Neural processing of healthy foods in normal-weight and overweight children and adults

Brain Center
Rudolf Magnus

Floor van Meer

NEURAL PROCESSING OF HEALTHY FOODS IN NORMAL-WEIGHT AND OVERWEIGHT CHILDREN AND ADULTS

FLOOR VAN MEER

Colophon

Cover: Ice on the Blindsee in Tirol, Austria.

Neural processing of healthy foods in normal-weight and overweight children and adults
PhD thesis, Utrecht University, The Netherlands

NEURAL PROCESSING OF HEALTHY FOODS IN NORMAL-WEIGHT AND OVERWEIGHT CHILDREN AND ADULTS

HERSENREACTIES OP GEZOND VOEDSEL IN KINDEREN EN VOLWASSENEN MET NORMAAL GEWICHT EN OVERGEWICHT
(met een samenvatting in het Nederlands)

PROEFSCHRIFT

ter verkrijging van de graad van doctor aan de Universiteit Utrecht op gezag van de rector magnificus, prof.dr. G.J. van der Zwaan, ingevolge het besluit van het college voor promoties in het openbaar te verdedigen op donderdag 31 oktober 2017 des middags te 2.30 uur.

door

ANNE-FLOOR VAN MEER

geboren op 17 augustus 1986
te Heidelberg, Duitsland

Promotoren: Prof.dr.ir. M.A. Viergever
Prof.dr. R.A.H. Adan

Copromotoren: Dr. P.A.M. Smeets
Dr. L.N. van der Laan

Contents

CHAPTER 1

THESIS OVERVIEW

1.1 Motivation

Childhood obesity is a growing problem almost everywhere in the world[1]. The chance for an overweight child to become an overweight adult is much larger than for a normal-weight child[2], which emphasizes the importance of prevention. Weight gain, and thus overweight and obesity, is largely caused by overconsumption[3], which in turn is driven by food choices[4]. These decisions on what, when, and how much to eat are made in the brain, which integrates a multitude of neural and hormonal signals arising in response to the body's internal state and the environment[4]. Understanding how the brain responds to food and how eating decisions are made in the brain, is crucial for elucidating the neural processes underlying maladaptive eating behaviors. This knowledge may provide novel approaches for the prevention of childhood obesity and for healthy eating interventions.

Functional Magnetic Resonance Imaging (fMRI) is a non-invasive neuroimaging technique which enables measuring which parts of the brain become more active when a certain task is performed. In the domain of food-related brain responses, fMRI has mostly been used to examine food cue reactivity and brain responses during food choice. Of these aspects, the neural responses to food cues, such as the sight, smell and taste of food, have been examined the most. The majority of fMRI studies present participants with food pictures. The way that the brain responds to the sight of food varies within and between individuals. For example, some brain areas respond differently to (certain kinds of) food when being hungry compared to satiated[5-8], and differences in responses to food between overweight and normal-weight people have been found in brain areas related to reward, self-control and interoception[9,10]. Interestingly, inter-individual variation in the brain response to food cues, in particular in brain reward and cognitive control regions, has been shown to predict future weight gain in adolescent girls[11] and female adults[12], food choice[13,14], snack consumption[15], weight status[16] and success in a weight-loss program[17]. Despite the global childhood obesity problem there have only been a handful of studies that examined

neural food cue reactivity in children[18], and hardly any studies directly compared children to adults. Likewise, the effect of body mass on the neural processing of food in children has only been the subject of a few studies using small numbers of participants, while this has been examined more often in adults (see[9,10] and Chapter 2 for an in-depth overview). Given the link between food cue reactivity and future weight outcomes it is important to know how food cue reactivity develops in the transition from childhood to adulthood.

In addition to food cue reactivity, we furthermore examined food decision-making. Making food choices comes closer to real-life eating behavior, which makes understanding how these choices are made in the brain of great interest. The neural correlates of food choice have been examined far less than those of food viewing, especially in children[19]. Additionally, to our knowledge, the effect of body mass on how food choices are made in the brain has not yet been examined. The neural correlates of food choice could potentially reveal what makes making healthy choices easy for some, but difficult for others. Moreover, examining food choices is of interest since it allows the investigation of different factors, such as tastiness, healthiness and calorie content of foods, that drive food choices, and how these may interact. Furthermore, fMRI choice tasks are more engaging than passive viewing tasks and they additionally provide behavioral data which can aid interpretation of the effects found in the imaging data.

Food-related brain activation in children is expected to differ from that in adults because their brain is still developing. This applies in particular to the prefrontal cortex (PFC), which is among the last brain regions to mature and which is involved in the control of behavior and the inhibition of impulsive responses[18,20].

The aim of this thesis was to examine the neural responses to healthy and unhealthy food viewing and food choice in normal- and overweight children and adults.

1.2 Organization of the thesis

The first step in determining how children's food-related brain responses differ from adults was synthesizing results from earlier work by means of a review and a meta-analysis (Chapters 2 & 3). In **Chapter 2** the existing literature on the effects of weight status and age on food-related decision-making in children and adults was reviewed. This chapter introduces both behavioral and neuroimaging findings. Subsequently, to identify the areas that have been most consistently reported to respond to food cues in children and brain areas in which children and adults might differ in their responses to food, we performed a meta-analysis on the neural correlates of food viewing in children and quantitatively compared these with those found in adults (**Chapter 3)**. From Chapter 4 onwards the results of our experimental studies are described. **Chapter 4** aimed to examine differences in the brain response to healthy and unhealthy foods in children and adults. Additionally, to identify brain areas that respond differently to food in children and adults who are overweight we determined the effect of body mass on the brain response to healthy and unhealthy foods. Subsequently, in **Chapter 5** we examined the effect of development over adolescence on brain responses to healthy and unhealthy food cues, in addition to the effect of body mass and the difference between children and adults.

In addition to food cue reactivity, the work in this thesis aimed to study brain responses during food choice. In **Chapter 6** we compared food choice behavior and brain responses related to the influence of the health and taste of food between children and adults. Furthermore, we examined differences between children and adults in the effect of attending to the healthiness of foods on brain responses during choice. **Chapter 7** focuses on the effects of development over adolescence, body mass and body mass change on healthy food choices and associated brain responses in children. **Chapter 8** summarizes and discusses the findings in this thesis in relation to its general aim and sheds some light on future research directions.

1.3 Context

The work in this thesis is part of the Idefics/I.Family study[21], which aimed to investigate the determinants of food choice, lifestyle and health in European children, adolescents and their parents. To study the brain responses during healthy food viewing and food choice we first developed suitable fMRI paradigms and used these to examine 32 children and adults in the Netherlands. Subsequently, 192 children and 188 adults of the Idefics/I.Family cohort were scanned in Germany, Hungary and Sweden using the same paradigms, adapted to regional food preferences. The studies in this thesis report both the results of the Dutch study and the larger study in the I.Family sample.

CHAPTER 2

INTRODUCTION

Abstract

Food decisions determine energy intake. Since overconsumption is the main driver of obesity, the effects of weight status on food decision-making are of increasing interest. An additional factor of interest is age, given the rise in childhood obesity, weight gain with aging and the increased chance of type 2 diabetes in the elderly. The effects of weight status and age on food preference, food cue sensitivity and self-control are discussed, as these are important components of food decision-making. Furthermore, the neural correlates of food anticipation and choice and how these are affected by weight status and age are discussed. Behavioral studies show that in particular poor self-control may have an adverse effect on food choice in children and adults with overweight and obesity. Neuroimaging studies show that overweight and obese individuals have altered neural responses to food in brain areas related to reward, self-control and interoception. Longitudinal studies across the lifespan will be invaluable to unravel the causal factors driving (changes in) food choice, overconsumption and weight gain.

2.1 Introduction

People make over 200 food decisions per day[22]. Food decisions are the choices made concerning what, when and how much to eat. Together, they determine energy and nutrient intake. When more energy is consumed than is expended, e.g. by eating energy-dense fast foods, overconsumption occurs. Since overconsumption causes a positive energy balance, which leads to weight gain, it is considered to be a main cause of obesity[3]. Rates of childhood obesity are rising at an alarming rate[1], and the chance that an obese child develops into an obese adult is much higher than that of a normal-weight child. Moreover, once people have become overweight or obese, it is quite challenging for them to revert to a stable healthy weight. Thus, prevention of overconsumption is crucial[2] and this requires knowledge on the drivers of food decision-making and how these are affected by weight status. Furthermore, since the prevalence of overweight, obesity and type 2 diabetes increases with age, determinants of food decisions in older adults are of vital importance as well. Although food choices are affected by many factors, such as availability, cultural, economic and ethical considerations, this review focuses on the effects of weight status and age, as two key characteristics. To give a comprehensive overview of how weight status and age influence food decision-making, both behavioral and neuroscience studies will be discussed (Figure 2.1). We aim to provide an understanding of the causes of mal-adaptive food decisions and identify knowledge gaps and new avenues for possible interventions.

2.2 Food choice behavior

There are many models of food choice, ranging from socio-psychological and cultural models to economic models. Food choice behavior has been studied with many research methodologies, such as qualitative measures, food frequency questionnaires, food choice tasks, intake measurements, eye-tracking and measurements of purchase.

Weight status

Age

Food decision-making

Behavior

Food preference

Food cue sensitivity

Self-control capacity

Neural correlates

Food anticipation

Food choice
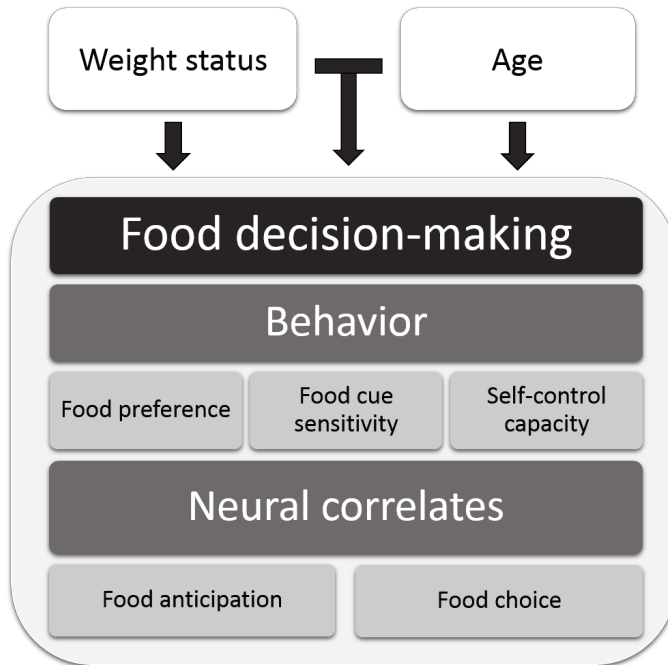
Figure 2.1 Schematic overview of the factors affecting food decision-making which are discussed in this review. Note that external factors are outside the scope. The effects of weight status and age on factors examined in behavioral studies (food preference, food cue sensitivity and self-control capacity) and factors examined in neuroimaging studies (food anticipation and food choice) are shown in the order in which they are discussed in the text.

Table 2.1 Key influencers of food decision-making and the strength of evidence for effects of weight status and age

	Weight status	Age
Food preference	+/-	+
Food cue sensitivity	+/-	+
Self-control capacity	+	+

+ = factor has been shown to have an effect
+/- = evidence for this factor having an effect is conditional or inconclusive

We grouped the literature into three topics that are relevant for understanding the role of weight status and age in food choice behavior: food preference, food cue sensitivity and self-control capacity (Figure 2.1, Table 2.1).

2.2.1   Food preference

Nutrient and energy rich foods appear to be naturally attractive to all humans[23]. Food preferences are largely learned by experience; only sweet taste preference is inborn[24]. It has been hypothesized that an innate preference for energy dense foods leads to higher consumption of these foods and thus obesity[25]. However, overweight and obese individuals do not give higher preference ratings when tasting food (both high and low energy) than normal-weight individuals[26]. Furthermore, in both children and adults there is no clear evidence for a relationship between taste sensitivity or preference for sweet, salty, sour or bitter tastes and weight status ([27], review in which studies that use taste sensitivity, taste preference and hedonic preference measures were included). There is some evidence for a higher preference for fatty foods in overweight and obese individuals and higher preference for salty foods in overweight and obese children[27]. Therefore, it is more likely that obesity is related to problems in dealing with food cues and the motivation to eat, than with heightened pleasure derived from eating or a stronger preference for energy dense foods[25,27].

Children's food preferences are highly determined by their experiences with the food and preferences of their parents[28]. Repeatedly exposing children to foods, for example green vegetable soup, increases preference and consumption[29]. Unfortunately, children are often exposed to advertisements for unhealthy snack foods, for example on television, which increases their preference for foods high in fat, sugar and salt[30]. Children's initial preferences last throughout adolescence, but may change as they eat more meals outside their home[31]. Elderly people experience loss of appetite associated with ageing and a functional decline of taste and smell that may lead to decreases

in food palatability[32] and may change their food choices towards more intense flavors[33]. In conclusion, higher preference for fat may be linked to overweight, but evidence for this is marginal. Although food preferences change over the lifespan, there are no studies showing that this leads to a changed risk of overconsumption.

2.2.2 Food cue sensitivity

Food cues are relevant for everyone from a biological perspective. In line with this, hungry normal-weight individuals have an attentional bias towards food cues (using a dot probe task[34] with food-related words), since these are then more relevant[35]. When sated, normal-weight subjects have a diminished attentional bias towards food cues, while overweight women have been found to exhibit greater attention for food compared to non-food cues when satiated, as measured with eye-tracking during visual probe tasks (based on[34] but then using pictures instead of words)[36,37]. A similar study did not find such differences between hungry and satiated women or weight groups in a viewing task showing pictures of objects vs. pictures of high energy foods. In a dot probe task done in the same individuals, however, overweight and obese individuals did automatically direct their attention to food-related stimuli to a greater extent than normal-weight individuals, in particular when hungry[23].

Although overweight children may have a higher food cue sensitivity than normal-weight children(as shown by their performance on a Stroop task[38] using food-related words[39]), it may be the case that all children have an attentional bias towards palatable foods when measured with an imbedded word test[40] and a visual probe task[41,42]. When comparing children to adults, adults are initially strongly attracted by unhealthy foods, but they shift their attention from the unhealthy to the healthy foods, suggesting a self-regulation process of avoidance when measured in with naturalistic viewing paradigm[43]. Children, on the contrary, attend more strongly to unhealthy foods and do not shift their attention away[44]. In older adults and elderly food

cue sensitivity has not been studied. In summary, overweight individuals may be more sensitive to food cues, and hunger status likely plays a role in the differences in study outcomes. Children may have a bias towards (palatable) unhealthy food and find it hard to direct their attention away from it.

2.2.3 Self-control capacity

The ability to regulate behavior effectively is relevant in many aspects of daily life, such as the consumption of healthy food, purchase decisions, or sexual behavior. Self-control refers to the ability to withhold a response with an immediately rewarding outcome in favor of a response with an outcome that is more advantageous in the long run. Thus, self-control is an important part of healthy food choice, as a lack of it may result in unhealthy food choices and overconsumption. In line with this, self-control capacity has been shown to be negatively related with body weight[45,46].

In adults, obesity is associated with impaired response inhibition capacity, greater delay discounting and reduced executive function in general[46-48]. Response inhibition refers to suppression of actions that are inappropriate in a given context and that interfere with goal-driven behavior[49]. Response inhibition is most often measured with go/no-go and stop-signal tasks (e.g.[50,51]). Delay discounting refers to the tendency for more remote outcomes to have less value[52]. This is often measured with a delay discounting task, in which a choice has to be made between an amount of money available immediately or a larger amount of money available later. In children delay of gratification has been measured with tasks in which children are asked to resist a small reward (e.g. a marshmallow) for 15 min in favor of multiple or greater rewards later[53]. Executive functioning is an umbrella term that includes cognitive control, the ability to sustain or flexibly redirect attention, the inhibition of inappropriate behavioral responses, initiation and execution of strategies, and the ability to flexibly switch among strategies[54]. All of these constructs contribute to self-control ability. In children, self-control improves as they grow older. Accordingly, children and

adolescents are more impulsive than adults, as is apparent from both response inhibition tasks and choice impulsivity tasks (such as delay of gratification and delay discounting)[55]. However, the relative level of self-control at a given age is a stable personality trait. In accordance with findings in adults, there is a consistent relationship between self-control and weight status in children. Overweight and obese children and adolescents exhibit reduced executive function[56,57], and less cognitive flexibility as measured with the Wisconsin Card Sorting Test (WCST)[58]. In line with this, a delay of gratification task at preschool age even predicts BMI 30 years later[59]. As adults age, self-control may improve as they become less impulsive and delay discounting tendencies decline[60]. To conclude, weight status and age are both related to self-control, and because of its stability over time and predictive value for weight status, further research on self-control mechanisms in food choice and how to increase self-regulatory success.

