Obesity: exploring neural pathophysiological pathways and improving diagnostic strategies

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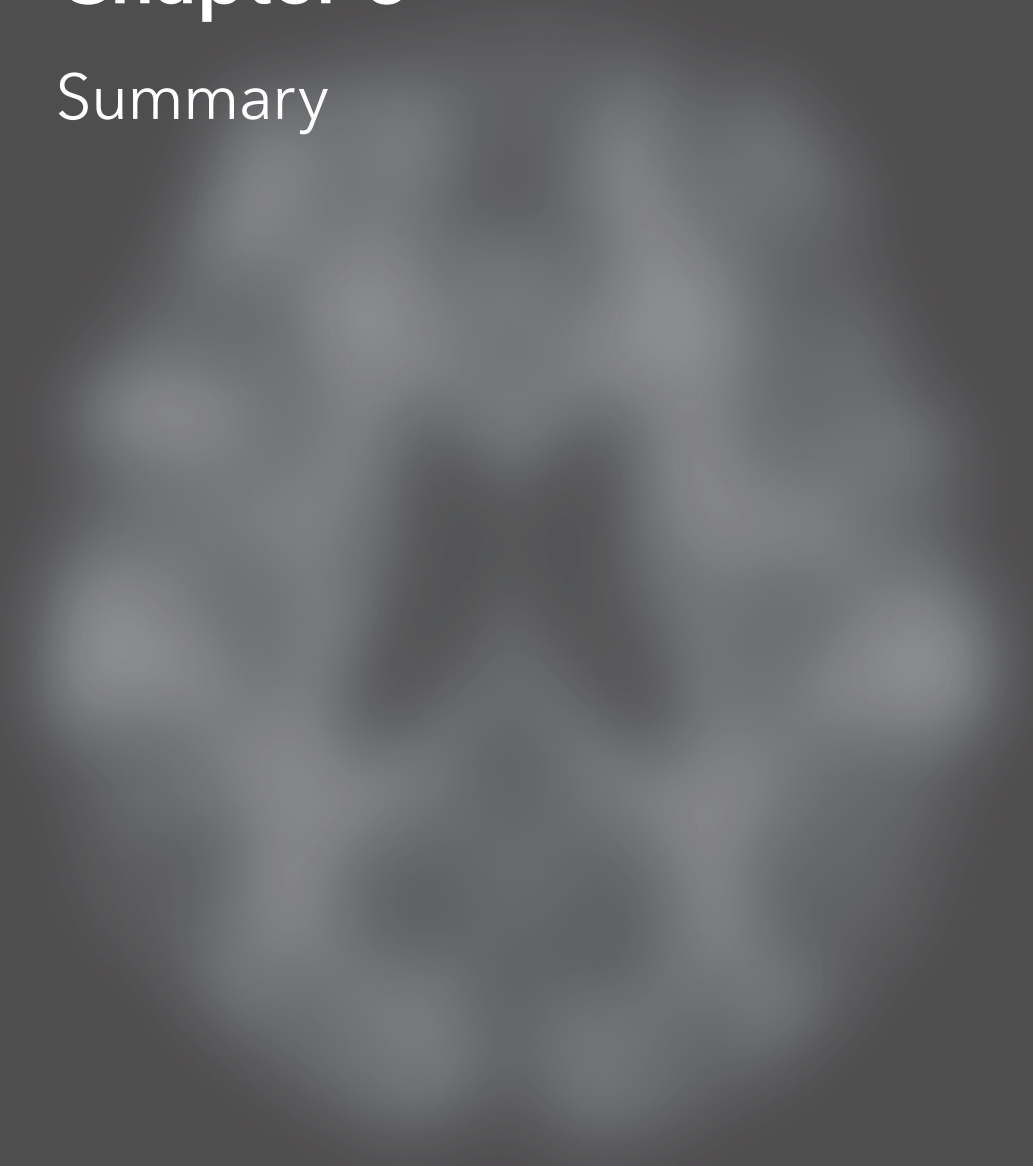
Chapter 8

Summary



ENGLISH SUMMARY

The aim of this thesis is to gain insight in two important aspects of human obesity. First, it aims to investigate structural and functional differences between subjects with and without obesity, specifically the relationship between these differences and behaviour and genetics. Secondly, it investigates the diagnostic strategy for finding causes and consequences of obesity in children, aiming to improve this strategy.

Chapter 1 provides an introduction into the research described in this thesis.

Chapter 2 reports on structural differences in subcortical and cortical brain structures involved in reward behaviour and executive function (brain functions involved in self-regulation) in adolescents with and without obesity and the relationship of these differences with behaviour. 44 adolescents (25 with obesity and 19 without obesity, aged 12-16 years) underwent an MRI-scan of their brain. The volume of various subcortical brain structures, involved in reward behaviour, as well as cortical thickness of structures involved in executive function, were measured. Furthermore, eating behaviour was investigated using a parental questionnaire (the Child Eating Behaviour Questionnaire) and executive functions were assessed using two tasks. The first was a Stop-Signal-Task, in which the ability to inhibit a impulsive response is tested. The second task was a Choice Delay Task, with which the ability to choose a larger, delayed reward over a smaller direct reward was tested. On both tasks it was shown before that children with obesity score lower than their lean peers. The results of this part of the thesis showed larger pallidum size in children with obesity ($p=0.014$, FDR corrected) and a larger amygdala in the uncorrected analysis ($p=0.03$). Specifically in the group of subjects with obesity, a positive association was found between pallidum size and the results of the Choice Delay Task ($p=0.012$). Furthermore, a marginally significant negative correlation between results of the Stop Signal Task and pallidum volume ($p=0.055$) were found. Given that a lower score on the Stop Signal Task means that the ability to inhibit responses is better, the latter result also indicated that larger pallidum volume was associated with better task performance. The pallidum has many functions. For this research it is interesting to know that the pallidum has an inhibitory influence on other reward related structures and is directly connected to several frontal lobe structures involved in executive function. The results of our research suggest that the overall larger pallidum size in these adolescents might be an adaptive mechanism in patients with obesity, aiming to control uninhibited feeding behaviour. In adolescents with obesity and larger pallidum volume it appears, given the results of neuropsychological testing, that this mechanism has developed more successfully. Further research, for instance using fMRI, could help to gain more insight in the specific mechanism through which the pallidum influences executive function.

