriers of a certain DRD2 coding gene does this increase the risk of gaining weight for that person.

Since consequences of food and eating are at the heart of obesity, it interesting to see what the effect of satiety status on brain activation is. Martin et al. (86) investigated the difference in brain response in lean and obese subjects to food images before and after a meal. The pre-meal scan was taken after a ~4hr fast and the post-meal images were acquired after a lunch containing about 500kcal. In the pre-meal contrast, obese subjects showed more activity in ACC and medial PFC, and also in the frontal, temporal, fusiform, and occipital gyrus, and cuneus, than the lean controls. The medial PFC activation correlated positively with intensity of hunger reported in the obese group, whereas the ACC activation correlated negatively with a disinhibition score. After having had lunch the difference in activation in medial PFC remained significant between the two groups, and also a difference in activation the caudate, hippocampus, precuneas and temporal and frontal gyrus was found. These results support suggestions of increased anticipation, higher value attribution and higher reward expectation for food in obese people. Both ACC and medial PFC are brain areas that have been shown to be key regions for value attribution and reward processing (87,88).

Cornier and colleagues (89) took their subjects a step further and investigated the effect of overfeeding on subsequent brain activation by food cues. Their subject sample consisted of obese people who entered into a weight loss program and managed to lose and maintain the loss of about 8% of their initial body weight (reduced obese) and matched lean controls. In both groups, the first scan was performed at a stable weight under a weight maintaining diet and the second scan took place after 2 days of 30% overfeeding. The obese individuals showed less activation in the insula and inferior visual cortex on the first compared to the lean controls. In obese individuals overfeeding failed to lead to a reduced activation in any area of the brain in response to visually presented food stimuli, whereas in normal weight people there was a significant reduction of signal in insula and hypothalamus (89). These results may point towards a reduced interoceptive sensitivity to detect the nutritional need state of the own body. Possibly, changes in satiation signalling by overfeeding my play a role.

McCaffery et al. (90) recorded the brain activation in response to high-caloric and low-caloric food pictures in previously obese subjects, who successfully maintained their weight loss. The team compared the brain activity of these subjects to that of currently obese and normal weight subjects. The post-obese subjects showed greater activation upon seeing food than both the obese and normal weight participants in the left superior frontal region, left inferior frontal region, and right middle temporal region, and decreased activation in the pre-central regions. The greater activation in the frontal brain regions might indicate that post-obese subjects show increased inhibitory control when seeing food, which could explain their ability to maintain their weight loss. The decreased activation in the pre-central regions could point to a decreased motor planning for initiating eating. McCaffery et al. (90) also report that obese subjects showed greater activation in the ACC, but normal weight people showed greater
activation in superior frontal regions, right precuneus and right superior parietal regions, and interpret this finding as a reduced inhibitory control capacity in the obese subjects. These results seem to contradict those of Stoeckel et al. (83), who found larger activation in frontal regions in obese people while viewing food pictures. However, an important distinction between the two studies is the duration of the fasting period before the scanning session (4 hours (90) versus 8-9 hours (83)). The unequal hunger-state of the subjects might be part of the explanation for the divergent findings (91).

Leptin is a hormone that acts on receptors in the mediobasal hypothalamus and inhibits appetite long term (92). Generally, leptin levels are proportional to body fat, but studies have shown that after dieting or fasting leptin levels drop (e.g. (93)). To find out how dieting and subsequent changes in leptin level affect brain activation in response to food cues Rosenbaum et al. (94) ran a placebo controlled study, in which 6 clinically obese patients performed a first scanning session at their initial body weight, and a second session after dieting and stabilizing at 90% of their starting weight. During the stabilization period subjects received daily injections of either leptin or a placebo (condition blind). The comparison of pre- and post dieting scans in the placebo condition showed a decrease in brain activity in hypothalamus, cingulate gyrus, and middle frontal gyrus in response to food images. Increases were found in areas of the limbic system (brainstem, parahippocampal gyrus, culmen, and globus pallidus), which may point towards an increase in craving after dieting, even when weight stable. The activation decreases in regions involved in executive functions and decision-making (middle temporal gyrus, inferior frontal gyrus, middle frontal gyrus, and lingual gyrus) possibly reflects a reduced control over behavior (94). Importantly, these changes were not present in the leptin condition, demonstrating that the injection induced increase in leptin levels was able to reverse the functional changes in brain activation in response to food cues. This leptin dependent reverse may help to decrease craving and reduce the need for intense inhibition and behavior control.

Geliebter et al. (95) performed a creative variation of the previously described studies by presenting both visual (food pictures) and auditory (food words) stimuli of high- and low-caloric foods to their subjects. The sample in this study consisted of relatively small groups of female obese and lean binge-eaters (n = 5, each) and obese and lean non-binge eaters (n = 5, each), which reduces the statistical power. The main outcome is a consistent, strong activation in the group of obese binge-eaters to high-caloric food in the pre-central cortex, a brain area that suggests enhanced motor planning in response to food stimuli.

The brain response to visual food stimuli can be modulated by medication. Killgore et al. (96) treated healthy subjects (BMI range 20.1 - 38.6) with citicoline, a drug with cognitive enhancing, neuroprotective and neuroregenerative effects that may affect the dopamine system. Before and after 6 weeks of treatment with citicoline the subjects’ brain response to high-caloric food pictures was measured with fMRI. Those subjects who had received 2 mg of citicoline per day showed increased activity in the amygdala, insula, and lateral orbitofrontal cortex after treatment. These increases in activity correlated negatively with the subjects’ self-reported appetite. The study shows that fMRI with visual food stimuli might be an instrument to be used in future for the evaluation of specific treatments for obesity that affect appetite, since best the treatment may depend on the subjects brain response pattern.

A different arm of research has concentrated on developmental aspects of obesity concerning brain function. Some researchers have chosen adolescent participants, e.g.
Wallner-Liebermann et al. (15-21 years of age; 97), while others tested younger children, e.g. Bruce et al. (10-17 years of age (98)) and Davids et al. (9-18 years of age (99)).

Wallner-Liebermann et al. (97) were interested in the role of the hippocampus in energy regulation. They presented images of high caloric food, low caloric food and neutral control pictures to lean and obese boys and girls. Before the imaging session all participants had not eaten for 2-4 hrs and had given a blood sample to measure the fasted plasma insulin level. Wallner-Liebermann reports finding a significant positive correlation between fasted insulin levels and activation of the (right) hippocampus in the high-caloric food versus fixation contrast. There was neither relationship between the subject’s BMI and insulin level, nor between BMI and hippocampal activation. However, waist circumference was significantly correlated with both insulin level and hippocampal activation. The researchers suggest that insulin-signaling pathways may be influencing the hippocampal control of eating behavior.

In children, Bruce et al. (98) assessed brain activation to a simple picture-viewing task of food, animals and blurred control images. FMRI images were acquired twice, in one pre- and one post-meal scanning session, similar to the study in adults by Martin et al. (86). In the pre-meal scan, the obese children showed more activation in the PFC and hippocampus and post-meal they showed more activation in the OFC. In addition, they displayed a smaller reduction of activation in limbic regions and paralimbic regions (nucleus accumbens, putamen, amygdala, insula, cingulate cortex) in the fasted compared to the satiated state than the lean control group, which suggests that the obese children might experience less reward or satiation from a meal.