For a summary of the behavioral results see Table 2.1. In the field of food decision-making older adults and elderly have not been the subject of many studies. Thus, it remains unclear which factors influence food choices later in life.

2.3 Neural correlates of food decision-making

Food choices are made in the brain, integrating a multitude of neural and hormonal signals reflecting internal state and the environment[4]. The brain does not reach full maturity until 21 year of age. Furthermore, not all brain areas mature at the same rate; relatively greater changes have been reported in the prefrontal cortex (PFC) compared with other brain regions between the age of 8 and the early 20-s for synaptogenesis[61], gray matter reduction[62], myelination increase[63] and resting level metabolism[64]. Areas in the PFC, such as its lateral areas, mediate the capacity to voluntarily inhibit desire for a short-term reward in favor of a (larger) long-term reward[65] and are thus important for self-control. As people grow old, there are gradual

structural changes such as decreases in gray matter density and synaptic pruning and cell shrinkage[66].

How the brain reacts to food is often measured by functional magnetic resonance imaging (fMRI). The most widely used fMRI technique is blood-oxygen level-dependent (BOLD) fMRI. This form of fMRI exploits the fact that at a site of increased neuronal firing (brain activation), changes in blood oxygenation occur which lead to a small increase in the fMRI signal (~1%). Neuroimaging studies that have examined processes underlying food decision-making can be divided into two categories: anticipation to food upon cue exposure and food choice. In Table 2.2 an overview is given of the brain regions most commonly implicated in food anticipation and choice.

Table 2.2 Brain areas most consistently implicated in studies on food anticipation and food choice

Area	Function
Ventromedial prefrontal cortex (vmPFC)/OFC	Incentive/subjective value of food
Dorsolateral prefrontal cortex (dlPFC)	Self-control, anticipation of reward, monitoring of behavioral consequences
Anterior cingulate cortex (ACC)	Conflict monitoring, self-control
Amygdala	Emotion, assigns value to sensory stimuli (valence)
Hippocampus	Episodic memory and learning aspects of food-related behaviors such as dietary learning
Striatum	Reward processing, motivated behaviors and incentive learning
Insula	Interoception, encoding of multimodal sensory features of foods
Lateral occipital complex/occipital gyrus	Visual attention, object recognition
Primary motor cortex/precentral gyrus	Motor coordination and planning, motivation
Posterior parietal cortex	Subjective value, decision-making

2.3.1   Neural correlates of anticipation to food

The process of food choice starts with the anticipation phase, when food or food-related cues are perceived or thought of. Upon perception of a food cue, multiple processes occur in the brain such as preparation for food ingestion and food evaluation[4,8]. Examining brain responses to food cue exposure helps to elucidate the mechanisms underlying eating behavior. This is supported by studies showing that brain reactivity to food cues predicts things like future weight gain in adolescent girls[11], women[12], food choice[13,14], snack consumption[15], weight status[16] and outcome in a weight-loss program[17]. When normal-weight individuals look at food pictures compared with non-food pictures, areas in the appetitive brain network become active. This network centers around four interconnected brain regions: (1) the amygdala and hippocampus, (2) the orbitofrontal cortex (OFC) and ventromedial prefrontal cortex (vmPFC), (3) the striatum, and (4) the insula[8,67]. Furthermore, brain areas involved in attention and visual processing (lateral occipital complex) are consistently more active in response to food compared with non-food pictures[8].

Functional neuroimaging has provided a means to investigate on a neural level whether overweight and obese individuals are more sensitive to food cues (see e.g. Schachter's externality hypothesis, which states that obese people are more reactive to external food cues and less sensitive to internal hunger and satiety signals than normal-weight individuals[68]) and may thus exhibit greater anticipatory brain activation upon food cue exposure. Indeed, overweight and obese individuals have increased activation in response to food cues in regions associated with cognitive evaluation of salient stimuli (OFC, dorsomedial prefrontal cortex; dmPFC, anterior cingulate cortex; ACC), motor responses (precentral gyrus) and explicit memory (parahippocampal gyrus), when compared with normal-weight individuals. Additionally, they have reduced activation in regions linked to cognitive control (dorsolateral prefrontal cortex; dlPFC) and interoceptive awareness (insular cortex) compared to normal-weight individuals[10]. Furthermore, hunger state has a

differential effect on obese than on normal-weight individuals. When hungry, obese individuals show greater activation in areas involved in emotion and memory (amygdala/hippocampus), and reduced activation in areas involved in interoception (insula) than those with normal-weight. When satiated, obese individuals have greater activation in reward areas (caudate body/striatum), areas associated with cognitive evaluation of salient stimuli (dmPFC) and attention (supramarginal gyrus) than normal-weight individuals[69]. Thus, overweight and obese individuals may have a stronger anticipatory response to food in areas involved in evaluation and memory and a lower response in areas important for cognitive control and interoception. Food-related brain responses of overweight and obese people may be differentially affected by satiation as they may have a higher reward response than normal-weight people when satiated. This may make them more likely to eat even when they are not hungry.

In response to food cues, children most consistently activate the same areas as adults do, which are part of the appetitive brain network[70]. There are some indications that children may not activate areas important for cognitive control (ventrolateral prefrontal cortex; vlPFC), but there are not enough studies in children to properly establish this[70]. Only a handful of studies has looked at the difference in brain activation in response to food cues between normal-weight and overweight children. When comparing overweight and obese with normal-weight children the former show higher activation during food anticipation in areas involved in cognitive control (dlPFC, vlPFC), interoception (insula) and cognitive evaluation of salient stimuli (OFC, ACC)[11,71-73]. Overweight and obese children deactivate areas involved in visual attention (middle occipital and fusiform gyrus), memory (hippocampus and parahippocampal gyrus) and reward (caudate/striatum) compared with normal-weight children[71]. In summary, children may have less inhibitory activation during food anticipation. Few studies have been done in overweight children and results appear to contradict those in adults, as children with overweight have a higher response in areas involved in cognitive control and interoception when compared with normal-weight

children while the opposite is found in adults. Intriguing as this finding may be, given the small number of studies and large age ranges of children studied (8-18 y), future studies should directly compare normal and overweight children and adults. So far, no studies have addressed the neural correlates of food anticipation in older adults or elderly.

2.3.2   Neural correlates of food choice

To date, the neural correlates of food choice have been studied relatively little. Various tasks and designs have been used to investigate aspects of the brain processes behind food decisions. These studies mostly use single or dual food choice paradigms[13,74-81], willingness to pay for different foods[82-85], or auction paradigms[86]. However, tasks, types of choices, stimuli and participant characteristics vary greatly between studies. In the decision-making process the different attributes of the stimuli (e.g., taste, healthiness, size, and packaging) are valued, weighed and integrated into a single stimulus value[87,88]. Neuroimaging studies have consistently shown that this stimulus value is encoded in the vmPFC, both for food and non-food (e.g. monetary) items[78-85,89]. For a comprehensive review on the neuro-computational perspective of dietary choice see Rangel[88].

In the context of overconsumption, it is interesting to investigate how healthiness of food impacts the food choice process. To elucidate what happens in the brains of people motivated to make healthy choices, dieters can be examined. When dieters successfully make healthy choices, the value signal encoded in the vmPFC is increased by the healthiness of the choice option. During healthy choice, vmPFC activation is modulated by the dlPFC when self-control is necessary (e.g. when refusing an unhealthy, but tasty food)[80]. In dieters that do not successfully exercise self-control the value signal in the vmPFC only reflects taste, while in successful self-controllers it incorporates both taste and health. Intriguingly, these neural mechanisms underlying successful self-control can be activated by merely asking people to consider the healthiness of the food. When considering healthiness, the

vmPFC value signal incorporates the health aspects of the food even in individuals without an explicit health goal. Furthermore, the vmPFC signal is again modulated by the dlPFC and they make healthier choices[81]. In everyday life, a health cue might come in the form of a health label used in marketing (such as 'high in calories' or 'low fat content'). When labels like this are shown alongside food in a food choice task the healthiness of the foods is encoded in the amygdala (emotion)[74]. Interestingly, there is a negative coupling between amygdala and dlPFC when these health labels are shown[74]. The difference between the neural responses to health considerations and health labels may be caused by the fact that the health labels were shown more implicitly compared with the explicit instruction to consider healthiness. Alongside health labels, health information is commonly encountered in the shape of nutritional value tables on food packaging. However, a more graphic design, a traffic light system, has been proposed as an alternative and is more effective in promoting healthy choices[90]. When the neural responses to this traffic light label are compared with text-based nutritional information, red traffic light signaling (for unhealthy foods) activates the dlPFC and there is increased coupling between dlPFC and vmPFC[91].This suggests that explicitly asking to attend to healthiness or a graphic health label leads to different neural processing than implicitly showing a health label. This should however be further examined.

An interesting way to look at the effect of caloric content and tastiness of foods is to make choice-pairs based on liking. When people choose a high calorie product over a low calorie product, while they are satiated and they have rated the foods as equally tasty, the superior temporal sulcus, a brain area involved in processing biological relevant information is activated[77]. This suggests that even when motivation to eat is low the brain still tracks caloric value. Choice-pairs can furthermore be made challenging by design, by pairing a liked high calorie food with a less liked low calorie food. Weight-concerned women, who are trying to limit their energy intake but are generally unsuccessful in this, show lower activation in the anterior cingulate cortex, an area involved in valuation and conflict monitoring when making

challenging choices, and accordingly fail to choose in line with their dieting goal[75].

To our knowledge, the effects of weight status or age on the neural correlates of food choice have not yet been examined. However, since the dlPFC is among the last brain regions to mature, the self-control system may be underdeveloped in children, which would make healthy food decisions more challenging for them. Furthermore, lower dlPFC activation in overweight/obese adults during food anticipation suggests that they may have poorer self-control.

In conclusion, there is a growing body of work on the neural correlates of food choice. Valuation activity in the vmPFC appears to be mostly related to tastiness in normal-weight individuals. When considering the healthiness of the food, or attending to graphic health labels, health value is encoded in the dlPFC and positively modulates vmPFC activation. More implicit health information is encoded in the amygdala and negatively coupled with dlPFC activation. Even when satiated the brain tracks caloric content during choice, and the lack of conflict related brain activation may cause self-control to fail in weight-concerned women. Future studies should expand this by exploring the role of weight status and age on healthy decision-making.

2.4 Discussion

Although the obesity epidemic has caused increased attention for food decision-making, there are still several underexplored areas. Without longitudinal studies it is impossible to establish the causality of any of the factors discussed that influence food decision-making. For example, we cannot say whether poor self-control causes weight gain or that the state of being obese causes diminished self-control. Large population-based cohorts can hopefully be used to collect valuable information on how weight gain and weight loss impact food decision-making. Furthermore, there is an overrepresentation of college-aged adults in the literature, little work has

been done in children, and almost no work has been done in older adults and elderly, while the latter two are very important groups to target. Since an overweight child has a large chance to develop into an overweight adult, prevention of overconsumption of unhealthy foods and formation of healthy eating habits in children is crucial. Moreover, many Western countries have an increasing elderly population, and many health problems experienced by the elderly such as type 2 diabetes, cognitive decline and cardiovascular disease have been associated with overweight/obesity and specific dietary factors, such as saturated fat intake and vitamin E and B12 deficiency[92]. Thus, additional research into food choice in older adults could be beneficial for multiple health outcomes. Lastly, the field would greatly benefit from standardization of methods, both in behavioral and neuroscience studies, to decrease between study variability and foster meta-analyses and replication studies.

2.5 Conclusions

Age and weight status both significantly influence the food decision-making process, however, more work, especially in children and elderly, is needed to better understand the drivers of dietary decision-making. Behavioral studies show that in particular poor self-control may have an adverse effect on food choice in children and in those with overweight and obesity. Neuroimaging studies show that overweight and obese individuals have different neural responses to food in brain regions involved in reward, self-control and interoception. More research into the neural correlates of food choice may provide better insight in the effects of age and weight on the food decision-making process and provide targets for healthy eating interventions, which may be tuned to different subgroups like children or dieters. Longitudinal studies including individuals differing in weight status will be invaluable to unravel the causal factors that shape food decisions.

CHAPTER 3

WHAT YOU SEE IS WHAT YOU EAT: AN ALE META-ANALYSIS OF THE NEURAL CORRELATES OF FOOD VIEWING IN CHILDREN AND ADOLESCENTS

Abstract

Food cues are omnipresent and may enhance overconsumption. The last two decades the prevalence of childhood obesity has increased dramatically all over the world, largely due to overconsumption. Understanding children's neural responses to food may help to develop better interventions for preventing or reducing overconsumption. We aimed to determine which brain regions are concurrently activated in children/adolescents in response to viewing food pictures, and how these relate to adult findings.

Two activation likelihood estimation (ALE) meta-analyses were performed: one with studies in normal-weight children/adolescents (aged 8-18, 8 studies, 137 foci) and one with studies in normal-weight adults (aged 18-45, 16 studies, 178 foci). A contrast analysis was performed for children/adolescents vs. adults.

In children/adolescents, the most concurrent clusters were in the left lateral orbitofrontal cortex (OFC), the bilateral fusiform gyrus, and the right superior parietal lobule. In adults, clusters in similar areas were found. Although the number of studies for a direct statistical comparison between the groups was relatively low, there were indications that children/adolescents may not activate areas important for cognitive control. Overall, the number of studies that contributed to the significant clusters was moderate (6-75%).

In summary, the brain areas most consistently activated in children/adolescents by food viewing are part of the appetitive brain network and overlap with those found in adults. However, the age range of the children studied was rather broad. This study offers important recommendations for future research; studies making a direct comparison between adults and children in a sufficiently narrow age range would further elucidate how neural responses to food cues change during development.

3.1 Introduction

In modern society, tempting food cues are ubiquitous. This may promote food overconsumption[15]. Overconsumption is the main driver of obesity, because it leads to a positive energy balance and, subsequently, weight gain[3]. The prevalence of obesity is increasing dramatically all over the world, and childhood obesity is following at an alarming rate[1]. Chances of an obese child to develop into an obese adult are much higher than for a healthy weight child, making it crucial to investigate the mechanisms underlying the eating behaviors which lead to weight gain in children[2].

Eating behavior is determined by eating decisions, which are taken in the brain. Food selection is primarily guided by the visual system and the sight of food elicits a variety of brain responses related to preparation for food ingestion, desire to eat, and cognitive processes such as memory retrieval and hedonic evaluation[4,8]. Examining brain responses to the exposure to food cues helps to elucidate the mechanisms underlying eating behavior. Moreover, brain reactivity to food cues has been shown to predict future weight gain in adolescent girls (mean age 16y)[11], and women (aged 18-19y)[12], to predict food choice[13,14], snack consumption[15], and weight status in women[16] and to predict outcome in a weight-loss program[17]. Thus, brain activation in response to food pictures seems to be a useful measure to examine both sensitivity to food cues and vulnerability to develop or maintain overweight. Furthermore, a previous meta-analysis that compared studies using visual food cues with studies using oral and nasal presentation of food, concluded that the visual food-cue paradigm was the most simple and robust tool to measure the neural mechanisms involved in eating behavior[93].