Chapter 3 describes the findings of research dedicated to exploring differences in functional brain connectivity between adolescents with and without obesity. In connectivity research, the degree of synchronous activity of a brain structure or brain network with other brain structures or networks is investigated. This is used as a proxy of communication between brain structures and/or networks and is usually measured either while performing a task or in rest. In this chapter, the connectivity of 32 adolescents (17 with and 15 without obesity, 12-16 years in age) are investigated in rest, while satiated. These investigations were on the connectivity of three brain structures: the amygdala (involved in reward processing), the pallidum (involved in executive function) and the hypothalamus (involved in hunger and satiety signalling). In addition, the connectivity of three networks was explored: the default mode network (mainly active during wakeful rest), the executive control network (involved in executive function) and the salience network (active when salient events occur in ones environment). In this study it was shown that adolescents with obesity have less functional connectivity in the executive control network of a part of the occipital lobe (the lateral occipital cortex) with the rest of the executive control network. This might suggest that this part of the brain, when triggered by visual food stimuli, activates the rest of the executive control network to a lesser extent. Furthermore, in adolescents with obesity, another part of the occipital lobe, the occipital pole, had increased connectivity with the salience network. This indicates that even in a resting state, the brain of these adolescents is programmed to process visual (food) cues with priority and give more attention to them. In conclusion, in adolescents with obesity, there appears to be a disturbed balance, even in rest and when satiated, with the brain being in a constant state of visual information being regarded more salient and triggering the part of the brain that exerts control over ones actions to a lesser extent.

Variants in the FTO gene have been associated with higher body weight in a wide variety of populations. Studies investigating the pathophysiological mechanism have thus far shown that these variants are associated with alterations in hunger and satiety signalling. There are, however, indications that FTO variants also affect subcortical and cortical signalling. This led to the investigations described in **chapter 4** in which the relationship between the FTO risk allele, RS9939609A, and reward related brain structures was studied in a group of 492 elderly participants, in which MRI and FTO genotyping were performed. It was shown that subjects homozygous for the risk allele A had significantly smaller volume of the nucleus accumbens those homozygous for the wild type T allele. This relationship was independent of BMI. Hereby it was shown that FTO does not only affect hunger and satiety signalling, but also effects reward related behaviour.

The results of investigation in to the pathophysiological mechanism driving advanced bone age in children with obesity are described in **chapter 5.** In many children with obesity, growth in height as well as bone age are advanced. In this patient category, it

is challenging for clinicians to determine whether these advancements can be contributed solely to obesity, or whether an endocrine or genetic cause should be considered. Therefore, more knowledge on the pathophysiological mechanism driving bone age advancement is necessary. In a total of 101 children with obesity, bone age was determined using an X-ray of the wrist and extensive endocrine testing was performed. The results showed that BMI SDS is, as expected, strongly correlated with bone age SDS. In multiple regression analysis, it was shown that dehydroepiandrosteron sulphate (DHEAS) SDS correlated independently with bone age SDS in the total cohort, as well as in subgroups based on sex and pubertal status. A possible pathophysiological explanation for the relationship between the concentration of DHEAS and advanced bone age is that DHEAS signals high levels of DHEA, which is converted at tissue level to oestrogens, thereby contributing to faster maturation of the bone. This research suggests that in paediatric patients with obesity and an advanced bone age and isolated rise in DHEAS, clinician can consider refraining from further diagnostic testing.

Chapter 6 is dedicated to early detection of impaired glucose tolerance and diabetes in children who are overweight or obese. The current Dutch CBO guideline recommends that children who are overweight or obese should be evaluated by an oral glucose tolerance test (OGTT) to rule out impaired glucose tolerance (IGT; two hour glucose in OGTT ≥ 7,8 mmol/L but < 11,1 mmol/L) or diabetes (two hour glucose in OGTT ≥ 11,1 mmol/L) if they have impaired fasting glucose (fasting glucose ≥ 5,6 mmol/L but < 7,0 mmol/L). A substantial amount of evidence has shown that this strategy misses a significant number of cases of IGT and diabetes. Therefore, we investigated whether combining diagnostic parameters, available in everyday practice, could improve the sensitivity of detecting patients with glucose derailment. In this study, a total of 145 overweight or obese paediatric patients the anthropometric data, fasting blood sample and OGTT data were analysed. It was shown that when all children with either elevated blood pressure, elevated liver enzymes or impaired fasting glucose were tested by OGTT sensitivity for detecting IGT would increase from 0.18 to 1.00. Given the fact that IGT in childhood, particularly in patients with ongoing increase in BMI, is predictive of diabetes in (young) adulthood, we advise, if our findings can be replicated in an independent cohort, to adjust the CBO guideline.

Chapter 7 contains the general discussion and conclusion of this thesis. It also gives suggestions for future research in the neuropathophysiology of obesity as well as the diagnostic strategy for children with obesity.