Davids et al. (99) also tested children with a range of BMI, from lean to obese, in a similar study design with an additional measure of self-esteem (self-report questionnaire). He found that obese children showed increased activation in DLPFC while viewing food images, compared to lean children. Self-esteem was negatively correlated with DLPFC activation, so children with a lower self-esteem and higher BMI seem to have more (inhibitory) activation while exposed to food cues. On the other hand, lean children showed stronger activation in caudate and hippocampus, ACC, thalamus and occipital cortex when viewing food pictures, which is opposite to most findings in adults (see table 4).

**Food consumption**

A different way to present food stimuli is letting subjects taste food or consume caloric substances. Stice et al. (100) used fMRI to test the brain response to tasting a chocolate milkshake versus a tasteless solution. When comparing lean and obese adolescent girls while tasting the milkshake, the obese group showed increased activation in the gustatory and somatosensory cortex and decreased activation in caudate nucleus. A non-food related visual cue, which had been presented in association with the tasting experience and thus triggered a conditioned response, exerted an increased activation in the gustatory cortex and somatosensory cortex in the obese girls. This means that when tasting or having a taste expectation, brain regions involved in (the initiation of) food intake activate more in obese girls. Stice et al. (101) confirmed their findings in another sample of obese and lean young women by showing that the brain activity in the caudate nucleus and putamen in response to tasting the milkshake correlated negatively with subject BMI, i.e. the obese women and girls showed a decreased activation in the striatum when tasting the milkshake. In both the adolescent girls and the young women sample the negative correlation between caudate and putamen activity and BMI appeared to be based on the results of a subgroup of girls, who carried the Taq1A allele of the DRD2 gene.
### Table 4. Functional neuroimaging studies on response to food stimuli

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* in children
** Moderated by genotype (DRD2 Taq1A A1 allele and DRD4 7R allele)
*** Obese subjects with stable weight loss compared to lean subjects
sat. = satiated

OFC = orbitofrontal cortex, PFC = prefrontal cortex, SSC = somatosensory cortex, PMC = premotor cortex, TC = temporal cortex, PC = parietal cortex, OC = occipital cortex, HC = hippocampus, Amyg = amygdala, Strtm = striatum, CC = cingulate cortex, Insl = insula, Thlm = thalamus, Hthlms = hypothalamus
It seems therefore that this allele indirectly modulates the response of caudate and putamen to food tasting in a BMI-dependent manner. Moreover, further results showed that the Taq1A allele modulates the relationship between caudate activity and risk for future weight gain. Stice et al. (101) showed that, on average, carriers of this allele gained more weight during one year if they had a low caudate response to the milkshake tasting, while non-carriers gained more weight if they had a higher caudate response, which they later confirmed in the described study using food pictures (85). In this respect, it is interesting to mention that the Taq1A allele has already previously been associated with an increased risk for obesity or pathological eating behavior, as well as with alcoholism and other substance addictions (48-50). Overall, these results suggest that carriers of the Taq1A allele of the DRD2 gene may be more likely to become obese, because of the disturbed response in their striatum to tasting high-caloric substances.

A hypofunctioning reward system seems to be a key feature of and a likely predisposing risk factor for obesity. Such a dysfunction could be a stable characteristic or a dynamic adaptation of the brain in obese people. Stice and his team tested whether weight gain over time can affect the response of the reward system to food consumption (102). They measured the BOLD-signal during consumption of a chocolate milkshake in 26 obese women in an initial baseline and a 6-months follow-up session. During the 6-months intermission period eight participants increased their initial BMI by >2,5%. The researchers compared the brain activity in these weight-gain subjects with the measurements from the weight-stable or weight-loss participants. They found that, at the follow-up assessment, the activation of the striatum in the weight gain group was reduced compared to the activation measured at baseline. There was a correlation between the increase in BMI and the reduction of activation (baseline – follow-up) in the (right) caudate. This study again shows that overeating can lead to a reduced striatal response to palatable food, and thereby reduce the reward value to be gained by food.

A different technique than fMRI to investigate the brain response to food stimulation is to measure the regional cerebral blood flow (rCBF) with \[^{15}O\]-water PET, which was used to measure the brain response to tasting a liquid meal and to the satiation after consuming the meal (103;104). For these studies, the subjects were scanned after a very long fasting period of 36 hours. Tasting the liquid meal resulted in significantly higher activations in the insular cortex in obese subjects compared to lean subjects. The obese subjects had greater decreases in rCBF in the posterior cingulate, temporal and orbitofrontal cortex. The insula activation may show enhanced interoceptive processing of tasting food.

The brain responses to tasting a liquid meal after consuming a satiating meal (as opposed to a 36 hours fast) also differ between obese and lean subjects. Obese subjects, compared to lean subjects, showed decreased activity in the posterior cingulate cortex, amygdala and hippocampus (103). Obese subjects seem to respond less to satiation, i.e. ingesting a liquid meal after a 36 hour fast, than lean subjects. Obese men showed decreased cerebral blood flow upon satiation compared to controls in DLPFC (105), insular cortex, hippocampus and parahippocampal areas, temporal cortex, occipital cortex, and cerebellum (106). Additionally, activity of the hypothalamus and thalamus was decreased to a lesser extent than in healthy, lean men. Obese women also showed a decreased activation upon satiation in the DLPFC (107), as well as in insular cortex, parahippocampal areas, caudate nucleus, and temporal cortex (108).

Summing up these results we can say that the brain regions consistently showing a decreased activation in obese people of both genders, compared to controls, when the subjects are...
in a satiated state, are the DLPFC, the hippocampus and parahippocampal areas, and the insular cortex and temporal cortex. Hence, obese people seem to exert reduced inhibitory or executive control, have lower learning and memory related activity, and reduced interoceptive and food-sensation processing upon satiation. In line with these findings, Le et al. (109) later reported in a re-analysis that the DLPFC of obese subjects shows a tendency to decrease their activity following a meal, rather than increasing it, as is the case in lean individuals.

To further elucidate possible mechanisms responsible for the response differences in brain activation after a satiating meal, Pannacciulli et al. (110) calculated the correlations between brain activity and peak plasma GLP-1 level after consuming a liquid meal. GLP-1 is a gut hormone that acts as a meal termination signal. They found that the peak GLP-1 level was positively correlated to rCBF in the DLPFC and hypothalamus in a combined sample of obese and lean subjects. As has been shown in the previously described results, in a satiated state the DLPFC activation is lower in obese compared to lean people. This reduced activation is associated with decreased GLP-1 levels, suggesting that a disturbance in the GLP-1 signaling pathways may be one underlying factor causing obese people to experience an attenuated satiation signal after eating.

DelParigi et al. (103) also studied formerly obese subjects and compared their results to data from currently obese and lean subjects. Upon food tasting, post-obese subjects showed higher insula activation than lean subjects, but at a similar level to the currently obese subjects. This would suggest that post-obese subjects are at risk for relapse every time they experience the taste of food. In response to satiation, post-obese and obese individuals show similar levels of reduction in activation in the posterior hippocampus. A potentially very important difference between the obese and post-obese group is that upon satiation posterior cingulate and amygdala activation are not significantly reduced in post-obese subjects, as they are in obese subjects. The activation level of the post-obese subjects is similar to the activation levels in healthy lean subjects. Given this apparent reestablishment of the satiation response in the posterior cingulated and amygdala this finding indicates that, like lean subjects, post-obese people may experience stronger satiation and may be better able to control their impulses towards food stimuli than obese people.