A mounting number of studies examined neuronal response to food viewing. However, most studies include adults; children and adolescents feature as subjects to a lesser extent in food viewing studies[18]. So far, results from studies that have examined neural correlates of food cues in children and

adolescents were inconsistent. Holsen et al.[94] found that children/adolescents (aged 10-17y) responded to food vs. non-food stimuli with activation in the same brain regions as previously described in adults (lateral OFC, LOC). Based on this finding they hypothesized that processing food cues is a basic function that is not affected by developmental changes in the brain. Contrarily to this, Killgore et al.[95] describe differences between adults and children/adolescents (aged 9-15y) (less OFC activation and more activation in the anterior cingulate gyrus in children). They state that adults process images of food in a more complex manner than children, by which they mean that with aging cerebral functioning develops from lower to higher-order sensory processing of food stimuli, as evidenced by the association they found between age and activation in higher-order processing regions. Other studies with children/adolescents report both regions found in adults and regions not found in adults[71,72,96-98].

Food-related brain activation in children and adolescents is expected to differ from that in adults because children's and adolescents' brains are still developing. This applies in particular to the prefrontal cortex (PFC), which is among the last brain regions to mature and which helps to control behavior and to inhibit impulsive responses[18,20]. This uneven neurobiological development, during which the more primal reward-related areas such as the limbic system mature before the PFC, may promote risk-taking behavior and behavior favoring short-term over long-term rewards in children and adolescents[99-101]. This kind of behavior could result in a greater consumption of high energy foods for children, since it may be harder for them to inhibit their response to this immediate reward and instead delay gratification[100].

Food marketing often targets children/adolescents, who are more receptive and for whom it is harder to distinguish advertising claims from the truth[102,103]. Therefore, it is important to investigate whether children's and adolescents' still developing brain makes them even more vulnerable to these tempting food cues. A recent study showed that 84 percent of food

and beverage product advertisements seen by children concern unhealthy products[104].

In a previous meta-analysis done by Van der Laan, et al.[8] moderate concurrence between studies (with mostly adult participants) examining brain responses during food viewing was found. The most consistent brain regions found for the food vs. non-food contrast in this meta-analysis were the lateral orbitofrontal cortex (OFC), the lateral occipital complex (LOC) and the middle insular cortex.

The first objective of this meta-analysis was to examine which brain regions are most concurrent in studies of neural responses to food cues in children/adolescents. The second objective was to examine how these relate to the corresponding regions found in studies with adults. To this end, we have conducted meta-analyses using Activation Likelihood Estimation (ALE)[105-108]. ALE is a contemporary fMRI voxel-wise meta-analysis tool that compares results of neuro-imaging studies using reported coordinates in a standardized 3D atlas space, and has been used in various other meta-analyses[8,10,109,110]. Based on previous findings and theories of brain development, we hypothesize that reward areas will be among the most concurrent brain regions in children/adolescents and that the PFC will be found less in children/adolescents than in adults. Understanding children's and adolescents' neural responses to food may indicate whether they are indeed more vulnerable to food cues, and might lead to ways to help children/adolescents resist food temptations.

3.2 Methods

3.2.1 Study selection

PubMed and Google Scholar were searched, and additional studies were found by examining the reference lists of the retrieved articles. The keywords used were (brain OR neural) AND (food OR nutrition) AND (pictures OR images), and for the meta-analysis in children/adolescents AND (children OR

adolescents). The inclusion criteria were that studies a) were published in a peer-reviewed journal, b) used a task in which images of food were presented, c) reported analyses for the contrast food vs. non-food or provided these on request d) used fMRI, e) reported coordinates in Talaraich or MNI space, f) reported whole-brain coordinates, not only from Regions of Interest (ROIs), g) included healthy normal-weight children/adolescents (age < 18 years; age corrected BMI between 18.5-25 kg/m^2), and for the meta-analysis in adults h) included healthy normal-weight adults (age 18 y or above, BMI between 18.5-25 kg/m^2). PET food viewing studies were not included since none could be found in children/adolescents. PET food viewing does not compare well with fMRI food viewing as well because of PETs low temporal resolution (minutes).

Table 3.1 shows an overview of the studies that were included in the two meta-analyses. For the meta-analysis in children/adolescents 8 studies were included, with a total of 132 participants (81 females) and 137 reported coordinates. Three of these studies did not report the coordinates for the food vs. non-food contrast[72,98,111] in the article, however the authors were kind enough to provide these unpublished data. For the meta-analysis in adults 16 experiments from 15 studies were included, with a total of 241 participants (141 females) and 178 reported coordinates. All these studies reported the contrast of activation during viewing of food vs. non-food pictures.

The statistical thresholds employed in the different experiments ranged between p<0.001 uncorrected for multiple comparisons with a cluster extent threshold k>8 and p<0.05 false-discovery rate-corrected for multiple comparisons. In case of unthresholded unpublished data we applied a threshold of p<0.001 uncorrected with a cluster extent k=11, which is an overall significance level of p<0.05, corrected for multiple comparisons across the whole brain based on Monte Carlo simulations of random noise distributions using the 3DClustSim module of AFNI[112,113].

Table 3.1. Studies included in the ALE meta-analyses.

Studies in children/adolescents

Study	Non food	Food stimuli	Task/Design	Time fasted	Age, range or Mean (SD); gender distribution	n	Number of foci
Bruce, et al.[72]	Animals, Gaussian blurred images	Low and high energy	Passive viewing-memorize, block design	4 H	10-17 5F	10	10
Cascio, et al.[96]	Blurred images	Palatable foods for children (pizza, ice cream etc.)	Passive viewing-memorize, block design	4 H	13.2 (3.4) 1F	18	8
Davids, et al.[71]	Landscapes, work related scenery's	Foods (pizza, hamburgers, sweets)	Passive viewing (watch attentively) block design	2 H	9-18 12F	22	15
Holsen, et al.[94]	Animals	Low and high energy	Passive viewing-memorize, block design	4 H	10-17 5F	9	17
Holsen, et al.[97]	Animals, blurred images	Low and high energy	Passive viewing-memorize, block design	4 H	14.4 (3.0) 6F	9	12
Killgore and Yurgelun-Todd[100]	Rocks, trees, flowers	Low calorie foods and high calorie foods	Passive viewing-memorize, block design	1 H	9-15 8F	8	14
Rubinstein, et al.[111]	Everyday objects (staplers, lamps)	Sweet, high fat and salty products	Passive viewing, block design	2 H	13-17 5F	12	52
Stice, et al.[98]	Glasses of water	Palatable and unpalatable foods	Imagined consumption, event-related design	4 - 6 H	14-18 39F	39	9
Total:					*81F*	*132*	*137*

Table 3.1. Studies included in the ALE meta-analyses (continued)

			Studies in adults				
Study	Non food	Food stimuli	Design	Time fasted	Age, range or Mean (SD) gender distribution	n	Number of foci
Beaver, et al.[114]	Objects (videocassettes, iron, etc.)	Highly appetizing foods (chocolate cake, ice cream sundae)	Passive viewing, block design	2 H	22 (2.4) 7F	12	16
Cornier, et al.[115]	Animals, trees, furniture, buildings	Foods of high hedonic value (cookies, plate of eggs and bacon)	Passive viewing, block design	Overnight fast	34.1 (5.1) 10F	22	23
Cornier, et al.[116]	Animals, trees, furniture, buildings	Neutral foods (bagels, fruit, bread)	Passive viewing, block design	Overnight fast	25-45 13F	25	2
Führer, et al.[117]	Objects (watch, pen, calculator, etc.)	Ready to eat edible objects	Viewing, attentional task (click if no picture), block design	14 H	21-29 0F	12	20
Killgore, et al.[118]	Rocks, trees, flowers	Low calorie foods and high calorie foods	Passive viewing-memorize, block design	1.5 H	21-28 13F	13	12
LaBar, et al.[6]	Tools	Food images	Viewing, attentional task (click if picture blinks), block design	8 H	19-44 8F	17	3
Malik, et al.[119] (control condition of control/ghrelin group)	Scenery, landscapes	Food images	Passive viewing-memorize, event-related design	3 H	24.1 (1.1) 0F	12	11

Table 3.1. Studies included in the ALE meta-analyses (continued)

Study	Non food	Food stimuli	Design	Time fasted	Age, range or Mean (SD) gender distribution	n	Number of foci
Malik, et al.[119] (control/control group)	Scenery, landscapes	Food images	Passive viewing-memorize, event-related design	3 H	23.2 (1.3) 0F	8	10
Malik, et al.[120]	Scenery, landscapes	Highly appetizing foods	Passive viewing, event-related design	8 H	25.8 (0.8) 0F	10	27
Miller, et al.[121]	Animals, tools	Food images	Passive viewing, block design	1 H	27.0 (7.0) 4F	8	2
Murdaugh, et al.[17]	Cars	High calorie foods	Passive viewing-memorize, block design	8 H	45.15 (10.01) 8F	13	3
Rothemund, et al.[122]	Rocks and flowers	Low calorie pictures	Passive viewing-memorize, block design	1.5 H	29 (5.6) 13F	13	1
Schienle, et al.[123]	Household articles	High calorie food (french fries, ice cream)	Passive viewing, event-related design	Overnight fast	22.3 (2.6) 19F	19	12
Simmons, et al.[124]	Locations, buildings	High fat high calorie foods (cheeseburger, cookie)	Viewing, attentional task (click if picture same as before), event-related design	Not reported	18-45 6F	9	6
Smeets, et al.[125]	Office utensils	Palatable, fattening foods	Passive viewing, block design	3 H	22.1 (2.0) 30F	30	25
Uher, et al.[126]	Objects (brushes, car, flower, etc.)	Pleasant, appetizing foods (hamburger, strawberries)	Rating food pictures, event-related design	3.5 H	20-44 10F	18	5
Total:					*141F*	*241*	*178*

3.2.2   ALE meta-analyses

The Brainmap GingerALE software (http://www.brainmap.org/ale/) was used to conduct the two ALE meta-analyses. These analyses were based on the revised ALE approach for coordinate-based meta-analysis of neuroimaging results[105,107,108]. The input for the first meta-analysis consisted of the peak coordinates of brain regions that were activated in response to viewing pictures of foods vs. viewing pictures of non-foods in children/adolescents. The second meta-analysis consisted of these peak coordinates reported in adults. Finally, we conducted a contrast analysis to determine whether there are statistically significant differences in convergence between the foci in children/adolescents and adults[106]. Coordinates reported in Talaraich space were converted to the standard space of the Montreal Neurological Institute (MNI space) using the GingerALE software.

ALE is a statistical modeling technique that uses reported coordinates as the center of a three-dimensional Gaussian kernel function to create a modeled activation (MA-) map for each study. Between-template and between-subject variance can cause uncertainty of spatial localizations, so they are used to compute kernel parameters. The algorithm takes differences in sample size into account by weighing the between-subject variance by the number of subjects in the experiment. Subsequently, the MA-maps are combined to calculate an experimental ALE map, which is then tested against an ALE null distribution map. This map represents the null-hypothesis that there is a random spatial association between the results of the experiments, while regarding the within-experiment distribution as fixed. A random effects model is employed by the ALE analysis technique, which assumes a higher than chance likelihood of consensus between different experiments, but not in relation to activation variance within each study. The null distribution map is derived from a permutation procedure and is created on the basis of the same number of experiments and reported coordinates as the experimental map. The contrast analysis compares and contrasts two ALE datasets. A

conjunction image showing the similarity between studies is created as well as two ALE contrast images, created by directly subtracting one input image from the other. The ALE contrast images are converted to Z scores instead of a direct ALE subtraction. Z score values are used in the image statistics and maxima. Generally contrast analyses are not recommended with less than 15 contrasts per dataset because the analysis will be underpowered. Thus, to prevent bias, the number of contrasts per data set was matched (as described in Albrecht, et al.[127]), 8 studies from the dataset in adults were randomly selected. The analysis was repeated using different selections of the 8 contrasts in adults. We used a statistical threshold of p<0.05 False Discovery Rate (FDR) corrected for multiple comparisons and a minimum cluster size of 100 mm^3 in line with recently published meta-analyses[8,10]. ALE maps were overlaid onto a standard brain in MNI space (Colin 27, a stereotaxic average of 27 single-subject anatomical scans, skull stripped) using the MRIcroN software (http://www.cabiatl.com/mricro/mricron/index.html).

One of the outcomes of the ALE analysis is the number of contributing studies, which describes the number of studies whose peak coordinates are located within the boundaries of an ALE cluster. However, this does not discount other studies, whose peak coordinates might be located near these boundaries, but outside of the ALE cluster and could also have contributed to its significance[10]. As an added quality criterion other studies only reported clusters if 33% or more of the included experiments contributed to them[8,128]. Accordingly, in the results section, we only reported clusters with more than 33% contributing studies. Additionally, in the discussion clusters in areas that we had an a priori hypothesis about (reward areas and the PFC) are included.

3.3 Results

3.3.1 Significant ALE clusters for viewing food vs non-food pictures in children/adolescents

The ALE analysis showed 14 significant clusters for the contrast between viewing food pictures vs. non-food pictures in children/adolescents (Figure 3.1a, Table 3.2), i.e., brain regions responding stronger to food than to non-food pictures in children/adolescents. Four of the 14 clusters met the 33% criterion, and will be described here. The most concurrent cluster, which was contributed to by six of the nine experiments (75%), was located in the left inferior frontal gyrus (ALE peak at MNI (-32, 34, -12), ALE value = $18.66*10^{-3}$, volume = 1832 mm^3). Concurrence was also found in the posterior fusiform gyrus (bilaterally) (left ALE peak at MNI (-40, -52, -20), ALE value = $17.46*10^{-3}$, volume = 1888 mm^3; right ALE peak at MNI (28, -56, -12), ALE value = $16.61*10^{-3}$, volume = 888 mm^3), and the right superior parietal lobule (ALE peak at MNI (28, -62, 60), ALE value $14.00*10^{-3}$, volume 536 mm^3) with three contributing experiments (37.5%). The remaining significant clusters are listed in Table 3.2.

3.3.2 Significant ALE clusters for viewing food vs. non-food pictures in adults

The ALE analysis revealed 23 significant clusters for the contrast between viewing food pictures and viewing non-food pictures in adults (Figure 3.1b, Table 3.3), i.e., regions responding stronger to food than to non-food pictures in adults. Three clusters had more than 33% contributing studies and will be described here. The most concurrent cluster, which was contributed to by seven of the 18 experiments (43.8%), stretched from the left insula to the amygdala (ALE peak at MNI (-38, -4, 6), ALE value = $29.78*10^{-3}$, volume = 4208 mm^3).
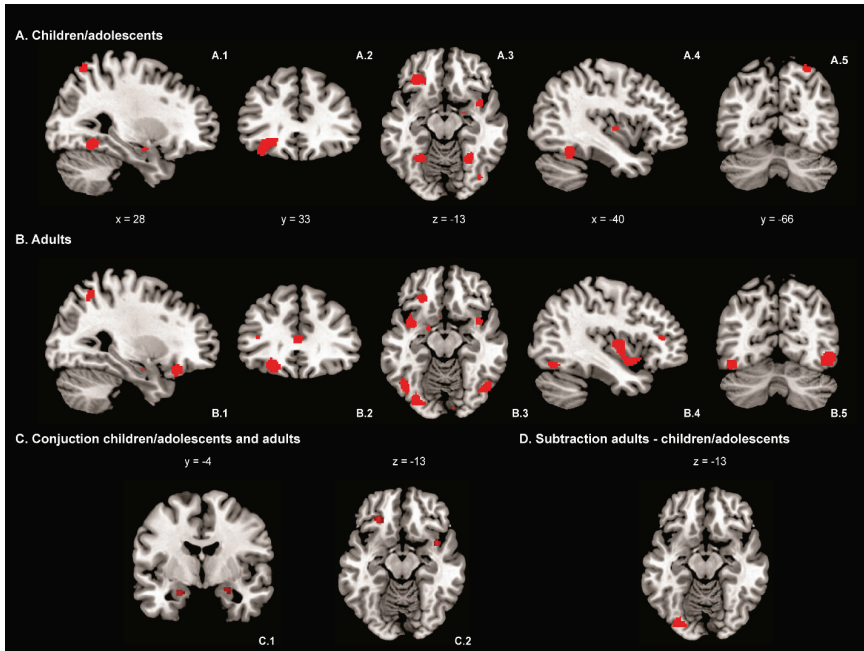
Figure 3.1. Selected results of the ALE meta-analyses showing clusters with significant ALE maxima (p<0.05, FDR-corrected for multiple comparisons, cluster size>100 mm³; coordinates in MNI space). A: ALE clusters for the food vs. non-food contrast in children/adolescents in: (A.1) the right posterior fusiform gyrus, the right superior parietal lobule and the right amygdala, (A.2) the left lateral OFC, (A.3) the left lateral OFC, the left posterior fusiform gyrus, the right posterior fusiform gyrus and the right middle insular cortex, (A.4) the left posterior fusiform gyrus and the left middle insular cortex, (A.5) the right superior parietal lobule. B: ALE clusters for the food vs. non-food contrast in adults in: (B.1) the right superior parietal gyrus and right inferior frontal gyrus, (B.2) the left lateral OFC, the left ACC and the left middle vlPFC (B.3) from the left middle insula to the left amygdala, the left lateral OFC, from the left posterior fusiform gyrus to the left lingual gyrus, the right middle insula, from the right inferior temporal gyrus to the right posterior fusiform gyrus, (B.4) from the left middle insula to the left amygdala, the left posterior fusiform gyrus and the left middle vlPFC, (B.5) from the right inferior temporal gyrus to the right posterior fusiform gyrus, the left posterior fusiform gyrus. C: ALE clusters for the conjunction analysis of children/adolescents and adults in: (C.1) the left amygdala and the right hippocampus, (C.2) the left lateral OFC and the right insula. D: ALE cluster for the subtraction analysis of adults –children/adolescents in the left lingual gyrus.