In another study, successful dieters and obese non-dieters were compared. The obese non-dieters showed increased cerebral blood flow in response to food tasting in the hippocampus and occipital gyrus. Upon satiation, the obese non-dieters had higher cerebral blood flow in the OFC, but lower in the dorsal striatum, DLPFC, and anterior cerebellar lobe (111). The higher cerebral blood flow in the dorsal striatum of successful dieters to satiation emphasizes the importance of the previous finding, that it is possible to partly return to the normal weight situation after losing weight and probably experience more reward from food again. Overall, the studies of DelParigi et al. (103;111) show that post-obese subjects maintain some of the functional brain characteristic of currently obese people when tasting food, but when satiated they show some similar responses to lean people in other brain areas, which might be an indication of a gradual adaptation of the brain to the post-obese state.

Other food stimulation
In our everyday life food odors are very potent predictors of food. This has been picked up by the food producing industry and in some shops artificial odours are being dispersed in the environment with the aim to induce appetite in the bypassing costumers, to boost the food stall’s sales (112). Bragulat et al. (113) were interested in the brain response to food odours, and
in the differences that occur between lean and obese. They exposed 5 lean and 5 obese women to odours of sweet foods, like chocolate cake or caramel ice-cream, or of fatty foods, like chips or pasta, while lying in an fMRI scanner and compared the BOLD-signal with the brain response to a non-food related odour, like grass or patchouli. The obese subjects revealed slightly more activation in bilateral hippocampus/parahippocampal area than their lean counterparts, while the healthy, lean participants responded with a stronger activation of the posterior insula to food odours than the obese.

Other studies on functional imaging in obesity
Apart from the brain activation in response to food stimuli, the brain activation related to inhibitory control has also been a subject of interest in obesity. Batterink et al. (114) set out to explore the relationship between activation of inhibitory control network and BMI, using fMRI and a food specific go/no-go task in adolescent girls (4-6 hrs fasted). As predicted by their hypothesis, they found that a higher BMI correlated with increased impulsivity in behavior and reduced activations of inhibitory control regions in the frontal cortex (DLPFC, medial and ventrolateral PFC, OFC). In addition, the study replicated the finding that activation of reward processing areas in response to food images correlates positively with BMI.

In adults, brain activation in response to a stop signal task has been studied by Hendrick et al. (115). There were no behavioral differences on the task, but brain activation was different between the lean and obese women. The lean women had greater activations in the insula, inferior parietal cortex, cuneus, and supplementary motor area than the obese women during stop versus go trials. This difference was based on diminished brain activations in the obese women. In addition, the brain activations in these regions inversely correlated to BMI across subjects. So, this shows that a higher BMI is related to lower activation of several brain regions in the case of response inhibition.

Some studies use fMRI in combination with a non-visual experimental design. Jastreboff et al. (116) tested the relationship of metabolic, hormonal, and functional activation changes to an increase in BMI using fMRI and a mental imagery task, in which lean and overweight/obese participants had to imagine themselves in individually pre-tested situations that made them feel stressed, neural/relaxed or craving alcohol. The results showed that the overweight/obese group had higher ventral striatum activation than the lean controls in both the stressful and the neutral imagery condition, while the alcohol craving condition was comparable. This may point towards a general dysregulation (both under stressed and relaxed conditions) of the reward system, in particular of the ventral striatum, which may influence reward related behaviors such as eating.

Another fMRI study in obese subjects that stands out from the previously described studies was conducted by Matsuda et al. (117). This study focuses only on hypothalamic activity in response to glucose ingestion. The hypothalamus plays a central role in integrating and communicating metabolic signals from the body to higher brain structures and the other way around. Thereby the hypothalamus is an important regulator of energy intake and thus, of eating behavior. Matsuda et al. measured the BOLD-signal in the hypothalamus from 8 minutes before and until 40 minutes after glucose ingestion. In control subjects the activity in the hypothalamus was decreased around six minutes after the glucose ingestion. In obese subjects this down regulation of activity was significantly delayed and also less pronounced. This finding confirms the PET study results of Gautier and colleagues, who measured a smaller
decrease in rCBF in the hypothalamus after satiation in obese participants (106). Together, these results suggest that in obese subjects the hypothalamus is not sufficiently inhibited after caloric intake, which might result in an insufficient satiety signal.

Gonzales et al. (118) used fMRI in a very different paradigm. They were interested in cognitive deficits in obese subjects, as they might be a predictor of cerebral atrophy in older age. Insulin sensitivity was measured, as it is a factor that directly influences the central nervous system functioning (119). Gonzales et al. (118) tested obese, overweight and normal weight participants on a cognitive memory task (two back task) using fMRI. The team found no significant performance differences between the groups, however the obese group had a significantly lower activation in the (right) parietal cortex than both other groups while doing the memory task. Overall, a high BMI was associated with low insulin sensitivity and insulin sensitivity was a strong predictor of parietal cortex activation during the task. They found that, in all subjects, low insulin sensitivity was a better predictor of decreased parietal cortex activation than BMI.

Discussion of functional imaging studies in obesity

Our understanding of the functional brain processes that are affected in obesity greatly profits from the advanced functional imaging techniques and number of studies on this topic has made a jump in the last five years. PET and spectroscopy studies have shown that body weight and brain metabolism are not independent from each other, although the results are not always consistent (table 3).

The brain’s response to food visual stimulation has been heavily investigated since it is likely to be an important factor for understanding why some people can easily confront exposure to food and refrain from eating, while others repeatedly succumb to their temptations and overeat. In everyday life we are constantly exposed to images of food from advertisements, food shops and stalls, and the ample food choice availability in most homes. Overall, increased brain activations in obese people in response to food stimuli have been reported in parietal and temporal cortex, OFC, PFC, ACC, caudate, putamen, NAc, amygdala, ventral pallidum, hippocampus, and insula. These areas can be grouped as processing reward sensitivity/expectation (caudate, putamen, OFC, NAc, amygdala), executive control and inhibition (PFC, ACC), gustatory, interoceptive and emotional processing (insula), and memory (hippocampus). An overview can be found in table 4.

Comparing the results of the food tasting and consumption studies to the results of the fMRI studies using visual food stimuli the main findings appear to contradict each other at first sight. Decreased brain activation in the striatum while tasting food (85;100;101) opposes the finding of increased activation during visual food stimulation (82;83). However, the difference in presentation of the food stimuli might explain this contradiction. Addiction theories have previously suggested that in the addicted state the rewarding effect of drugs shifts from the effect of the drug itself to the cue that predicts the drug (120). A similar process might be taking place with respect to food. The increased activation of the brain reward system to a visual food stimulus could point to an increased motivation of the food in obese subjects, while the decrease in upon tasting the food could point to a decreased reward when actually consuming the food.

Stice et al. hypothesized that the lower striatal BOLD response to tasting of a milkshake at a higher BMI may reflect a blunted dopamine release in the striatum that becomes apparent in the subdued activation of the striatum during food consumption. This hypothesis is in accord
with the reward deficiency syndrome theory of a hypodopaminergic reward system that has already been mentioned in the molecular imaging part. However, one should be cautious with interpreting a decreased activation measured with fMRI as a blunted dopamine release (121). For a reliable measure of a blunted dopamine release during food tasting in obese subjects, PET or SPECT studies could provide more conclusive results.

It is sometimes difficult to directly compare the results of all the reviewed studies, because small differences in experimental design can have a huge impact on the resulting brain response. Possibly the most important factor influencing brain activation to food stimuli is the nutritional state of the subjects. While in lean people, there is a clear decrease in limbic/paralimbic activation when satiated this reduction is strongly diminished or not present in obese people (86). Interestingly, even two days of overfeeding does not influence brain activation in obese as in lean people. It might be that the ability to sense the nutritional need of one’s own body is compromised in obesity, but what could be the underlying cause of this malfunctioning interoceptive system in not clear. The finding that even after a period of extreme fasting (36 hours fast) obese and lean people still respond differently to food consumption (obese show increased insula activation) is interesting. It suggests that even in the undoubtedly hungry state, the tasting of food still leads to more active processing and sensation of the food in obesity. After receiving a full meal, the reviewed studies repeatedly find less frontal cortex activation in obese compared to lean participants. Probably, this shows a lowered response to satiation in obese people so that they exert only reduced inhibitory control after a meal. In lean people, the frontal activation most likely represents increased control over behavior so that they can better refrain from eating.

The external validity of all the imaging studies on food consumption is limited by the fact that in none of the studies to date measures brain activity during the consumption of a real, solid meal been investigated directly in a scanner. Due to the absolute requirement to lie still during image acquisition, researchers have to content themselves with using fluids as food stimuli in their experiments. Stice et al. prepared a creamy chocolate milkshake for their subjects, and it seems to work as a good compromise to limit movement artifacts and at the same time have the subjects experience something most similar to what they would consider “real food” in their everyday life.

A subject’s brain activity in response to food interacts with his/her genotype. Depending on specific features in a person’s genotype the same brain activation pattern to food can shift the balance for risk of future weight gain in either direction. Stice et al. (85;101) observed that a reduced activation of the reward network (striatum: i.e. caudate, putamen) after food consumption interacts with the genotype of the subject to predict the risk of future weight gain. Carriers of the Taq1A allele of the DRD2 gene seem to be at an increases risk for gaining weight over the following months, which points to a further link between eating behavior and the (deregulated) dopamine system. The reduced BOLD signal recorded in the dorsal striatum could be revealing a reduced dopamine release of a hypoactive system.

Some obese people do manage to loose weight in a diet, and some even stabilize and maintain their new BMI. It is interesting to see that this subgroup shows similarities in brain activation with obese subjects when tasting food, but when satiated their brain activity pattern shows more resemblances with the pattern in lean subjects. Thus, the brain activation in response to food in the satiation state might be essential in the ability to maintain weight loss
and control food intake. It also suggests that weight gain and weight loss can possibly change the sensitivity of the reward system within a person over time.

While the majority of the functional imaging studies focused on the brain response to food-related stimuli, a few also assessed brain function related to inhibitory control. Parallels between obesity and drug addiction have previously been described and not only regarding craving, but also regarding response inhibition these parallels can be made. The drug addiction model on impaired response inhibition and impaired salience attribution could also be useful for obesity (122). Batterink et al. (114) and Hendrick et al. (115) indeed show that obese adolescent girls and women have less brain activation in several brain regions, including the prefrontal cortex (only in (114)), in different tasks testing inhibitory control. This could be related to the lower basal glucose metabolism in the PFC that was found by (75). However, the results on brain function in inhibitory control in obesity are still preliminary and more attention for this topic is welcome.

STRUCTURAL IMAGING IN OBESITY

Introduction to structural imaging

Apart from the differences in functional brain activations investigated in obese and normal weight subjects some structural differences have been observed. It remains a point of debate whether these structural changes are pre-dating (and potentially causal to) or resulting from the obese state. On the one hand, it is clear that repeated and extended activation of a set of neural connections can lastingly influence brain structure, making some connections between areas grow stronger at the cost of some others that become weaker (e.g. (123)). On the other hand, a pre-existing structural abnormality in brain connectivity may have an effect on cognition and behavior and could for instance lead to a decreased inhibitory control capacity, or to increased reward processing for food and propensity to overeat. In the section below we will present studies that investigated the structural differences in connectivity and volume between the brains of obese people compared to those of lean controls. An overview of all the publications include in this section of the review is given in table 5.

Structural changes in obesity

Three publications report that the total brain volume is smaller in obese compared to normal weight subjects (124-126). Ward et al. (125) added to this that, in their sample, BMI and cognition were not associated. The effect of a decreased brain volume may generally not have clinically detectable effects, but a correlation between BMI and decreased executive functioning has been reported (127). It is a possibility that a decreased brain volume might lead to an accelerated cognitive decline, and midlife obesity is believed to increase the risk of future dementia (128). A recent study suggests that it may be the visceral fat that is most predictive of a decrease in brain volume, as Debette et al. (126) found that, in a large sample of 733 males and females, visceral adipose tissue had a strong negative correlation with total brain volume that was independent of BMI. Supporting the critical role of visceral fat, Jagust et al. found that waist-hip ratio (WHR) explained significant proportion of the variance in hippocampal volume (129). These researchers previously showed that a low hippocampal volume and white matter hyperintensities (WMH) are related to executive functioning, and that both are risk factors for
<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>Imaging method</th>
<th>Subjects</th>
<th>Primary outcome measures</th>
</tr>
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<tbody>
<tr>
<td>Gunstad et al. (124)</td>
<td>2008</td>
<td>T1-3D MRI</td>
<td>21 OB, 63 OW, 117 NW</td>
<td>Whole brain, grey and white matter volume</td>
</tr>
<tr>
<td>Ward et al. (125)</td>
<td>2005</td>
<td>T1-3D MRI</td>
<td>114 subjects, BMI 19 – 39.7</td>
<td>Global brain volume</td>
</tr>
<tr>
<td>Debette et al. (126)</td>
<td>2010</td>
<td>T1-3D MRI, T2 MRI, CT</td>
<td>733 participants, 53% female, mean BMI 28 ± 5</td>
<td>Total brain volume, waist-hip ratio, CT-based measure of subcutaneous and visceral adipose tissue</td>
</tr>
<tr>
<td>Jagust et al. (129)</td>
<td>2005</td>
<td>T1-3D MRI, T2 MRI, CT</td>
<td>112 subjects, BMI 19.8 - 45.6</td>
<td>Waist-hip ratio, hippocampal volume, white matter hyperintensities</td>
</tr>
<tr>
<td>Taki et al. (131)</td>
<td>2008</td>
<td>T1-3D MRI</td>
<td>17 OB, 273 OW, 1128 NW/UW</td>
<td>Grey matter volume</td>
</tr>
<tr>
<td>Gazdzenski et al. (132)</td>
<td>2008</td>
<td>MRS + T1 MRI</td>
<td>50 subjects, BMI 18.7 – 36.8</td>
<td>Grey and white matter volumes and brain metabolite concentrations</td>
</tr>
<tr>
<td>Walther et al. (133)</td>
<td>2010</td>
<td>T1-3D MRI</td>
<td>20 OB, 22 OW, 33 NW aged females</td>
<td>White and grey matter volumes, cognitive functioning</td>
</tr>
<tr>
<td>Ho et al. (134)</td>
<td>2010</td>
<td>T1-3D MRI</td>
<td>700 patients with MCI or AD</td>
<td>Brain volume</td>
</tr>
<tr>
<td>Pannacciulli et al. (135)</td>
<td>2006</td>
<td>T1-3D MRI</td>
<td>24 OB, 36 NW</td>
<td>Grey and white matter density</td>
</tr>
<tr>
<td>Pannacciulli et al. (136)*</td>
<td>2007</td>
<td>T1-3D MRI</td>
<td>16 OB, 16 NW*</td>
<td>Grey matter volume and plasma leptin levels</td>
</tr>
<tr>
<td>Raji et al. (137)</td>
<td>2009</td>
<td>T1-3D MRI</td>
<td>14 OB, 51 OW, 29 NW</td>
<td>Grey matter and white matter volume</td>
</tr>
<tr>
<td>Soreca et al. (138)</td>
<td>2009</td>
<td>T1-3D MRI</td>
<td>48 women, BMI 21.63–39.44</td>
<td>White and grey matter volumes, change in BMI</td>
</tr>
<tr>
<td>Horstmann et al. (139)</td>
<td>2011</td>
<td>T1-3D MRI</td>
<td>122 subjects, BMI 19-43</td>
<td>Grey matter volume</td>
</tr>
<tr>
<td>Haltia et al. (140)</td>
<td>2007</td>
<td>T1-3D MRI</td>
<td>30 OB, 16 NW</td>
<td>Grey and white matter volumes and the effect of dieting</td>
</tr>
<tr>
<td>Ho et al. (141)</td>
<td>2010</td>
<td>T1-3D MRI</td>
<td>206 healthy elderly subjects, BMI 21.5 – 31.6</td>
<td>Brain volume, genotype for FTO risk allele</td>
</tr>
<tr>
<td>Cazettes et al. (143)</td>
<td>2011</td>
<td>T1 MRI, T2 MRI, FLAIR, DTI</td>
<td>44 OW/OB 31.4±5.9, 19 NW 21.7±1.9</td>
<td>Association between fibrinogen levels and brain volumetric data.</td>
</tr>
<tr>
<td>Alkan et al. (144)</td>
<td>2007</td>
<td>DWI</td>
<td>81 OB, 29 NW</td>
<td>Water molecule diffusion as indication of pathology</td>
</tr>
<tr>
<td>Stanek et al. (145)</td>
<td>2011</td>
<td>DTI</td>
<td>17 OB, 31 OW, 55 NW, 44.7% female</td>
<td>FA in fornix and corpus callosum, relationship with BMI and age</td>
</tr>
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</table>