Table 3.2. Clusters with significant ALE values for food versus non-food viewing in children/adolescents.

Region[a]	Peak voxel coordinates[b]			Cluster size	ALE value (×10⁻³)	No./% of contributing experiments[c]	
	x	y	z				%
Inferior frontal gyrus L /Lateral OFC L	-32	34	-12	1832	18.66	6	75
Posterior fusiform gyrus L	-40	-52	-20	1888	17.46	3	38
Posterior fusiform gyrus L	-26	-54	-12		15.39		
Posterior fusiform gyrus R	28	-56	-12	888	16.61	3	38
Superior parietal lobule R	28	-62	60	536	14.00	3	38
Amygdala L	-22	-2	-20	840	13.88	2	25
Middle insular cortex R	40	6	-12	368	13.95	2	25
Amygdala R	24	-4	-16	288	10.81	2	25
Calcarine gyrus R	22	-96	4	208	10.63	2	25
Middle insular cortex L	-38	-10	4	168	10.36	2	25
Posterior fusiform gyrus R/Cerebellum R	40	-48	-24	296	10.57	1	13
Parietal gyrus, supramarginal gyrus L	-64	-22	34	232	9.72	1	13
Inferior occipital gyrus, R	40	-78	-14	176	10.64	1	13
Anterior cingulate L	0	48	0	160	9.97	1	13
Precentral gyrus L	-44	-2	28	236	9.16	1	13

[a] L = left, R= right, [b] coordinates are given in MNI space, [c] number of experiments within boundaries of ALE-clusters

Table 3.3. Clusters with significant ALE values for food versus non-food viewing in adults.

Region[a]	Peak voxel coordinates[b]			Cluster size	ALE value (×10⁻³)	No./% of contributing experiments[c]	
	x	y	z				%
Middle insular cortex L	-38	-4	6	4208	29.78	7	44
Amygdala L	-18	-2	-18		17.75		
Middle insular cortex L	-38	4	-12		16.49		
Amygdala L	-26	2	-20		14.62		
Middle insular cortex L	-38	18	-6		10.01		
Inferior temporal gyrus R	48	-66	-8	1936	19.10	6	38
Posterior fusiform gyrus R	38	-70	-16		11.96		
Posterior fusiform gyrus L	-32	-78	-14	1192	14.16	6	38
Lingual gyrus L	-24	-84	-14		12.72		
Posterior fusiform gyrus L	-44	-64	-14	1088	16.41	5	31
Inferior frontal gyrus L/lateral OFC L	-24	32	-14	1144	19.65	4	25
Middle insular cortex R	38	-4	6	896	20.24	4	25
Calcarine sulcus L	-16	-98	-2	888	17.25	4	25
Superior parietal gyrus R	30	-56	56	520	12.68	3	19
Fusiform gyrus L	-34	-58	-18	432	14.04	3	19
Anterior cingulate L	-2	36	10	656	17.56	2	13
Lingual gyrus R	10	-92	-8	392	14.48	2	13
Middle insular cortex R	38	8	-14	344	15.52	2	13
Caudate nucleus L/Dorsal striatum L	-8	10	-8	264	12.89	2	13
Hippocampus R	24	-6	-18	248	13.23	2	13
Inferior parietal gyrus L	-46	-38	50	248	12.66	2	13
Superior parietal gyrus L	-32	-58	58	248	11.59	2	13
Inferior frontal gyrus, pars triangularis L/ middle ventrolateral PFC L	-40	36	12	192	11.19	2	13
Inferior frontal gyrus opercular part L/posterior ventrolateral PFC L	-52	8	26	184	12.10	2	13
Inferior frontal gyrus R/lateral OFC R	28	26	-18	688	20.23	1	6
Parahippocampal gyrus L	-26	-6	-30	264	12.02	1	6
Inferior frontal gyrus L/lateral OFC L	-32	16	-24	192	10.20	1	6
Inferior occipital gyrus R	24	-92	-2	168	11.81	1	6
Middle occipital gyrus R	44	-80	2	152	9.99	1	6

[a] L = left, R= right [b] coordinates are given in MNI space [c] number of experiments within boundaries of ALE-clusters

Concurrent activation was also found in a cluster including the fusiform gyrus, inferior temporal gyrus and lingual gyrus (bilaterally) (right ALE peak at MNI (48, -66, -8), ALE value = $19.10*10^{-3}$, volume = 1936 mm^3; left ALE peak at MNI (-32, -78, -14), ALE value = $14.16*10^{-3}$, volume = 1192 mm^3) with six contributing experiments (37.5%). The remaining significant clusters are listed in Table 3.3.

3.3.3 *Contrast analysis children/adolescents vs. adults*

The results of the contrast analysis comparing the dataset of foci in children/adolescents with the dataset of 8 randomly chosen contrasts in adults[114,115,117-120,123,125] are displayed in Figure 3.1c and Table 3.4. The conjunction analysis showed 5 significantly overlapping clusters, none of these clusters had more than 33% contributing studies. The subtraction of the foci in children/adolescents minus the foci in adults did not reveal any significant clusters. A cluster in the left lingual gyrus with 75% contributing studies was found for the subtraction of the foci in adults minus the foci in children/adolescents. To ensure that the findings were not specific to the 8 randomly selected contrasts, we repeated the contrast analysis with different random selections of the 8 contrasts in adults. For both the conjunction and subtraction analysis the same number or fewer clusters (in the same locations) were found.

3.4 Discussion

We determined which brain regions are most consistently found in studies of brain responses to food cues in children/adolescents. Significant concurrence was found in the left inferior frontal gyrus, bilateral posterior fusiform gyrus and the right superior parietal lobule for the food vs. non-food contrast in studies in children/adolescents. Concurrent brain regions were compared between children/adolescents and adults. A conjunction analysis showed clusters with a relatively low amount of contributing studies (all <33%). This analysis was likely underpowered due to the low number of contrasts per dataset.

Table 3.4. Clusters with significant ALE values for the conjunction and subtraction analyses of children/adolescents and adults

Region[a]	Peak voxel coordinates[b]			Cluster size	ALE value (×10⁻³)	No./% of contributing experiments[c]	
	x	y	z				%
Conjunction							
Amygdala L	-22	-2	-20	728	13.88	4	25
Insula R	40	6	-12	288	13.95	4	25
Inferior frontal gyrus L/lateral OFC L	-28	32	-12	408	14.19	3	19
Hippocampus R	24	-4	-18	136	10.63	2	13
Insula L	-38	-10	4	104	10.35	1	6
Subtraction adults - children/adolescents							
Lingual gyrus L	-29	-83	-14	1032	2.75	6	75

[a] L = left, R= right, [b] coordinates are given in MNI space, [c] number of experiments within boundaries of ALE-clusters.

The most concurrent clusters in the meta-analysis in adults were similar to those in children/adolescents. The subtraction analysis for adults minus children/adolescents yielded one cluster in the left lingual gyrus. Only four clusters in the analysis in children/adolescents met the 33% criterion, and three clusters in the analysis in adults.

3.4.1 Concurrent regions in the appetitive brain network

The amygdala, OFC and insula, are all considered part of the appetitive brain network[67]. The OFC was consistently found in both children/adolescents and adults, the amygdala and insula were found consistently in adults, in a few studies in children/adolescents as well as in the conjunction analysis. The amygdala and OFC encode the current incentive value of food cues[129]. More specifically, the amygdala passes information about sensory cues on to the OFC, and has an important role in reward processing[130]. The lateral OFC is involved in the computation of the value of available stimuli[67], and the activation found in the food vs. non-food contrast may reflect the expected pleasantness of the food cue[8]. Alternatively, the lateral OFC has been

implicated in more complex forms of response inhibition[131,132], as displayed in reversal learning tasks. The activation found in the OFC activation could, along with the superior parietal lobule activation, reflect the multisensory integration with regards to chemosensory processes as well[133]. In children/adolescents, the cluster in the left lateral OFC was by far the most robust finding, inasmuch as 6 out of 9 studies contributed to this cluster. In adults, a cluster overlapping with that seen in children/adolescents was found, but only 4 out of 16 studies contributed to this cluster. Thus, children/adolescents may activate the left lateral OFC more consistently in response to food cues than adults. A possible explanation for the fact that the findings in adults in the left lateral OFC were less consistent, could be that in adults there was a larger variation in hunger state (1H-overnight fast) than there was in children/adolescents (1H-6H), since in the meta-analysis of Van der Laan, et al.[8] a modulation of lateral OFC activation by hunger state was reported.

We found activation in the middle part of the insula in adults. There was middle insula activation in a small amount of the studies in children/adolescents and in the conjunction analysis. The insula receives information about external cues (anterior part) and internal state (posterior part). The function of the middle part of the insula is less known. It is activated in reaction to taste stimuli[134], and Van der Laan, et al.[8] suggested that the activation of this part of the insula in response to visual food cues may represent memory retrieval of previous experiences with the food.

The other clusters found in children/adolescents are located in the bilateral posterior fusiform gyrus and the right superior parietal lobule (primary visual cortex). In adults there was consistent activation in the bilateral posterior fusiform gyrus, additionally there was right superior parietal lobule activation in a small amount of studies. The contrast analysis showed consistent activation in adults but not children/adolescents in a cluster in the left lingual gyrus. The fusiform and lingual gyri are part of the visual association cortex and are important in object and face recognition[5]. It is proposed that the

activation in the fusiform and lingual gyri is modulated by the emotional salience of the stimuli, and therefore leads to more elaborate visual processing of food cues[8,135]. In other studies hunger and calorie content of the stimuli have been found to modulate activation of the fusiform gyrus in response to viewing high vs. low calorie food pictures[5,7]. Hunger state and energy content of the stimuli influence the salience of food pictures, underscoring the idea that fusiform gyrus activation reflects this higher salience. Next to its possible role in multisensory integration, activation in the superior parietal lobe likely reflects greater attention to food than non-food cues due to greater salience as well[17,136,137]. Perhaps food cues have greater salience to adults than they do to children/adolescents, explaining the cluster in the lingual gyrus not found in children/adolescents.

3.4.2   A priori areas of interest

We hypothesized that reward areas would be among the most concurrent brain regions in children/adolescents and that the PFC will be found less in children/adolescents than in adults. In only a few of the studies in both children/adolescents and adults (13% of the studies), activation in the anterior cingulate cortex (ACC) was found. The ACC has been proposed to be a gateway between mesolimbic reward areas and top-down cognitive control mechanisms, as well as an important area for error detection and conflict monitoring[138]. Stronger ACC activation in response to food images has been found in obese compared with lean persons[10]. Previous research comparing reward processing in children/adolescents and adults (age range 10-25y) found that the ACC activates during monetary reward anticipation, and that the magnitude of this activation correlates positively with age[139]. Killgore and Yurgelun-Todd[100] compared children/adolescents (age range 9-15y) and adults and found higher ACC activation in children/adolescents than in adults, when subtracting images acquired in adults from images in children/adolescents. However, they did not find significant ACC activation in food vs. non-food contrast in children/adolescents. Since ACC activation

was only found in a small amount of studies in both children/adolescents and adults, it remains unclear what role it plays in the reaction to food cues.

In adults we found significant clusters in the vlPFC (2 studies contributing to the cluster in the middle vlPFC (13%) and 2 different studies contributing to the cluster in the posterior vlPFC (13%). No vlPFC activation was found in children/adolescents. The vlPFC is involved in the cognitive aspects of emotional stimuli, differences in perceived valence and cognitive control[71,140]. It is thought to use object information to guide goal-directed behavior[98]. A study that compared the neural correlates of response inhibition in children/adolescents (aged 8-12y) and adults, a greater activation of the vlPFC was found in adults during inhibitory tasks, which correlated with performance[140]. The authors pose that this region plays an important role in suppressing interference between competing stimuli and response options. A possible explanation for the finding that adults may activate the vlPFC more consistent than children/adolescents in response to food vs. non-food images could be that the food cues do not elicit conflict or inhibitory responses in children/adolescents.

Furthermore, in contrast with our hypotheses, we found a significant cluster in the caudate nucleus (dorsal striatum) a small amount of studies (13%) in adults but not in children/adolescents. The dorsal striatum relates to food motivation, maintains caloric requirements for survival and has been implicated in stimulus-response habit learning[67,122]. Previous studies have found that the striatum matures earlier than frontal areas, and exaggerated ventral striatal responses to reward are found in adolescents (aged 14-15y), but less in children aged 10-12y and young adults aged 18-23y[141]. It has been suggested that striatal responses may show an inverted U function across development in response to rewarding cues[142], reflecting a shift from reward outcome to reward anticipation[139]. Perhaps we did not find striatal activation in children/adolescents due to the small amount of studies. Another possibility is that we found no concurrent striatal activation in

children/adolescents because the wide age range of the children/adolescents included in the studies concealed this effect.

The fact that clusters were found in the vlPFC in a few studies in adults but not children/adolescents is in line with Killgore et al.'s proposition that adults use more higher-order processes in response to food cues than children/adolescents[100]. The finding that children/adolescents do not activate vlPFC in response to food cues could mean that they are less able to control appetitive impulses, making them more vulnerable to tempting food cues. Another reason that we did not find concurrent clusters in the vlPFC in children/adolescents could be the small amount of studies.

Initiatives for prevention of overconsumption in children could be based on their possibly increased vulnerability to food cues. Previous research (in adults) has shown that brain activation in response to food cues differs between lean and obese people and is predictive for eating behavior[14-17,72,95,143]. Based on these findings, it is theorized that by changing reactivity to food cues, eating behavior would change[144]. A paradigm has been designed to decondition food craving by cue exposure with response prevention. Imaging showed less brain activation in reward areas (caudate nucleus and striatum) and less food consumption after this intervention, even though subjective craving did not decline (in adults)[144]. Interventions such as this might help to make specific food cues less rewarding to children/adolescents prone to obesity, and help them to resist food temptations. Future research might shed light on better prevention or treatment strategies based on individual's food cue reactivity.

3.4.3 Previous meta-analyses in adults

Compared to the meta-analyses of the neural correlates of visual food cues of Van der Laan, et al.[8] and Huerta, et al.[93] our results are very similar. We find the same clusters, with only some minor differences in the number of studies contributing to clusters between our analysis and that of Van der

Laan, et al.[8] (Huerta, et al.[93] do not report this information). Both analyses describe activation in the fusiform gyrus, the insula and left inferior frontal gyrus. Since there is large overlap in the studies included in these analyses and the meta-analysis in adults described here, this is not surprising. Our meta-analysis in adults should thus be viewed as a confirmatory update of these meta-analyses.

3.4.4   Number of contributing studies

The number of studies contributing to the significant clusters varied from 13-75% in children/adolescents and from 13-44% in adults. This moderate concurrence of studies might be explained by differences in paradigms, stimuli, scanners and analyses, as well as participant characteristics such as personality characteristics and BMI[8]. The relatively low number of studies contributing to some clusters can raise questions whether this is a stable phenomenon, or rather specific for the characteristics of the contributing studies. A study on the reproducibility of fMRI results found 50% reproducibility in the same participants in the same task[145]. A recent study showed that test-retest reliability (even in a single subject) is influenced mainly by subject motion and that different tasks have different test-retest reliabilities[146]. This means that our findings fall into an expected range of reproducibility, especially considering the different stimuli, paradigms and wide age ranges used in the studies analyzed here.

3.4.5   Strengths, limitations and directions for future research

We have compared multiple peer-reviewed studies with a total number of 132 (children/adolescents) and 241 (adults) participants, creating a relatively large combined dataset. A limitation of the ALE analysis is that only reported local maxima are included while cluster size, Z- or T-statistics and statistical significance are not taken into account. If children/adolescents and adults would have activation in the same area but either group would have higher activation, this would not be reflected in the ALE results. None of the

included studies reported the weight- and eating history of the children/adolescents included. It would be good if future studies would include such information, which can be used in the analysis as a covariate. In addition, it is important to note that the age range of the children/adolescents included in the studies in our meta-analysis is relatively wide (9-18y). The brain matures considerably over the course of those years[142], which makes the children/adolescents group rather inhomogeneous. To shed light on the developmental effects involved in the neural responses to foods, future studies should focus on narrower age ranges as well as on their comparison. There is a need for studies that employ the same fMRI paradigm in different age groups as well. Such studies, that would compare children/adolescents from a narrower age range and adults with the same paradigm, could reach more reliable conclusions on age differences in brain reactions to food cues because they are not confounded by variability caused by differences in age range, task paradigms, stimuli, scanners and analyses approaches. Differences in brain anatomy between children/adolescents and adults may constitute another source of variability in when comparing their neural responses[140]. None of the studies in children/adolescents included here used an anatomical template specific for the age group that was investigated; all brains were normalized to an MNI or Talairach template instead. However, the gross morphology of the brain is in place by mid-childhood so that size and organization of brain anatomy are roughly equivalent in children (age 7 and up), adolescents, and adults[147,148]. Because of this, from age 7 and up the use of adult templates is widely accepted, since differences between age groups are smaller than most commonly used scan resolutions can detect[94,149]. However, even though structural differences might not be large, future studies should use templates based on the age of their participants, to minimize differences in activation caused by anatomical differences. In that way the influence of structural and functional developmental differences can be disentangled.

CHAPTER 4

DEVELOPMENTAL DIFFERENCES IN THE BRAIN RESPONSE TO UNHEALTHY FOOD CUES: AN FMRI STUDY OF CHILDREN AND ADULTS

Abstract

Food cues are omnipresent and may trigger overconsumption. In the last two decades, the prevalence of childhood obesity has increased dramatically. Since children's brains are still developing, especially in areas important for inhibition, children may be more susceptible to tempting food cues than adults. The aim of this study was to examine potential developmental differences in children and adults' response to food cues and to determine how these responses relate to weight status. 27 children (age 10-12 y) and 32 adults (age 32-52 y) were included. fMRI data were acquired during a food viewing task in which unhealthy and healthy food pictures were presented. Children had stronger activation in the left precentral gyrus than adults in response to unhealthy vs. healthy foods. In children, unhealthy foods elicited significantly stronger activation in right inferior temporal and middle occipital gyri, left precentral gyrus, bilateral opercular part of the inferior frontal gyrus, left hippocampus and left middle frontal gyrus. Adults had stronger activation in the bilateral middle occipital gyrus and the right calcarine sulcus for unhealthy vs. healthy foods. Children with a higher BMI had lower activation in the bilateral dorsolateral prefrontal cortex while viewing unhealthy vs. healthy foods. In adults there was no correlation between BMI and neural response to unhealthy vs. healthy foods. Unhealthy foods might elicit more attention, both in children and in adults. Children had stronger activation while viewing unhealthy compared to healthy foods in areas involved in reward, motivation and memory. Furthermore, children activated a motivation and reward area located in the motor cortex stronger than adults did in response to unhealthy foods. Finally, children with a higher BMI had less activation in inhibitory areas in response to unhealthy foods, which may mean they are more susceptible to tempting food cues.

4.1 Introduction

In modern society there is an abundance of food cues. This constant exposure to food may promote overconsumption[15]. In light of the current rise in childhood obesity[150], it is crucial to investigate the neural mechanisms underlying food selection and overconsumption in children. Food selection is mainly guided by the visual system[151] and the sight of food leads to an array of responses ranging from preparation for food ingestion (cephalic phase responses), to desire to eat and hedonic evaluation[4,8]. An activation-likelihood estimation meta-analysis of fMRI studies examining the neural responses to food compared with non-food viewing in children showed that the brain areas most consistently activated by food viewing in children correspond with the appetitive brain network[67,70], and largely overlap with those found in adults[8]. However, children may not activate areas important for inhibitory control such as the ventrolateral PFC (vlPFC)[70]. Children may be particularly susceptible to food cues because their brain is still developing. Not all brain areas mature at the same rate; greater changes have been reported in the prefrontal cortex (PFC) relative to other brain regions for synaptogenesis[61], gray matter reduction[62], myelination increases[63] and resting level metabolism[64]. Weight status may interact with the effect of development. A meta-analysis showed that overweight/obese individuals have more activation in the left dorsomedial PFC, orbitofrontal cortex and anterior cingulate cortex (areas associated with cognitive evaluation of salient stimuli), right precentral gyrus (motor response) and right parahippocampal gyrus (explicit memory) compared to normal-weight individuals. Additionally, reduced activation was found in overweight and obese individuals in the left dorsolateral PFC (dlPFC; cognitive control) and insula (interoception)[10]. This analysis included mostly studies in adults. In contrast, the opposite pattern has been found in children, when comparing obese and overweight to normal-weight children the former had increased activation in response to food cues in the left dlPFC, vlPFC, orbitofrontal cortex, and insula and decreased activation in the left anterior cingulate cortex and right caudate nucleus[11,71-73] However, one study reported a

negative correlation between BMI and bilateral dlPFC and left vlPFC activation in response to anticipation of consumption in teenage girls[152]. Thus, it remains unclear what the effect of BMI is on food cue reactivity in children. Another factor that may vary with age is the perceived healthiness of foods. High calorie, unhealthy foods may be more rewarding for children than adults[42,153]. Children showed higher craving in a regulation-of-craving task for unhealthy but appetizing foods than adolescents and adults[154]. Furthermore, children had more attention for unhealthy foods than adults, and could not divert their attention away from unhealthy foods[44]. In view of the highlighted knowledge gaps, this study aimed to determine differences between children and adults in neural reactivity to foods differing in healthiness, and the extent to which these are affected by weight status.

4.2 Methods

4.2.1 Participants

Thirty-two same-sex parent-child dyads participated in the study. Five children were excluded from analysis due to movement (n = 4) or incomplete data (n = 1) (for characteristics of the final sample see Table 4.1). All the analyses were repeated leaving out the five parents of the excluded children, this did not lead to different results. Children between 10-12y were included. By examining the same-sexed parents of these children, who are alike in socioeconomic status, diet and environment and who are 50% genetically identical, using the same experimental task, we sought to have an adult control group that differed primarily in age. Exclusion criteria were, in addition to the general MRI exclusion criteria, being left-handed, having an eating disorder, having a food allergy, following a diet (medically prescribed or to lose weight), and having a gastro-intestinal disorder or a history of surgical or medical events that might significantly affect the study outcome. Additionally, regular smokers (>1 cigarette per day) or participants with a history or current alcohol consumption of >28 units per week were excluded. The exclusion criteria were the same for children and adults.

Table 4.1 Mean (and SD) of demographic variables per group

	Children (*n* =27, 18F)			Adults (*n* =32, 21F)		
	Mean	Range	SD	Mean	Range	SD
Age	10.9	10-12	0.80	43.8	32-52	3.94
(SDS) BMI[1]	0.31	-0.92-2.32	0.85	25.3	19.4-36.9	4.24
Hunger rating[2]	9.89	0-20	4.99	10.53	1-17	3.93
Time since last meal[3]	3.99	1-14	4.33	4.46	2-15	3.65
Tanner stage[4]	2.0	1-4	0.83			

[1]BMI in kg/m^2 is reported for adults, BMI standard deviation score (SDS BMI) is reported for children. BMI in kg/m^2 for children was: Mean 17.8, Range 15.6-24.3, SD 2.09.
[2]There was no significant difference between adults and children in hunger ratings ($t(57)=-0.55$, $p=0.58$.
[3]Time since last meal in hours. There was no significant difference between adults and children in time since last meal ($t(57)=-0.45$, $p=0.65$.
[4]There was no significant difference in Tanner stage between girls (M 2.0, SD 0.77) and boys (M 2.0, SD 1.00) $t(25)= 0.001$, $p=1.00$.

Examinations took place from April 2014 until May 2015 at the imaging facility of the University Medical Center Utrecht. Since no preliminary data were available, sample size was estimated based on the literature. Food viewing studies in children tend to have rather small samples, with older studies having n<12[70]. Because no direct comparison of children and adults has been performed and we expected variance due to developmental differences and movement-related noise we aimed for n=32 per group.

4.2.2 Procedure

The procedures followed were in accordance with the ethical standards of the University Medical Center Utrecht and were approved by the Utrecht Medical Center Medical Ethical Committee. The study consisted of two sessions. During the first session children were familiarized with the scan protocol using a mock scanner. Using a mock scanner to train children

decreases anxiety and greatly increases data quality[155,156]. Before the second session participants were instructed to refrain from eating and drinking (except water) for two hours prior to the session. Hunger ratings were collected on a visual analogue scale and the time of the last meal was recorded. Parents and children were always scanned during the same session, children were scanned first. Examinations usually took place in the early morning, 3 pairs were scanned in the afternoon. Participants' height and weight were measured and they were scanned with fMRI (3T) while they performed a food choice and subsequently a food viewing task, of which only the food viewing task is analyzed for this Chapter. After the scan participants rated a representative subset of the pictures featured in the food viewing task on healthiness and liking (5-point Likert scale). Children provided self-reported Tanner stages by indicating the best matching drawing showing external primary and secondary sex characteristics from a set of five (see Table 4.1).

4.2.3 Food viewing fMRI task

In the 8-minute food viewing task participants viewed 8 blocks of healthy and 8 blocks of unhealthy food pictures with 8 pictures per block (block duration 24 s). Each picture was presented for 2.5 s with a 0.5 s inter-stimulus interval and blocks were interspersed with 3-9 s rest blocks showing a crosshair. Stimuli were presented on a screen (viewed via a mirror) with use of the PRESENTATION software (Neurobehavioral Systems Inc., Albany, CA). Participants were instructed to attend to the pictures, as a picture recall test would be done after the scan. Standardized food pictures from the Full4Health Image Collection were used[157]. The Nutrient Rich Food (NRF) index was utilized[158] to quantify the healthiness of the depicted foods. The NRF9.3 algorithm used produces a single score per food based on the sum of the percentage of daily values for 9 nutrients to encourage (protein, fiber, vitamin A, vitamin C, vitamin E, calcium, iron, magnesium, and potassium) minus the sum of the percentage of maximum recommended values for 3 nutrients to limit (saturated fat, total sugar, and sodium), with all daily values

calculated per 100 kcal and capped at 100%. The mean NRF index was 127.8 (SD 204.6) for the pictures in healthy blocks and -2.9 (SD 9.5) for the pictures in unhealthy blocks. Both children and adults rated a subset of pictures from the healthy blocks as significantly higher in healthiness than a subset of pictures from the unhealthy blocks (children: $F(1,26) = 350.64$; $p = .000$; adults: $F(1,31) = 1111.15$; $p = .000$).

4.2.4 fMRI analyses

4.2.4.1 Image acquisition

MRI scanning was performed on a 3 Tesla scanner (Philips Achieva, Philips Healthcare, Best, The Netherlands), using an 8-channel SENSE head coil. A T_1-weighted structural image was acquired at a resolution of $1 \times 1 \times 1$ mm ($TR = 8.4$ ms, $TE = 3.8$ ms, total scan duration = 284 s). The functional scan was a T_2*-weighted gradient echo 2D-echo planar imaging sequence (TR/TE = 1400/23 ms, flip angle = 72.5°, nr slices = 30, voxel size = $4 \times 4 \times 4$ mm).

4.2.4.2 Preprocessing

Data preprocessing and analysis was conducted with SPM8 (Wellcome Department of Imaging Neuroscience, London, United Kingdom) run with MATLAB R2012a (The Mathworks Inc, Natick, MA). After slice time correction using the middle slice as a reference, functional images were realigned to the mean of the time series. The anatomical scan was co-registered to the mean of the realigned functional scans. A study-specific anatomical template was created using Diffeomorphic Anatomical Registration using Exponentiated Lie algebra (DARTEL,[159]) which estimates a best set of smooth deformations from every subject's tissues to their common average, applies the deformations to create a new average, then reiterates the process until convergence. The template was matched to MNI space (Montreal Neurological Institute) using an affine-only registration, and each subject's functional scans were warped using its corresponding smooth, reversible

deformation parameters to the custom template space, and then to MNI space. The data were smoothed with an 8 mm full width at half maximum isotropic Gaussian kernel. The Volume Artefact tool from ArtRepair[160] was used to detect and repair anomalously noisy volumes. Volumes that had over 1.0 mm scan-to-scan movement and scans with more than 1.5 % deviation from the average global signal, were replaced by using linear interpolation of the values of neighboring scans. Participants with more than 30% of repaired volumes were excluded from analysis. These thresholds were chosen based on the ArtRepair Instructions[161] and our own data, to minimize movement artifacts while at the same time minimizing the amount of repaired data and amount of children excluded. Based on this detection four children had to be excluded from analysis because of too many volumes that had to be repaired.

4.2.4.3 Subject level analyses

Data were high-pass filtered with a cutoff of 128 s and statistical maps were generated for each participant by fitting a boxcar function to the time series, convolved with the canonical hemodynamic response function. Two conditions were modeled: viewing healthy foods and viewing unhealthy foods. A contrast image was calculated for each participant by subtracting the mean response during healthy blocks from the mean response during unhealthy blocks (Unhealthy Foods > Healthy Foods; UF>HF) and vice versa (Healthy Foods > Unhealthy Foods; HF>UF), which formed the primary outcome measures of this study.

4.2.4.4 Group level analyses

4.2.4.4.1 Whole-brain

First, brain activation by unhealthy food versus healthy food images was assessed within the groups using a one-sample t-test with sex and age added as control variables. In all analyses effects were tested for in both directions (so UF>HF and HF>UF). Age and sex were added as control variables because

of the unequal number of males and females, and the relatively large age range in adults. To test for the effect of BMI or standardized BMI score in case of the children (SDS BMI) we performed an additional analysis with (SDS) BMI as a covariate of interest in the one-sample t-tests. Between-group differences were tested with a two-sample t-test with sex, age and (SDS)BMI (normalized within the groups) as control variables. A cluster level threshold of $p<0.05$ corrected for multiple comparisons across the whole brain was derived using Monte Carlo simulations (10,000 iterations) of random noise distribution in the whole brain mask using the 3dClustSim in AFNI[112,113]. This approach combines an individual voxel probability threshold with a minimum cluster size to estimate the probability of a false positive. The resulting threshold was $p<0.005$ with a cluster extent $k\geq90$.

4.2.4.4.2 Region of interest analysis

To test for effects in a priori regions of interest (ROIs) a mask was generated using the Automated Anatomical Labeling (AAL) atlas as implemented in the Wake Forest University Pickatlas toolbox[162,163]. ROIs were based on the appetitive brain network[67] which consists of brain regions typically activated during fMRI studies of food cue reactivity. The mask contained the following areas (bilaterally): superior frontal gyrus (AAL labels: superior frontal gyrus, orbital part of the superior frontal gyrus, medial superior frontal gyrus), middle frontal gyrus (AAL labels: middle frontal gyrus, orbital part of the middle frontal gyrus), medial frontal gyrus (AAL label: orbital part of the medial frontal gyrus), inferior frontal gyrus (AAL labels: opercular part of the inferior frontal gyrus, triangular part of the inferior frontal gyrus, orbital part of the inferior frontal gyrus), insula, anterior cingulate, amygdala, hippocampus (AAL labels: hippocampus, parahippocampal gyrus), striatum (AAL labels: caudate, putamen and pallidum). The results of the ROI analyses were thresholded at $p<0.001$.