*Sample overlap with Pannacciulli et al. 2006

OB = obese (BMI > 30), NW = normal weight (BMI < 25), OW = overweight (BMI 25-30), UW = underweight, MRS = magnetic resonance spectroscopy, DWI = diffusion weighted imaging, DTI = diffusion tensor imaging, FA = fractional anisotropy, MCI = mild cognitive impairment, AD=Alzheimer’s disease, FLAIR = fluid-attenuated inversion recovery.
dementia (130). Most likely, the decreased total volume is a result of a decreased volume of grey matter, since a decrease in grey matter volume has been found in obese subjects (124) and Taki et al. (131) found a relationship of BMI and total grey matter volume, which appeared to be based on a negative correlation between total grey matter volume and BMI in men, but not in women. Several studies similarly reported a decrease in the grey matter volume of different subregions: Gazdzinsky et al. (132) associated BMI with a reduced grey matter volume in parietal cortex. Taki et al. (131) found negative correlations between BMI and grey matter volumes of several cerebral subregions (bilateral medial temporal lobes, anterior lobe of the cerebellum, occipital lobe, frontal lobe, precuneus, and midbrain) in men, but not in the women. Walther et al. (133) controlled for hypertension in their subject sample and still report significant negative correlations between BMI and grey matter volumes in left orbitofrontal gyrus, the right inferior and precentral frontal cortex, the right posterior cortex extending from the parahippocampal gyrus to the fusiform and lingual gyri, and the right posterior and lateral cerebellar grey matter. Moreover, lower grey matter volumes in frontal and cerebellar regions predicted worse cognitive and executive performance on several tests (133).

In patients with Alzheimer’s disease (AD) or Mild Cognitive Impairment (MCI) correlations of grey matter volume reductions and BMI were found in several brain region across the frontal, temporal, parietal, and occipital lobes (134), i.e. obese patients showed smaller grey matter volumes than leaner patients. Pannacciulli et al. (135) described a reduced grey matter density in several brain regions in obese subjects (right cerebellum, left post-central gyrus, right frontal operculum, right and left putamina, and right and left medial frontal gyri). In line with this, they demonstrated a negative correlation between fasting plasma leptin levels and grey matter volume in several of the same regions (left frontal operculum, left postcentral gyrus, and right putamen) (136). Later, Raji et al. (137) managed to show strong negative correlations between BMI and grey matter volume in the orbitofrontal cortex, anterior cingulate gyrus, and medial temporal lobe. In a longitudinal study, Soreca and colleagues (138) assessed BMI and grey and white matter volumes of 48 middle-aged women, whose BMI had already been measured 20 years before. In this sample, the size of the increase in BMI over the 20-year period was a significant predictor of grey matter volumes: a greater weight gain was associated with reduced total grey matter. White matter volumes did not appear to be related to a change in BMI.

Even if most papers seem to show that several, in particular frontal, grey matter regions of the brain are negatively affected in their size and density at a high BMI, some publications have also reported an increase in grey matter volume in some cerebral sub-regions. Taki et al. (131) described significant, positive correlations with BMI and grey matter volumes in several brain areas in men (bilateral inferior frontal gyri, posterior lobe of the cerebellum, frontal lobes, temporal lobes, thalami, and caudate heads). Pannacciulli et al. (135) found higher grey matter densities in the left calcarine cortex, left medial occipital gyrus, left inferior frontal gyrus, and right cuneus of obese subjects. Recently, Horstmann et al. (139) reported positive correlations between BMI and grey matter volume in the OFC, ACC, putamen and hypothalamus. They also found positive correlations between leptin levels OFC, ACC, putamen and hypothalamus, DLPFC and fornix, although there were some gender differences.

The researchers of one study did not find any significant differences in grey matter volumes between obese and lean subjects, although in some regions there was a trend for smaller volumes in the obese subjects (CC, DLPFC, brain stem, and cerebellum) (140).
Overall, it seems that in obese subjects the total gray matter volume is reduced (table 6) and this is due to smaller volumes in several cerebral subregions, including reward processing areas, i.e. the putamina, inhibitory control regions, i.e. the medial frontal gyri, and food intake related areas, i.e. frontal operculum and somatosensory cortex. At the same time, an increase in grey matter volumes of some other brain areas, that are involved in similar processes, e.g. inferior frontal gyri for inhibitory control and caudate heads for reward processing, has been observed. These results don’t form a consistent pattern and therefore no definite conclusions can be drawn as yet. The link between brain structure and function also remains somewhat unclear and more research is needed. In a recent publication, Ho and colleagues (141) brought to light an interesting clue for the origin of these volumes changes of grey matter in obese people. The team of scientists genotyped a sample of 206 elderly subjects and created 3D

<table>
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<th>Table 6. Structural changes in obesity</th>
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<tr>
<td><strong>Total brain volume</strong></td>
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<tr>
<td>Gunstad et al. (124)</td>
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<tr>
<td>Ward et al. (125)</td>
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<td>Debette et al. (126)</td>
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<td>Taki et al. (131)</td>
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<td>Gazdzinski et al. (132)</td>
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<td>Walther et al. (133)</td>
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<td>Ho et al. (134)</td>
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<td>Pannacciolli et al. (135)</td>
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<td>Raji et al. (137)</td>
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<td>Soreca et al. (138)</td>
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<tr>
<td>Horstmann et al. (139)</td>
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<td>Haltia et al. (140)</td>
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</table>

TC = temporal cortex, OC = occipital cortex, FC = frontal cortex, PC = parietal cortex, OFC = orbitofrontal cortex, ACC = anterior cingulate cortex, NAcc = nucleus accumbens, CC = cingulated cortex
maps of their cerebral grey matter volumes. Their main finding was that those participants who carried a specific variant of the FTO gene (fat mass and obesity-associated gene) had, on average, an 8% smaller total grey matter volume than the non-carriers. This FTO gene variant is carried by ~48% of the western/central Europeans population and is associated with an increased risk for developing obesity (142).