4.2.4.5 Additional statistics

Additional statistics such as comparing demographics and ratings between groups and correlation analyses were run in IBM SPSS Statistics 23 (IBM SPSS, 2015).

4.3 Results

4.3.1 Brain responses to unhealthy compared with healthy food cues in children

In children there was a stronger response to unhealthy than to healthy food pictures (UF>HF) in the right temporal/occipital gyri and the left precentral gyrus (Table 4.2, Figure 4.1). SDS BMI correlated negatively with the response to unhealthy food pictures (UF>HF) in the right dlPFC (Table 4.2, Figure 4.2; r = -0.55, r^2 = 0.30). In the ROI analysis, clusters were found in the bilateral opercular part of the inferior frontal gyrus and the right precentral gyrus, the left hippocampus and the left middle frontal gyrus/dlPFC. SDS BMI correlated negatively with the response to unhealthy food pictures (UF>HF) in the left dlPFC (r = -0.68, r^2 = 0.46).

4.3.2 Brain responses to unhealthy compared with healthy food cues in adults

In adults there was a stronger response to unhealthy than to healthy food pictures (UF>HF) in the bilateral middle occipital gyrus and the right calcarine sulcus. The ROI analyses did not yield additional clusters in adults and there were no correlations between brain activation in the UF>HF contrast and BMI.
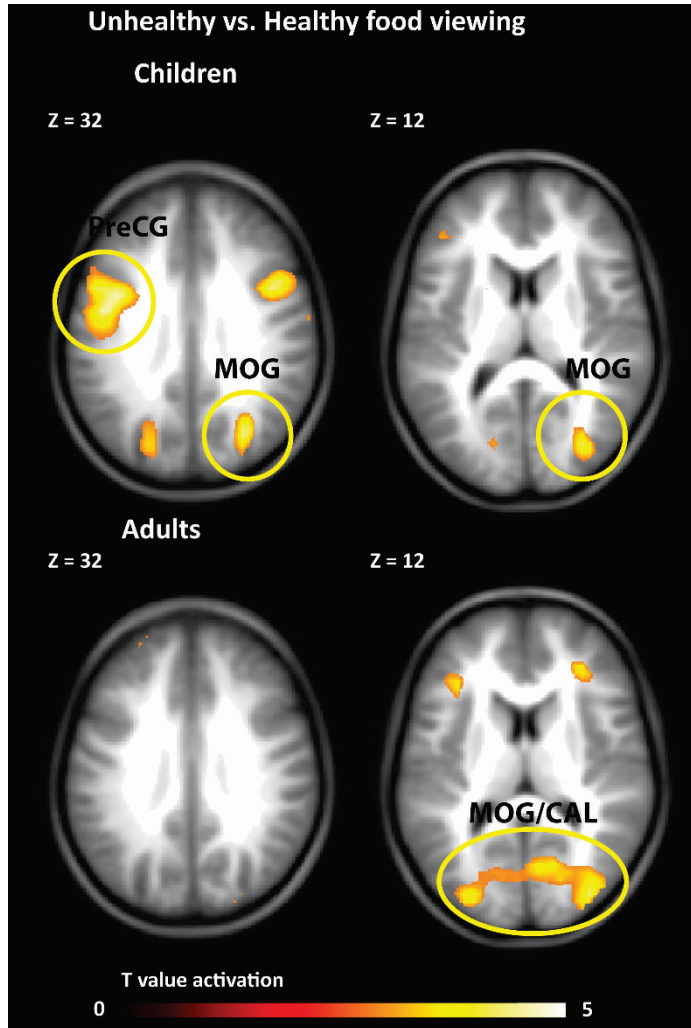
Figure 4.1 Brain regions in which there is activation for unhealthy vs. healthy food viewing in children and adults. T-maps overlaid on mean T_1 image, $p<0.005$, $t>2.8$. Circles denote significant clusters. Children (n=27): top left figure shows clusters in the right middle occipital gyrus (MOG) and the left precentral gyrus (PreCG), the top right figure the right middle occipital gyrus. Adults (n=32): the bottom right figure shows a cluster in the bilateral middle occipital gyrus/calcarine sulcus (MOG/CAL). One-sample t-tests performed for the children and the adults on the unhealthy foods – healthy foods contrast, controlled for age and gender.

Table 4.2 Brain regions with significant activation in, or correlation with, the unhealthy vs. healthy contrast

Brain region	Side	Cluster size	x	y	z	Z-value
Children UF > HF						
Whole brain[1]						
Inferior temporal gyrus	R	234	40	-60	-8	3.92
Middle occipital gyrus			32	-76	16	3.79
Middle occipital gyrus			28	-72	32	3.73
Precentral gyrus	L	236	-48	-4	28	3.92
Precentral gyrus			-40	4	32	3.90
Supramarginal gyrus			-60	-20	40	3.37
ROIs[2]						
Precentral gyrus/Inferior frontal gyrus, opercular part	R	10	44	8	32	3.70
Inferior frontal gyrus, opercular part	L	9	-48	8	28	3.54
Hippocampus	L	12	-24	-16	-12	3.53
Middle frontal gyrus/dlPFC	L	3	-36	8	36	3.36
Children UF > HF negative correlation with BMI z-score						
Whole brain[1]						
Superior frontal gyrus/dlPFC	R	140	20	36	32	4.26
Superior frontal gyrus/dlPFC			20	48	32	4.11
Inferior frontal gyrus triangular part/dlPFC			32	32	28	4.02
ROIs[2]						
Middle frontal gyrus/dlPFC	L	19	-24	40	28	3.78
Middle frontal gyrus/dlPFC			-32	28	24	3.17
Adults UF > HF						
Whole brain[2]						
Middle occipital gyrus	L/R	323	36	-84	20	3.94
Middle occipital gyrus			-28	-88	16	3.67
Calcarine sulcus			16	-68	12	3.56
Children > Adults; UF > HF						
Whole brain[2]						
Precentral gyrus	L	117	-44	-4	28	4.49
Precentral gyrus			-28	0	28	3.07
Precentral gyrus			-52	0	44	2.99

UF = unhealthy foods, HF = healthy foods
[1] Peaks of clusters significant at p<0.005 uncorrected, k>90 voxels are reported
[2] Peaks of clusters in regions of interest significant at p<0.001 uncorrected
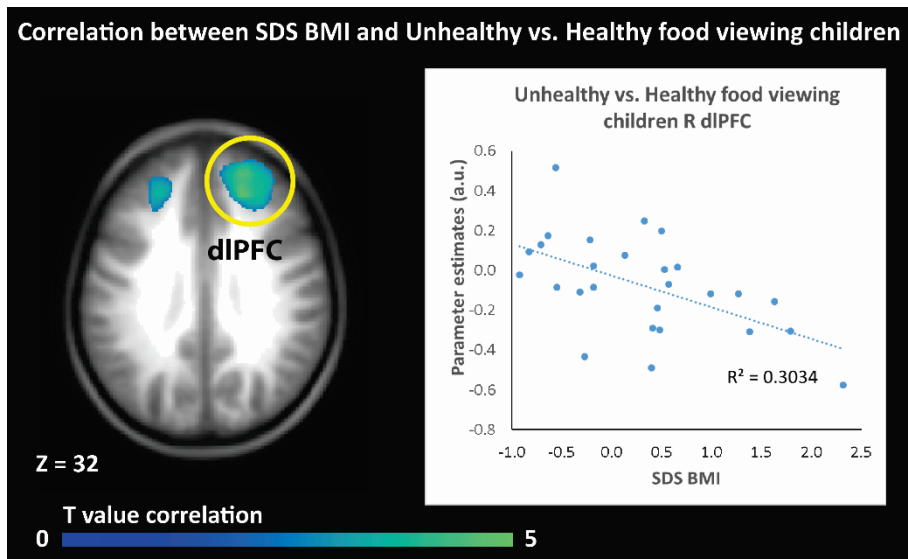
Figure 4.2 Significant correlation between SDS BMI and activation in response to unhealthy vs. healthy food viewing in children (n=27). Left: cluster in the right dlPFC (shown in circle), T-map overlaid on mean T_1 image, $p<0.005$, $t>2.8$, right: parameter estimates of the right dlPFC cluster plotted against SDS BMI. One-sample t-test performed for the children on the unhealthy foods – healthy foods contrast with SDS BMI as a covariate of interest, controlled for age and gender.

4.3.3 Differences between children and adults

Children had a stronger response to unhealthy compared with healthy foods than adults in the left precentral gyrus (see Figure 4.3). No differences in the ROIs were found between children and adults in the UF>HF contrast or vice versa.

When including healthiness ratings, liking ratings, hunger ratings, time since last meal or Tanner stages as covariates in the fMRI analyses, the clusters found did not change. For the average food cue ratings of children and adults see 4.6 Supplementary material. There were no significant results in any of the analyses for the HF>UF contrast.
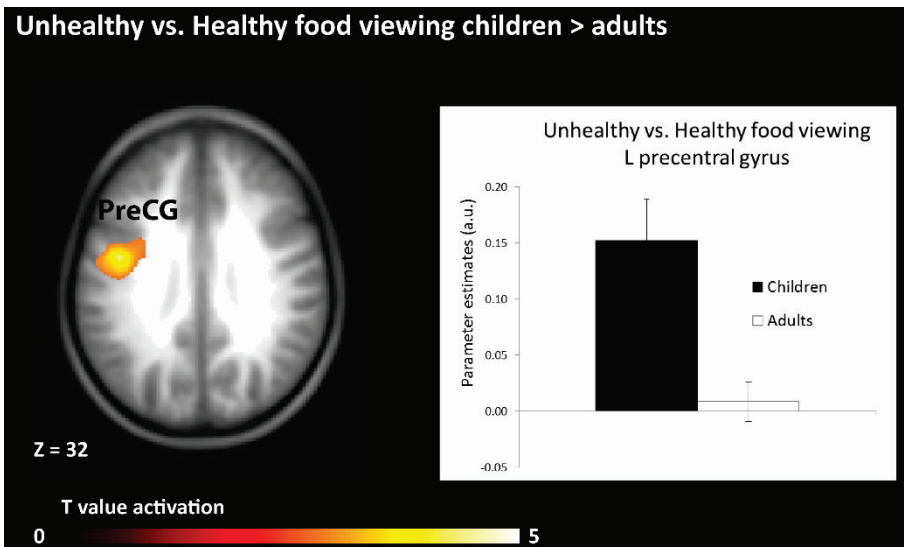
Figure 4.3 Difference between children (n=27) and adults (n=32) in the unhealthy vs. healthy food viewing contrast in the left precentral gyrus (PreCG) (left) and mean parameter estimates and SEM for this cluster in children and adults (right). T-map overlaid on mean T_1 image, $p<0.005$, $t>2.8$. Independent sample t-test was performed comparing the children and adults on the unhealthy foods – healthy foods contrast controlled for age (within group) and gender.

The difference between children and adults remains the same when only the parents of the included children are included in the analysis.

4.4 Discussion

We examined differences between children and adults in brain responses to unhealthy and healthy foods and to which extent these are associated with weight status. We found that children activated the left precentral gyrus more than adults did in response to unhealthy vs. healthy food pictures. Furthermore, children with a higher BMI had lower activation in the bilateral dlPFC while viewing unhealthy compared with healthy foods.

4.4.1 Unhealthy foods elicited stronger responses in the middle occipital gyrus, opercular part of the inferior frontal gyrus, middle frontal gyrus and hippocampus

Previous studies have found that unhealthy food cues lead to heightened attention[44,153], are considered more rewarding[42], and are more likely to trigger memories/simulations of eating these foods than healthy/low calorie foods[164]. In line with these findings, we found higher activation for unhealthy than healthy food cues in areas related to attention and memory processing. In contrast to our expectations we did not find greater reward activation for unhealthy compared to healthy foods in children or adults. Unhealthy foods elicited stronger activation in the middle occipital gyrus in both children and adults. The part of the middle occipital gyrus we found in both adults and children is involved in visual processing and attention[17]. Since the unhealthy and healthy food pictures were visually very similar, we infer that the middle occipital gyrus activation may reflect heightened visual attention for unhealthy foods. The opercular part of the inferior frontal gyrus and the middle frontal gyrus are part of the ventral frontoparietal network involved in stimulus driven attentional control[165]. The stronger activation in these areas in unhealthy compared with healthy food could thus reflect heightened attention for unhealthy foods as well. The hippocampus is a main part of the appetitive brain network[67]. Aside from its role in recalling memories of previous experiences with foods, the hippocampus has a role in sensorimotor processing and emotion[166]. The stronger activation in response to unhealthy foods found in children suggests that unhealthy foods are more associated with memory related processes than healthy foods in children. To conclude, unhealthy foods might elicit more attention in both children and adults. Additionally, children may have higher activation in memory areas in response to unhealthy compared with healthy foods.

4.4.2 Precentral gyrus

Children had stronger activation in the left precentral gyrus in response to unhealthy compared with healthy food pictures. Moreover, they had stronger activation in this area than adults. The precentral gyrus contains the primary motor cortex and is involved in motor coordination and planning. Higher activation in this area has been found in obese vs. lean subjects in a meta-analysis on responses to food vs. non-food[10]. Furthermore, this area activates during anticipation of reward (seeing a cue that signals a later monetary reward[167,168]). Activation in the precentral gyrus in response to food stimuli has been interpreted as reflecting past encoded or concurrent motor planning about ingesting such foods[169] or representing the motivational value of these foods[10]. This suggests that children may have a higher motivational/motor response towards unhealthy foods than adults.

4.4.3 Inhibitory responses in adults

The fact that no activation in inhibitory areas in response to unhealthy foods in adults was found, while other studies did[100,125], could be due to several factors. Since adults liked the healthy foods better than the unhealthy foods, this could explain the lack of inhibitory activation. However, when we controlled for the difference in liking of unhealthy and healthy foods, still no inhibitory activation was found. The mere viewing of food pictures might not be enough to elicit activation in inhibitory regions in adults who may not have an explicit weight-loss or health goal (this was not measured in our sample). Furthermore, most food cue reactivity studies in adults have used samples drawn from student populations, making the average age often between 20 and 30 y (see van Meer, et al.[70] for an overview). As people age, they place less emphasis on the importance of the body's appearance and weight[170]. Thus, the higher age of the adults included in our study (average 44 y) may explain the lack of activation of inhibitory control regions in response to unhealthy food pictures.

4.4.4 Effects of weight status

In children there was a negative correlation between BMI and the brain response to unhealthy vs. healthy foods in the bilateral dlPFC. The dlPFC is an area involved in top-down/cognitive control[171], self-control[81], appetite regulation[172] and response inhibition[173]. Thus, children with a higher BMI may have a lower inhibitory response to unhealthy foods. Our findings are consistent previous studies that compared foods and non-foods in obese vs. normal-weights, which found reduced activation in the left dlPFC in obese groups[10]. However, previous studies in overweight and obese children have reported both higher dlPFC activation (in response to food vs. non-food cues and anticipation for consumption)[71-73] and lower dlPFC activation (in response to palatable food in a go/no-go task)[152]. None of these studies have compared unhealthy with healthy foods, age ranges were wide and the average age of the included children was older. Thus, replication in different age groups looking at the unhealthy vs. healthy contrast is needed to elucidate the discrepancies in findings. In conclusion, in our 10-12 y-old sample, children with a higher BMI had less activation in an inhibitory brain area.

In adults we did not find a correlation with BMI in the dlPFC or any other area. A previous study that examined developmental differences in high calorie food craving found that greater BMI predicted less left vlPFC activity during regulation of craving in younger, but not older, individuals[154]. However, his study used a very different paradigm (regulation-of-craving task) and found these effects in a slightly different region (ventro- instead of dorsolateral PFC). Possibly, in adults the relationship between unhealthy food cue reactivity and BMI is less straightforward. Previous studies have shown that the relationship between BMI and the neural response to food cues is moderated by several variables that were not examined in this study. These include for example hunger state, which was not manipulated in this study[69,174], genetic variance[98,175], impulsivity and dietary restraint[176].