Cazettes et al. (143) investigated a different possible cause for the grey matter volume reduction in obesity. They noted that an overweight or obese state is associated with subtle, but chronic, systemic inflammation and they hypothesized that this inflammation might impact on the structural integrity of the brain, in particular in some reward and feeding related areas. To test their idea they measured fibrinogen levels, a marker of inflammation, and collected MRI data from 44 overweight/obese and 19 lean controls to calculate diffusion tensor imaging (DTI) maps. The main findings of the study were that in obese subjects, the volume of the bilateral OFC was negatively associated with the inflammation marker, and that fibrinogen levels correlated positively with diffusion in the amygdala and the right parietal cortex. By contrast, in healthy lean subjects there was a negative correlation between OFC volume and diffusion in the left prefrontal, right parietal and left occipital lobe.

Contrary to the frequently observed volume decrease of grey matter, there are indications that the white matter volume is increased in obesity. Haltia et al. (140) report an expansion of the total white matter volume in their obese sample compared to the controls. Walther et al. (133) describe BMI associated increases in white matter volumes in frontal, temporal, and parietal lobes. Pannacciuoli et al. (135) found greater white matter density in the vicinity of the striatum of obese subjects and Gazdzinsky et al. (132) describe a positive association between BMI and frontal white matter volume in obese participants. In contrast to this, Raji et al. (137) found a negative correlation between BMI and subcortical white matter. However, the subject sample in Raji’s study differed from that the other studies as the mean age was above 77 years, and hence the reported white matter reduction might be age-related. An interesting addition comes from Haltia et al., who scanned their obese subjects again after a 6-week period with a very low-caloric diet (2.3 MJ per day) (140). It turned out that at this post-diet measurement the white matter volume was reduced and approached the volume measured in normal weight subjects. One may wonder whether this is not an acute effect of the diet, but it is nevertheless an indication that the reported difference in white matter volume between obese and lean subjects is reversible. No changes in grey matter volume following the diet were reported. In sum, the data support the conclusion agree that the white matter volume tends to be increased during obesity and might be adaptable to diet and current weight.

Interestingly, the increase in white matter volume does not seem to provide increased functionality of the white matter tracts. In contrast, the integrity of both white and grey matter appears to be compromised in obesity. Results of research using several different imaging techniques agree that integrity of several brain structures is affected by a high BMI. By use of proton magnetic resonance spectroscopy, Gazdzinsky et al. (132) showed that BMI negatively correlated with N-acetylaspartate levels in frontal, parietal, and temporal white matter and in frontal gray matter. This is an indication that the integrity and amount of neurons is negatively affected in these brain regions at a higher BMI. Furthermore, the choline-containing metabolite level, a measure of cell membrane turnover, negatively correlated with BMI in the frontal white matter. Altogether, these findings show that especially in the frontal brain regions
the neuronal integrity in obese people is compromised, which may be a sign of accelerated cognitive decline. Alkan et al. (144) performed diffusion weighted imaging in obese subjects and controls. Increased diffusion is thought to reflect microstructural damage to the brain. The team reported that the obese subjects had higher diffusion vectors in the hypothalamus, hippocampal gyrus, amygdala, insula, cerebellum and midbrain. BMI correlated positively with diffusion in the amygdala, insula, orbitofrontal and middle temporal cortex, showing that areas involved in the regulation of food intake are adversely affected by obesity.

Stanek et al. (145) suggest that the obesity related reduction in executive function and memory capacity may be a consequence of impaired white matter integrity, since this leads to reduced neural transmission speed and slower cognitive processing. Stanek and her colleagues investigated the relationship between fractional anisotropy (FA) and BMI in the corpus callosum and fornix of lean, overweight and obese humans. They found that greater diffusion, indicated by lower FA values, was correlated with BMI. Obese, but not overweight participants had significantly lower FA values in both fornix and corpus callosum, compared to lean participants. Importantly, all subjects in this study were completely healthy (apart form the high BMI), which means the observed white matter impairments do not seem to be causally related to diabetes, depression or other obesity related conditions. Also, the results of the analyses on the role of age in the BMI–FA relationship suggest that normal age-related decline in white matter integrity may interact with BMI, such that age-related negative effects may occur at an earlier age in morbidly obese.

Discussion of structural changes in obesity
The reviewed studies demonstrate that there are structural alterations in the brain that are associated with obesity and suggest that these changes may be partly responsible for some of the functional deficits in obese people. It is shown that obesity is associated with a loss in total brain volume, which can be attributed to an overall reduced grey matter volume. Specifically, grey matter volume loss was reported (although not always consistently) in a wide network of cerebral regions including much of the frontal and temporal cortex, ACC, parahippocampal area, and cerebellum and seem to be even smaller with a rising BMI. This is most likely a result of decreased neuronal integrity or even neuronal loss. This highlights a new and critical point that has not yet become apparent from the research on neurotransmitter levels and functional brain activation: obesity may lead to accelerated cognitive decline. Indeed, obesity has been associated with increased risk for dementia, in particular Alzheimer’s disease (12;128).

Again, the question rises whether the reduced grey matter volume is a cause or a result of the disease. In how far genetic variances are responsible for reduced grey matter in obesity still has to be demonstrated, but it seems likely that the FTO gene plays an important, predisposing role.

White matter changes in obesity also have been quite clearly established. Most studies show increases in white matter volume in obese subjects, however, no association with cognitive performance is observed.

Part of the structural abnormalities might be reversible by dieting, as Haltia et al. (140) have shown. The fact that the volume increases can be brought back to normal levels by a diet-induced weight loss is very promising. However, the diet did not show any effect on grey matter volumes, so it remains to be seen if the reduced executive control and cognitive function can be increased by weight loss towards a healthy BMI.
GENERAL DISCUSSION

Much has been done in neuroimaging to elucidate the role of reward processing in obesity. Studies from the field of imaging in obesity have provided convincing evidence that molecular processes, functional activations and connectivity, and structure are all affected by an unhealthy weight status. The most robust findings show that in obesity the striatal DRD2 availability is lower, that obese people more highly activate several brain regions in response to visual food stimuli than normal weight subjects and that obese subjects have smaller brain volumes, probably due to lower gray matter volumes. Brain regions that are repeatedly listed as affected in the different studies are the striatum (NAc, caudate, putamen), prefrontal cortex, orbitofrontal cortex, amygdala, hippocampus, somatosensory cortex, and the insula (gustatory cortex). The list of affected brain regions shows that there is a strong overlap between the areas affected by a high BMI and the corticolimbic reward systems, which chiefly consists of the ventral striatum, and orbitofrontal cortex (7;146;147). Several studies have focused specifically on the striatum as the dopaminergic reward center. They show amongst others that the DRD2 receptor availability is down regulated in obesity and it seems indicated that this constitutes a predisposing risk factor, as well as being a consequence of the constant overfeeding that leads to the obese state. Dopaminergic brain areas of the reward system (putamen, caudate, NAc) also show reduced functional activation levels after food consumption in fMRI studies e.g. (100;101), while the BOLD signal indicates that the same areas respond with hyperactivation to the presentation of food stimuli (e.g. (82;83). In vivo measurements of extracellular dopamine levels in rodents have confirmed that there is a reduced dopamine release in the NAc of obese compared to lean animals (54) and Johnson and Kenney (41) demonstrated that overfeeding leads to a down regulation of DRD2 in the striatum. Together, these changes in the normal balance of the dopamine system are possibly underlying the addiction-like aspects of obesity. Reduced dopamine signaling after food intake promotes further eating to compensate for the low reward intensity, while the increased striatal activation to food cues may trigger a high reward expectation and as a motivator to seek food.