4.4.5 Directions for future research

Our study is the first to examine developmental differences in unhealthy and healthy food cue reactivity in preadolescent children using their parents as the adult group. However, to better assess the effect of age on unhealthy and healthy food cue reactivity our results should be reproduced in a longitudinal fMRI study. Moreover, to further explore the role of inhibition in the neural response to unhealthy food cues, future studies should include measures of impulsivity and inhibitory control capacity. Also, future studies should ideally take into account food intake as well, to be able to clarify the link between food cue reactivity and dietary behavior.

4.5 Conclusion

In conclusion, in contrast to our expectations, we found no support for reduced activation in inhibitory areas in children compared with adults in response to viewing unhealthy foods. However, we did find some evidence that children have stronger activation than adults in brain sites implicated in motivation in response to unhealthy foods. We also found decreased activation in inhibitory areas in children with higher BMIs. This suggests that children who are overweight may have less control over their motivational responses towards foods. Taken together, our findings indicate that children are more susceptible to unhealthy food cues than adults, especially if they are overweight. This calls better protection of children from targeted food marketing to prevent overconsumption of unhealthy foods.

4.6 Supplementary material

Food cue ratings

Children and adults differed in their ratings of the food picture categories. On average children rated the unhealthy foods higher on liking than the healthy foods (mean rating of unhealthy foods – mean rating of healthy foods; $M = 0.30$, SD = 0.63) and adults rated the healthy foods higher on liking than the unhealthy foods (mean rating of unhealthy foods – mean rating of healthy foods; $M = -0.99$, SD = 0.77), difference between children and adults ($t(57) = 6.97$, p<0.001). The perceived healthiness of the categories differed between adults and children as well, with children rating the differences in healthiness between unhealthy and healthy foods as smaller ($M = -1.67$, SD = 0.46) than adults *(M = -2.67, SD = 0.45; $t(57) = 8.38$, p<0.001).*

CHAPTER 5

HIGHER BODY MASS IN CHILDREN IS ACCOMPANIED BY WEAKER DLPFC ACTIVATION IN RESPONSE TO UNHEALTHY FOOD

van Meer, F., van der Laan, L. N., Eiben, G., Lissner, L., Wolters, M., Rach, S., Hermann, M., Erhard, P., Molnar, D., Orsi, G., Viergever, M. A., Adan, R. A., & Smeets, P. A. – On behalf of the I.Family Consortium

In preparation for submission

Abstract

Unhealthy food cues are all around and promote overconsumption. Although childhood obesity rates are increasing, there is no strict regulation of the marketing of unhealthy foods towards children. This is problematic since children's brains, especially areas important for cognitive control, do not mature until their early 20s. It is not known whether the brain response to unhealthy foods pictures differs with body mass and age. To investigate this, 168 children (10-17 y) and 182 adults (30-67 y) from the European IDEFICS cohort were scanned with fMRI while viewing healthy and unhealthy foods. Activation in the precentral gyrus, an area involved in motivation, in response to unhealthy foods correlated negatively with pubertal development. In response to unhealthy foods, adults had stronger activation than children in dorsolateral prefrontal cortex (dlPFC), an area involved in inhibition. Children but not adults with a higher BMI had lower dlPFC activation in response to unhealthy foods. Taken together, our findings suggest that activation in response to unhealthy food cues in an area involved in motivation declines over adolescence and that the magnitude of responses in an area involved in cognitive control in older children does not yet reach the level of adults. These neuroimaging data support that younger and overweight children may be particularly susceptible to tempting foods and underscore that they should be shielded from unhealthy food marketing.

5.1 Higher body mass in children is accompanied by weaker dlPFC activation in response to unhealthy food

The constant exposure to unhealthy foods in modern society is thought to be a major contributing factor to the worldwide rise in obesity[15]. Children may be more susceptible to unhealthy food cues than adults, as they have heightened attention for these cues[41,42] and a lower ability to inhibit their responses towards them[44]. This could make children more sensitive to unhealthy food marketing. Nevertheless, there has been little government regulation to limit the marketing of unhealthy foods targeting children[177]. There have been many industry-led pledges on food advertising to children under twelve years old such as the EU-pledge[178] in Europe and the Children's Food & Beverage Advertising Initiative[179] in North America. However, these voluntary food industry initiatives are frequently criticized because of weak standards and commitments, and a lack of both transparency and enforcement mechanisms[180-183]. Very little is known about how neural responses towards unhealthy foods change over the course of adolescence. Since brain maturation continues until the early twenties[64], the age limit of twelve appears arbitrary and is likely too low. Additionally, some children may be more sensitive to unhealthy foods than others, as several studies suggest that children with a higher body mass have altered brain reactions to (unhealthy) food cues, although the direction of these findings varies[11,71-73,184]. In the present study, we aimed to determine the effect of pubertal development and body mass on neural food cue reactivity. Examining brain responses to food cues helps to elucidate the mechanisms underlying eating behavior. For example, brain reactivity to food cues in reward related areas predicts future weight gain in adolescent girls[11], and women[12], food choice[13,14], snack consumption[15], weight status in women[16], and outcome in a weight-loss program[17]. Children's brains are still developing, and not all brain areas mature at the same rate; between age 8 and 21 greater changes have been found in the prefrontal cortex (PFC) relative to other brain regions for synaptogenesis[61], gray matter reduction[62], myelination increases[63] and

resting level metabolism. In line with this, a previous study has shown children had stronger activation in response to unhealthy foods than adults did in a brain area involved in motivation (precentral gyrus)[184].

It is unknown whether body mass has the same effect on brain responses to food cues in children as in adults. Both in children and adults differences in food cue reactivity between normal and overweight individuals have been studied[9-11,71-73,152,184], but results are inconsistent. In adults, overweight/obese individuals compared with normal-weight individuals had stronger activation in areas associated with evaluation of salient stimuli (left dorsomedial PFC, orbitofrontal cortex and anterior cingulate cortex), an area involved in motivation (precentral gyrus) and in explicit memory (parahippocampal gyrus). Additionally, reduced activation was found in overweight and obese individuals in an area involved in cognitive control (left dorsolateral PFC; dlPFC) and in an area involved in interoception (insula)[10]. Others found increased insula activation in overweight individuals[9]. In contrast, in obese and overweight compared with normal-weight children more as well as less dlPFC and ventrolateral PFC (vlPFC) activation has been found[11,71-73,152,184]. We hypothesized that with the maturation of the prefrontal cortex, activation in response to unhealthy foods in areas involved in cognitive control (e.g. dlPFC and vlPFC) increases over adolescence, while such activation decreases in the precentral gyrus (Hypothesis 1). Nevertheless, we expected that adults still have stronger responses in areas involved in cognitive control and weaker responses in the precentral gyrus than older children. Furthermore, we hypothesized that individuals with a higher body weight will have weaker activation in response to unhealthy foods in areas involved in cognitive control (Hypothesis 2).

To test these hypotheses, we scanned 168 children (10-17 y, mean age 13.3) and 182 adults (30-67 y, mean age 44.8) from the European IDEFICS/I.Family cohort[21,185] with fMRI while they viewed healthy and unhealthy foods (for more information see the Experimental Procedures in 5.2 Supplementary material; see Table S5.1 for demographics). This task consisted of the

presentation of 8 blocks of 8 healthy or unhealthy food pictures. Healthiness of the depicted foods was quantified by the Nutrient Rich Food (NRF) index[158]. Both children and adults rated a subset of the pictures in the healthy blocks as significantly healthier than a subset of the pictures from the unhealthy blocks (paired sample t-test, children: $t(165) = 46.2$; $p < 0.001$; adults: $t(1,179) = 71.8$; $p < 0.001$).

To test our first hypothesis, we examined the difference in brain response between viewing unhealthy and healthy foods and how it covaried with pubertal development (Tanner Stage) in children with a one-sample t-test. To assess the unique effect of pubertal development, we controlled for BMI. Pubertal development stage was associated with weaker activation in response to unhealthy foods in the bilateral pre- and postcentral gyrus (see Figures 5.1 A and B), rolandic operculum, left lingual gyrus, bilateral middle and inferior occipital gyrus, and right middle temporal gyrus. This confirms our hypothesis that as children age, their approach and reward activation in response to unhealthy foods decreases. However, in contrast to our first hypothesis, we found no relationship between age or pubertal stage and the response in areas involved in cognitive control such as the dorsolateral PFC. Next, we examined differences in the response to unhealthy food cues between children and adults with an independent-sample t-test. Compared to children, adults had stronger activation in response to unhealthy foods in the right dlPFC (see Figures 5.2 A and B). Furthermore, adults showed greater activation in response to unhealthy foods in a cluster that stretches from the right opercular part of the inferior frontal gyrus to the triangular part (dlPFC) and in the putamen. Thus, adults show stronger dlPFC activation in response to unhealthy foods than children do. Children, instead, have stronger dlPFC activation towards healthy foods. For main effects within the groups for the unhealthy vs. healthy food comparison, we refer to the 5.2 Supplementary material (Results section; Table S5.2 and Figure S5.1).

Figure 5.1 A: Negative correlation of Tanner stage with unhealthy food > healthy food in the left precentral/postcentral gyrus in children. B: Mean parameter estimates of the cluster in the left precentral/postcentral gyrus MNI(-21,-30,63) in children plotted against Tanner stage. C: Negative correlation of BMI Cole score with unhealthy food > healthy food in the right dlPFC in children. D: Mean parameter estimates of the cluster in the right dlPFC MNI(33,39,21) in children plotted against BMI Cole score. Peaks listed are significant at $p < 0.05$ based cluster level corrections (individual voxel threshold $p = 0.001$, cluster extent threshold k = 22 voxels, 3x3x3 mm voxels). HF = healthy food; UF = unhealthy food.

As a next step we examined the effect of BMI in children (Hypothesis 2). There was a negative correlation between BMI (Cole score) and activation in response to unhealthy compared with healthy foods in the right supramarginal gyrus, right insula and right middle frontal gyrus (dlPFC; see Figure 5.1 C and D). In adults, we found no correlation between body weight and neural responses to unhealthy vs. healthy foods.

Figure 5.2 A: Difference between children and adults in the unhealthy > healthy food viewing contrast in right dlPFC and triangular part of the inferior frontal gyrus. B: Mean parameter estimates and SEM for the cluster in the right dlPFC MNI(48,27,30) in children (white) and adults (black). Peaks listed are significant at $p < 0.05$ based cluster level corrections (individual voxel threshold $p = 0.001$, cluster extent threshold k = 22 voxels, 3x3x3 mm voxels). HF = healthy food; UF = unhealthy food.

Thus, in children BMI correlated negatively with activation in an area involved in cognitive control and with activation in an area involved in interoception, while in adults BMI did not correlate with any brain responses to unhealthy vs. healthy foods, contrary to our second hypothesis. This, however, is in line with our previous study, employing the same paradigm, in which we also found a negative correlation between BMI and dlPFC activation in response to unhealthy foods in children but no correlation between BMI and brain activation in adults[184].

There is barely any regulation of the marketing of unhealthy foods to children, despite the increase in childhood obesity. Furthermore, existing industry-initiated pledges are ineffective and only try to limit marketing to children under twelve[177]. Our study population of 10-17 y-old children with a median age of 13 still responded with lower activation in areas important for cognitive control than in adults when exposed to tempting unhealthy foods. Furthermore, it is worrying that children with a higher BMI exhibit weaker activation in areas involved in cognitive control in response to unhealthy foods. Since this was a cross-sectional study we cannot infer causality.

However, earlier studies showed that weaker activation to food in these areas predicted lower success in a weight loss program[17], and weaker activation in this area when obese women make choices between long-term vs. short-term rewards predicted future weight gain[186]. This suggests that children who are already overweight may be at increased risk for gaining even more weight and it may be more difficult for them to lose weight. We found that younger children have more activation related to motivation in response to unhealthy foods but older children do not show more self-control activation than younger children. This underlines the importance of decreasing the exposure of children of all ages to unhealthy food cues, such as television and in-store marketing for unhealthy foods, and to decrease the availability of unhealthy foods in their school environment. We show that the effect of BMI on unhealthy food cue reactivity in the dlPFC may be age dependent. Since children had less dlPFC activation than adults, perhaps as dlPFC maturation reaches a certain level it is no longer influenced by body mass. This could explain the differences in outcomes with previous studies[9-11,71-73,152,184], as age ranges greatly varied between studies. In conclusion, our findings make a strong case for discouraging unhealthy food marketing directed at children of all ages, not just younger children (below 12) e.g. by imposing stricter regulation through evidence-based policy.

5.2 Supplementary material

5.2.1 Experimental procedures

5.2.1.1 Participants

The children included were part of the IDEFICS cohort which was followed-up during the I.Family study. In the IDEFICS (Identification and prevention of dietary- and lifestyle-induced health effects in children and infants) baseline survey in 2007/2008, a population-based sample of 16.228 children aged 2 to 9.9 years from eight European countries (Belgium, Cyprus, Estonia, Germany, Hungary, Italy, Spain, Sweden) was examined. Follow-up examinations were conducted two years and six years (I.Family study; 7105 children) later; the study design has been described in detail elsewhere[21]. A subsample of 190 out of these 7105 children in I.Family centers in Germany, Hungary and Sweden and 187 adults (the gender-matched parents of the children) were scanned with fMRI. Care was taken to prioritize the inclusion of overweight children to ensure enough variation in the sample. Children were included if they matched MRI inclusion criteria, and none of the exclusion criteria: being left-handed, having an eating disorder, having a food allergy, following a diet (medically prescribed or to lose weight), and having a gastro-intestinal disorder or a history of surgical or medical events that might significantly affect the study outcome. Additionally, smokers (>1 cigarette per day) or participants with a history or current alcohol consumption of >28 units per week were excluded. The data of 24 children and 5 adults could not be used for analysis, because of excess movement (n=16 children), missing weight and height measurement on the scan day (n=3 adults) or insufficient scan quality (n=8 children, n=2 adults). This leaves a final sample of 168 children and 182 adults (see Table S5.1 for demographics).

5.2.1.2 Procedure

In a visit prior to the scan, children were familiarized with the procedure. Participants were instructed to refrain from eating and drinking (except water) for two hours prior to the scan session. Participants' height and weight were measured. After that they performed a food choice and a food viewing task while being scanned. Only the results of the food viewing task are presented in this Chapter. After the scan, participants were asked to rate the healthiness and tastiness of a subset of the pictures of the food viewing task (80%) on a five point scale in a computerized rating task.

5.2.1.3 Food viewing fMRI task

In the 8-minute food viewing task participants viewed 8 blocks of healthy and 8 blocks of unhealthy food pictures with 8 pictures per block (block duration 24 s; total number of pictures 128; no repetitions). Each picture was presented for 2.5 s with a 0.5 s inter-stimulus interval and blocks were interspersed with 3-9 s rest blocks showing a crosshair. Stimuli were presented on a screen (viewed via a mirror) with use of the PRESENTATION software (Neurobehavioral Systems Inc., Albany, CA). Participants were instructed to attend to the pictures, as a picture recall test would be done after the scan. Standardized food pictures from the Full4Health Image Collection were used (24). The Nutrient Rich Food (NRF) index was utilized (25) to quantify the healthiness of the depicted foods. The NRF9.3 algorithm used produces a single score per food based on the sum of the percentage of daily values for 9 nutrients to encourage (protein, fiber, vitamin A, vitamin C, vitamin E, calcium, iron, magnesium, and potassium) minus the sum of the percentage of maximum recommended values for 3 nutrients to limit (saturated fat, total sugar, and sodium), with all daily values calculated per 100 kcal and capped at 100%. Because of local differences in food familiarity a different set of pictures was used in each country. The mean NRF index was 149.3 (SD 235.8) in Germany, 160.0 (SD 243.8) in Hungary and 159.4 (SD 236.2) in Sweden for the pictures in healthy blocks and -3.9 (SD 10.3) in

Germany, -1.6 (SD 11.6) in Hungary and -3.7 (SD 10.7) in Sweden for the pictures in unhealthy blocks.