Further parallels with addiction are the reduced level of striatal DRD2 that have been found in both disorders (20;21) and the particular pattern of activation in response to cues of the addiction substance (food, drugs). The simple cue exposure can stimulate intense craving and trigger a strong sensation of “wanting” (as opposed to “liking” in the incentive-sensitization theory) (148) which is a typical symptom of any kind of addiction. The areas that show increased responding to food cues in obese subjects are the same as those activated during cue induced drug craving in addicts. Mainly, these regions include the insula, OCF, ACC, (DL)PFC, amygdala, (ventral) striatum, and hippocampus (149).

Another parallel that should be highlighted is the impaired inhibitory control that plays a central role in addiction and possibly also in obesity (122). Both disorders are accompanied by a diminished inability to control behaviour (75), which seems to be reflected in different brain activation patterns on inhibitory control tasks (114;115). Impaired inhibitory control makes it increasingly difficult to abstain from the addictive substance or consume it in a measured way. The brain’s capacity for inhibitory control, exerted primarily from the prefrontal cortex, seems to be a central factor in the aetiology of obesity. Research has shown that obese adults tend to have reduced inhibitory control and already obese children are more impulsive and more reward
responsive than their lean peers (150;151). Children who are less able to inhibit actions are more likely to develop overweight later in life (152;153). Increased impulsivity therefore appears to be a predisposing risk factor for obesity. The neural mechanisms underlying impulsivity as a risk factor for future obesity have not been extensively studied with neuroimaging. One fMRI study reviewed above used a food related go/no-go task in obese and lean girls and found that the food images produced greater reward related BOLD-signal and lower prefrontal activation in obese adolescents (114) and another used a stop-signal task in adults. Weight gain to a BMI >30 correlates with lower volume of cortical frontal grey matter and with reduced executive functioning, which implies that weight gain can lead to a reduction a person’s inhibitory control capacity and that impulsivity is thus both a cause and a consequence of the obesity. The ability to resist temptation can be trained. A recent study in restrained eaters managed to show that by pairing a craved food stimulus with a fear stimulus, impulsivity towards the desired food can be controlled and reduced (154). Strengthening behavioral control may be a useful strategy to increase the chances of successful weight loss, and it may even be possible to benefit from existing treatments used in addiction, if these could be adapted to be suitable for obesity (i.e. food related impulse control training). The threat of relapsing to old habits (overeating) after a diet is well established and recent evidence from rodents suggests that dieting can increase stress reactivity by disregulation of the HPA-axis, which in turn promotes binge eating and intake of high-fat foods (155). Total abstinence, which is practiced after drug addiction to limit the chance of relapse, is of course impossible when food is the object of addiction and the daily repeated exposure to food may add to the difficulty of controlling their eating behavior for obese subjects.

A difference between obesity and addiction might be the prominent role of metabolic signals in guiding eating behavior. It is of interest that a few studies report correlations between metabolic parameters and brain function. A high level of insulin in a fasted state predicts increased hippocampal activation in response to food images and is associated with a high BMI (97), which indicates that hippocampal feeding regulation interacts with insulin signaling and can increase a person’s susceptibility to (over)eat. Pannacciulli et al. (110) showed that post meal peak GLP-1 level was positively correlated to rCBF in the DLPFC and hypothalamus in obese and lean subjects. Rosenbaum et al. (94) demonstrated that daily leptin injections were effective in dampening the hyperactive reward sensitivity state after weight loss and reduced the rewards system activation to food cues. These studies show that it will be possible to further elucidate the role of these metabolic signals on the brain. A recent publication reported on a role of GLP-1, describing that activation of the GLP-1 receptor may have a protective effect on cortical and dopaminergic neurons (156), which might be very interesting with regard to the affected dopamine system in obesity. Given the previous comparison to addiction, these findings in obesity might even lead to advances in the field of addiction. For example, neural signals from the food regulation center of the hypothalamus also appear to play a role in addiction, e.g. (157), and understanding the influence of metabolic signals on motivation and behavior may add important information to our current knowledge of addiction and may offer a target for new treatment options. It has been been shown that signaling of the hypothalamic neuropeptides orexin/ hypocretin (HCRT) affects substance addiction, possibly through a motivational pathway involving the mesolimbic dopamine system (158). This example shows that research on obesity and substance addiction can provide mutual benefits and lead to an improved understanding of both disorders.
One important question that has not been resolved is whether weight loss can restore or lead to improvements in the affected obese brain. The evidence from studies until now is dual: there are signs that this is possible, but definitely not in all aspects. In the case of white matter changes, it seems that dieting can indeed normalize the increased volume back to a baseline level (140), but for grey matter this regulation effect has not been demonstrated. If grey matter normalization could be achieved by weight loss, it would be particularly intriguing if also the cognitive and executive function could be regained. The loss of these functions in obesity is believed to be a result of the reduced cortical grey matter and therefore it may be amendable through dieting as well. Studies in patients after bariatric surgery show that these patients loose a lot of weight very rapidly. Two research groups have tested how this strongly reduced weight affects the DRD2 system (23;27). The results of these investigations are not very conclusive, since they partly contradict each other. It seems that there is a complex interaction between BMI and the striatal DRD2 system and that simple weight loss alone is insufficient to bring the DRD2 system back into balance and the DRD2 availability back to baseline. Regarding functional changes, it has been shown that after successful weight loss the reduced PFC activations upon satiation are gradually increased again (90). Therefore, normalizing the post-diet leptin levels appears to help reverse the obesity induced changes in the brain and may aid the body in regulating its food intake motivation.

Finally, the first studies on the role of genetics mediating brain function or structure in obesity have been published. The A1 allele of the TaqIA polymorphism in the dopamine D2 receptor gene (DRD2) has previously been implicated in substance addiction and impulsivity (159), which makes it a likely candidate to be involved in obesity as well. Stice et al. found out that women who carry the DRD2 TaqIA A1 allele or the DRD4–7R allele have an increased likelihood of becoming obese, if their brain response to food cues or food tasting follows a certain activation pattern (85;101). In addition, FTO is associated with lower total grey matter volume (141) and has come forward as an important gene related to BMI in genome-wide association studies (142). These studies need replication, but will also be helpful to answer the question whether some brain changes are the results of the obese state or the other way around.

**CLINICAL IMPLICATIONS**

Medical treatment options for obesity are unfortunately only limited in their success. The main options are the traditional methods of (supervised) dieting and exercise, medication and surgery. The results of medication have been disappointing, since to date, no drug has been able to induce lasting and substantial weight loss in a range of patients or drugs have been withdrawn from the market due to their side effects. Because of the more reliable and enduring success, surgery (e.g. gastric bypass) has been the principal choice option and the number of surgical interventions has largely increased over the past 10 years. However, most operations are very drastic and lead to lifelong, serious restrictions on eating behaviour with side-effects such as vitamin deficits. Neuroimaging studies have the potential to provide important new findings to improve our knowledge about the aetiology of obesity and can possibly point towards new targets for intervention.

The similarity between obesity and addiction discussed previously makes it conceivable that treatments that are effective in cases of addiction may also benefit obese patients once the
treatments have been tailored to address the specific object of addiction. Further treatments may be developed based on theories of cognitive therapy, possibly targeting impulsive behaviour (e.g. binge-eating) by strengthening cognitive control capacities, or aiming to improve weight-loss outcomes and life-style by reducing anxiety and body-dissatisfaction through guided exposure therapy (160). Pharmacologic treatments for obesity can possibly benefit from medication research concerning addiction, because similar underlying neurochemical pathways are affected in both disorders that can be influenced through drugs. In treating obesity, medications that target just one mechanism produce relatively little weight loss (decrease of 5%-10% body weight) and the associated risk factors diminish their practical usefulness (161). New combinations of pharmacotherapy are currently being tested (e.g. phentermine with the serotonin precursor L-5-hydroxytryptophan and the peripheral decarboxylase inhibitor carbidopa) (162). Neuroimaging studies could to support these kind of processes by screening the effect of anti-obesity drugs in lean, but also in obese people and evaluating the functional changes of brain activation to different in response to different cues, and at baseline. For example, treatment with the cannabinoid-1 receptor antagonist rimonabant, which is an anti-obesity drug, reduces the neural response to visual food stimuli in reward related brain regions (163). As we now know that these brain regions are affected in obesity, these paradigms could be used in the development of new drugs.

Deep brain stimulation (DBS) is a method that is used in neurologic disorders (Parkinson's disease) and sometimes for the treatment of psychiatric disorders such as severe depression or obsessive compulsive disorder (OCD). Given the role of the nucleus accumbens in reward from food, which has been indicated by the neuroimaging studies, one can imagine that NAc DBS could be a potential treatment in morbid obesity. There is one case report showing that DBS of the NAc can lead to remission of the obsessive compulsive symptoms, accompanied by successful weight loss (-44 kg, from BMI 37 to BMI 25) and lasting cessation from smoking without any cravings or withdrawal symptoms (164). In this case, as a side effect, the OCD treatment intervention facilitated both weight loss and quitting of smoking. In view of the remarkable success, it seems promising to continue the investigation of DBS in obesity since it could develop into a powerful tool to aid morbidly obese patients. It is likely that among obese patients there is a spectrum of varied underlying causes, but the role of diagnostics to differentiate subtypes of obesity is very limited until now. Neuroimaging studies could in future help to predict cases in which DBS may be successful, based on neuroimaging data of NAc activation in response to food stimuli and food consumption.

In the same way, neuroimaging data could potentially inform the decision of what type of treatment should be applied in individual cases of obesity. For instance, one can imagine that medication with the GLP-1 like analogues (exenatide, liraglutide) may be more effective in cases where very low levels of GLP-1 correlate with reduced regional cerebral blood flow (rCBF, measured with PET) in the prefrontal cortex and hypothalamus (see e.g. (110)). A role for neuroimaging in these kind of decisions needs a high sensitivity and specificity to detect the right category of patients. Thus, this will not be implicated in short-term.
FUTURE DIRECTIONS

Neuroimaging in obesity is a relatively young field, which has been developing very quickly in the last five years. Although this study has enabled us to learn much about the key factors, many questions on the role of the brain in obesity still remain unanswered.

A lot of studies have used neuroimaging techniques to elucidate the role of reward processing in relation to obesity. Future research should also direct its focus towards other functional processes, such as impulsivity, learning and memory, and executive functions, and investigate the interaction of all these with reward processing in obese people. Interestingly, the role of emotions in obesity has not received much attention in neuroimaging studies so far, even though the importance of emotional eating and the impact of emotions on motivation and action have clearly been demonstrated in lean individuals (165). In normal weight subjects, the affect state influences brain activation on food pictures (166), so it can be expected that in obese subjects this also plays a role. Hedonic memories relating to food and feeding probably play a powerful role in the maintenance of obesity by creating a motivation to consume food (167). Furthermore, women seem to relate cue-induced cravings for sweet food, like chocolate, with negative emotions like guilt, anxiety, or depression, when on a diet (168). The involvement of central emotion processing areas like hippocampus and amygdala in the network regulating food-intake is a definite indication of a key role for emotional memories, current mood state, and emotion regulation in food related decision-making, clearly warranting the need for more neuroimaging studies with this focus in future.

The hypothalamus is a central regulator of basic homeostatic food intake, so one would expect a lot of research concentrating on this structure. However, imaging activation in this area has been difficult due to technical limitations. Advanced imaging protocols and studies using a 7-Tesla MRI might be able to fill this gap and provide new insights into the effect of obesity on hypothalamic functioning.

To date, it remains unclear whether many of the changes observed in brain during obesity are a cause or a consequence of the disorder. Prospective studies are of course very difficult to execute, but are necessary to definitely answer this question. Stice et al. (102) showed the predictive value of striatal activation for weight gain one year later. This study is a valuable example of how longitudinal data can inform our understanding of causal relationships, so studies spanning even longer periods of time would add highly interesting and relevant data.

In the discussion of cause and consequence one persuasive argument is the case of a predisposition by genetic effects. Nevertheless, even a predisposing gene does not guarantee the expression of a specific behavioural phenotype with certainty. The human brain is remains flexible to some extent in adulthood and can adapt itself to the weight status. These adaptational changes may still be reversible, but future research will need to determine the extent of this reversibility and more neuroimaging studies should provide follow-up data on weight status to investigate functional long-term effects of weight gain and weight loss.

Regarding structural changes in the brain related to an obese state, there remains some ambiguity of which areas are most affected and whether weight loss can restore the brain to its normal state. Longitudinal data of structural measurements would be highly relevant for answering this question. In the same way, not very much is known about the precise effect of obesity on cognitive functioning (e.g. decline in executive functions, memory) or on the long-term effect of weight loss on cognition...
and neuropsychological functions. The question of reversibility of all of the (negative) consequences of obesity on the brain is of course of great importance for all those concerned.

Finally, one limitation of much of the research to date concerning food related processing and obesity is that the majority of studies have used mostly women in their sample of participants. Among the obese population in the Western world the distribution is roughly gender balanced (1), therefore both sexes seem equally prone to develop overweight. It has even been shown that there is a gender effect on brain activation to food stimuli in lean subjects (169). Also, Haltia et al. (25) showed that there are gender differences in the DRD2 levels and that expectations moderate the dopamine release to a different extent in males and females. The systematic bias in the gender distribution of study samples should be addressed in future research by focusing on male subjects and comparing the effects of obesity on the brain between both sexes. There may be gender specific differences in causes, maintenance mechanisms, and vulnerability of brain and body to the effects of obesity, so more research is needed that investigates this field.

In conclusion, neuroimaging research in obesity has brought much insight in the etiology and effects of obesity on the brain. However, many questions remain unanswered and this still young field will needs further development in future. As the obesity epidemic steadily rises, the urgency increases for effective, knowledge based interventions to target obesity, and future neuroimaging research can contribute to their development.

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