5.2.1.4 MRI data acquisition

MRI scanning was performed in the three centers on 3 tesla MRI scanners (Germany: Siemens Skyra; Hungary: Siemens Trio, Siemens AG, Erlangen, Germany; Sweden: GE Discovery MR750w, GE Healthcare Systems, Milwaukee, USA), using a 32-channel head coil (Germany, Sweden) or a 12-channel head coil (Hungary). A T_1-weighted structural image was acquired at a resolution of 1 × 1 × 1 mm with 176 sagittal slices and a field of view of 256x256 (Germany: repetition time (*TR)* = 1900 ms, echo time (*TE)* = 2.07 ms, flip angle 9°; Hungary: TR = 2530 ms, TE = 3.37 ms, flip angle 7° ; Sweden: TR = 6.928 ms, TE = 2.53 ms, flip angle 7°). The functional scan was a T_2*-weighted gradient echo 2D-echo planar imaging sequence (TR/TE = 2000/30 ms, flip angle = 76°, 36 axial slices, voxel size = 3 × 3 × 3 mm, at all sites).

5.2.1.5 fMRI data preprocessing

Data preprocessing and analysis was conducted with SPM12 (Wellcome Department of Imaging Neuroscience, London, United Kingdom) ran with MATLAB R2015b (The Mathworks Inc, Natick, MA). After slice time correction using the middle slice as a reference, functional images were realigned to the first scan. After grey and white matter segmentation, a study-specific anatomical template was created using Diffeomorphic Anatomical Registration through Exponentiated Lie algebra (DARTEL)[159]. After co-registration DARTEL was used to normalize this template and the functional scans to MNI space (Montreal Neurological Institute–International Consortium for Brain Mapping). The data were then smoothed with a 6 mm full width at half maximum isotropic Gaussian kernel. The Volume Artefact tool from ArtRepair (http://cibsr.stanford.edu/tools/human-brain-project/artrepair-software.html) was used to detect and repair anomalously noisy volumes. Volumes that moved more than 1mm/TR were repaired. 16

children were excluded from the analysis because too many volumes (>25%) had to be repaired.

5.2.1.6 Subject level analyses

Data were high-pass filtered with a cutoff of 128 s and statistical maps were generated for each participant by fitting a boxcar function to the time series, convolved with the canonical hemodynamic response function (HRF). Two conditions were modeled: viewing healthy foods and viewing unhealthy foods. Contrast images were calculated for each participant by subtracting the mean response during healthy blocks from the mean response during unhealthy blocks and vice versa.

5.2.1.7 Group level analyses

First, brain activation in response to unhealthy versus healthy food images was assessed within the groups using a one-sample t-test with study center, BMI (Cole score) and age (for adults) and Tanner stage (for children) added as covariates. In all analyses effects were tested for in both directions (so UF>HF and HF>UF). Between-group differences were tested with a two-sample t-test with center and age (normalized within the groups) as covariates. The analysis was confined to gray matter with a gray matter mask (made by thresholding the mean of the DARTEL gray matter segmentations at a probability of 0.5). A cluster level threshold of p<0.05 corrected for multiple comparisons across the whole brain was derived using Monte Carlo simulations (10,000 iterations) of random noise distribution in the whole brain mask using the 3dClustSim in AFNI[112,113]. This approach combines an individual voxel probability threshold with a minimum cluster size to estimate the probability of a false positive. The resulting threshold was p<0.001 with a cluster extent k≥22.

5.2.2 Results

5.2.2.1 Main effect unhealthy compared with healthy foods children and adults

In a one-sample t-test with BMI Cole score and Tanner stage as covariates we found that children have stronger activation towards unhealthy foods in the bilateral middle occipital gyrus and middle cingulum (see Figure S5.1). In response to healthy foods activation was stronger in the bilateral dlPFC, middle cingulum, bilateral supramarginal gyrus and the opercular part of the inferior frontal gyrus. In a one-sample t-test in adults with BMI and age as covariates adults we found an opposite pattern regarding dlPFC activation; stronger activation in the right dlPFC towards unhealthy foods than healthy foods. Additionally, in adults we found a stronger response towards unhealthy foods in the inferior temporal gyrus, left supplemental motor area, bilateral middle insula, right putamen, left hippocampus, the paracentral lobule and stronger activation towards healthy foods in the middle occipital gyrus, bilateral precuneus, middle cingulum, medial orbitofrontal gyrus and left supramarginal gyrus.

Figure S5.1 A: Brain regions with significant differences in activation in the contrast of unhealthy vs. healthy food viewing (red-yellow color bar) and healthy vs. unhealthy food viewing (blue-green color bar) in children. B: Brain regions with significant differences in activation in the contrast of unhealthy vs. healthy food viewing (red-yellow color bar) and healthy vs. unhealthy food viewing (blue-green color bar) in adults. Peaks listed are significant at $p < 0.05$ based cluster level corrections (individual voxel threshold $p = 0.001$, cluster extent threshold k = 22 voxels, 3x3x3 mm voxels). HF = healthy food; UF = unhealthy food.

Table S5.1 Mean (and SD) of demographic variables per group

	Children (n =168, 94F)			Adults (n =183, 96F)		
	Mean	SD	Range	Mean	SD	Range
Age	13.3	1.82	10-17	44.8	5.2	30-67
(SDS) BMI[1]	0.42	0.99	-2.83-2.87	26.9	5.37	17.6-46.8
Tanner stage	1.95	0.66	1-3			

[1]BMI in kg/m^2 is reported for adults, BMI standard deviation score (SDS BMI) is reported for children. BMI in kg/m^2 for children was: Mean 20.0, range 14.4-32.4, SD 3.62.

Table S5.2 Brain regions with significant activation in the unhealthy vs. healthy food contrast, or with significant correlation with Tanner stage or BMI (Cole score).

Brain region	Side	Cluster size	x	y	z	Z-value[a]
Children						
Unhealthy food > healthy food						
Middle occipital gyrus	R	1358	36	-84	9	Inf
Inferior temporal gyrus	R		48	-60	-9	Inf
Fusiform gyrus	R		30	-45	-18	7.42
Inferior temporal gyrus	L	1265	-45	-63	-6	7.09
Middle occipital gyrus	L		-36	-87	9	7.08
Inferior occipital gyrus	L		-45	-57	-12	6.92
Inferior frontal gyrus orbital part	L	28	-24	30	-15	4.31
Inferior frontal gyrus orbital part	L		-33	33	-12	3.52
Calcarine sulcus	L	53	-9	-72	12	4.04
Calcarine sulcus	L		-21	-69	6	3.81
Precentral gyrus	R	26	42	6	30	3.96
Healthy food > unhealthy food						
Middle frontal gyrus (dlPFC)	R	104	36	39	24	4.72
Middle frontal gyrus (dlPFC)	R		36	48	24	4.36
Middle frontal gyrus (dlPFC)	R		24	57	27	3.56
Middle cingulum	R	33	6	-33	45	4.52
Inferior frontal gyrus triangular part (dlPFC)	L	50	-39	42	24	4.45
Middle frontal gyrus (dlPFC)	L		-33	33	30	3.45
Middle frontal gyrus (dlPFC)	L		-27	33	24	3.35
Supramarginal gyrus	L	58	-63	-36	30	4.42
Inferior parietal gyrus	L		-60	-36	45	3.78
Supramarginal gyrus	R	248	60	-30	27	4.39
Superior temporal gyrus	R		60	-21	18	4.09
Supramarginal gyrus	R		57	-42	33	3.82
Middle frontal gyrus (dlPFC)	R	40	27	24	42	3.94

Table S5.2 continued

Brain region	Side	Cluster size	x	y	z	Z-value[a]
Superior frontal gyrus	R		21	15	45	3.57

Negative correlation between BMI Cole score and unhealthy food > healthy food

Supramarginal gyrus	R	33	54	-42	33	3.92
Middle frontal gyrus (dlPFC)	R	35	33	39	21	3.78
Middle frontal gyrus (dlPFC)	R		36	54	24	3.46
Middle frontal gyrus (dlPFC)	R		39	45	27	3.44
Insula	R	60	39	15	-12	3.73
Insula	R		42	21	0	3.69

No positive correlation with BMI Cole score

Negative correlation between Tanner stage and unhealthy food > healthy food

Postcentral/precentral gyrus	L	24	-21	-30	63	4.44
Rolandic operculum	R	56	63	-3	12	4.36
Superior temporal gyrus	R		57	-3	0	3.70
Cuneus	L	398	-6	-96	15	4.13
Superior occipital gyrus	R		21	-90	21	3.98
Middle occipital gyrus	R		33	-81	9	3.97
Lingual gyrus	L	77	-21	-75	-9	4.06
Fusiform gyrus	L		-30	-54	-15	3.93
Middle temporal gyrus	R	57	45	-69	0	3.94
Inferior occipital gyrus	R		45	-75	-9	3.45
Middle temporal gyrus	R		51	-63	6	3.42
Inferior occipital gyrus	L	22	-51	-63	-12	3.81
Inferior parietal gyrus	L	68	-33	-66	48	3.71
Superior occipital gyrus	L		-24	-75	36	3.54

Adults

Unhealthy food >healthy food

Inferior temporal gyrus	R	947	48	-60	-9	Inf

Table S5.2 continued

Brain region	Side	Cluster size	x	y	z	Z-value[a]
Middle occipital gyrus	R		33	-81	15	Inf
Middle occipital gyrus	R		42	-81	6	Inf
Fusiform gyrus	R	1319	27	-45	-15	Inf
Inferior occipital gyrus	L		-45	-66	-6	Inf
Middle occipital gyrus	L		-27	-87	21	7.76
Inferior frontal gyrus opercular part (dlPFC)	R	675	45	6	24	7.32
Insula	R		33	24	-3	6.01
Inferior frontal gyrus triangular part	R		48	27	27	5.94
Supplemental motor area	L	199	-6	15	57	5.57
Supplemental motor area	L		-3	24	51	5.30
Medial superior frontal gyrus	L		-6	51	36	5.08
Insula	L	163	-30	24	0	5.11
Insula	L		-39	30	-3	4.60
Inferior frontal gyrus opercular part	L		-39	33	-12	3.30
Precentral gyrus	L	397	-45	0	45	5.11
Inferior frontal gyrus opercular part (dlPFC)	L		-42	6	27	4.86
Inferior frontal gyrus triangular part	L		-42	33	12	4.35
Inferior frontal gyrus orbital part	R	37	30	33	-9	4.73
Putamen	R	96	33	-9	-6	4.56
Hippocampus	R		21	-9	-12	4.25
Amygdala	R		33	0	-21	4.09
Supplemental motor area	R	41	9	18	48	4.21
Middle cingulum	R		3	18	54	3.83
Hippocampus	L	29	-21	-9	-18	4.15
Inferior frontal gyrus triangular part	L	47	-48	18	9	4.13
Healthy food > unhealthy food						
Precuneus	L	71	-6	-57	57	4.74

Table S5.2 continued

Brain region	Side	Cluster size	x	y	z	Z-value[a]
Middle cingulum	R	85	6	-36	45	4.34
Medial orbitofrontal gyrus	R	80	12	48	-3	4.26
Precuneus	R	119	12	-60	24	4.09
Cuneus	L		-15	-60	24	4.01
Precuneus	R		6	-63	30	3.92
Supramarginal gyrus	L	31	-60	-33	30	4.07
Supramarginal gyrus	L		-63	-33	39	3.62
Adults > children in unhealthy foods > healthy foods						
Inferior frontal gyrus opercular part	R	149	54	18	12	4.60
Inferior frontal gyrus triangular part	R		45	21	6	4.46
Putamen	R		48	9	9	3.69
Middle frontal gyrus	R	61	45	45	6	4.05
Middle frontal gyrus (dlPFC)	R	33	33	39	21	3.88
Middle frontal gyrus	R		27	45	12	3.56
Inferior frontal gyrus triangular part (dlPFC)	R	36	48	27	30	3.78
Inferior frontal gyrus triangular part	R		45	21	39	3.53

No significant differences in children > adults in unhealthy foods > healthy foods

[a] Infinite Z score is due to the P value being so small that the Z score is effectively infinite

CHAPTER 6

CONSIDERING HEALTHINESS PROMOTES HEALTHIER CHOICES BUT MODULATES MEDIAL PREFRONTAL CORTEX DIFFERENTLY IN CHILDREN COMPARED WITH ADULTS

Abstract

Childhood obesity is a rising problem worldwide mainly caused by overconsumption, which is driven by food choices. In adults, food choices are based on a value signal encoded in the medial prefrontal cortex (mPFC). This signal is modulated by the dorsolateral prefrontal cortex (dlPFC), which is involved in self-control.

We aimed to examine the neural correlates of food choice in children, and how considering healthiness affects neural activity and choice behavior.
24 children and 28 adults performed a food choice task while being scanned with fMRI and provided health and taste ratings of the foods afterwards. During the choice task participants considered either the healthiness or tastiness of the food or chose naturally.

Health rating was a positive predictor of choice in adults, but a negative predictor in children. Children had weaker dlPFC activation than adults during yes vs. no independent of health or taste condition. Both children and adults made healthier choices when considering healthiness. Taste rating modulated mPFC activation in both children and adults. When considering the healthiness, health rating positively modulated mPFC activation in adults, but negatively in children. Considering the healthiness increased connectivity between dlPFC and mPFC in adults, but not in children.

In conclusion, considering healthiness can promote healthier choices in both children and adults, but is accompanied by an opposing pattern of brain activation in the mPFC. Since the absolute number of healthy choices remained lower in children, this suggests that children may not yet be geared to modify their choices away from their natural tendency to choose unhealthy tasty foods. Thus, this study suggests that it may be promising to develop interventions that increase children's preference for healthy food, for example by increasing the habitual consumption of healthy foods from a young age.

6.1 Introduction

Childhood obesity is a rising problem almost everywhere in the world[150]. Compared to normal-weight children, overweight children have a much higher chance to develop into overweight adults[2]. Weight gain, and thus overweight and obesity, is mainly caused by overconsumption[3,187], which is driven by food choices[4]. Examining the neural correlates of healthy and unhealthy food choices in children may elucidate the mechanisms underlying maladaptive eating behavior in children. When decisions such as food choices are made, the different attributes of choice options (e.g., taste, healthiness, portion size, and packaging) are valued, weighed and integrated into a single value for each option[87,88]. In adults, neuroimaging studies have consistently shown that value is encoded in the ventromedial prefrontal cortex (vmPFC)[78-83,85,89]. During food choice, the tastiness of foods contributes to the valuation signal in the vmPFC[81]. Healthiness is included in the valuation signal as well, when individuals with a health goal make healthy choices[80] or when people without an explicit health goal consider the healthiness of foods during their choices[81]. When asked to consider healthiness, the vmPFC signal is modulated by the dorsolateral prefrontal cortex (dlPFC) and participants make healthier choices[81]. There are several reasons why it may be harder for children than for adults to choose healthy foods. First, choosing a healthy food over a tasty unhealthy food requires self-control, which is not fully developed yet in children and adolescents. This is apparent from both response inhibition and choice impulsivity tasks such as delay discounting tasks[55]. Second, children may be more susceptible to food cues than adults[70,184]. For example, in an eye-tracking study adults were initially strongly attracted by unhealthy foods, but shifted their attention from unhealthy to healthy foods, while children attended more to unhealthy foods and did not shift their attention away[44]. Furthermore, children showed more craving than adults both in behavioral and neuroimaging measures in a regulation of craving task and older age predicted less craving and enhanced lateral prefrontal recruitment[154]. The underlying cause of these differences between children and adults is that the brain of children has not

yet matured. Notably, not all brain areas mature at the same rate; relatively greater developmental changes have been reported in the prefrontal cortex (PFC)[64]. The PFC is involved in various aspects of cognitive processing including valuation (vmPFC) and response inhibition (lateral PFC). In children, the neural correlates of (healthy) food choice are largely unknown[188], only one study examined the neural correlates of healthy food choice in children[19]. When children chose foods for themselves the vmPFC value signal encoded only the taste of the foods. However, when children indicated the foods their mothers would pick for them, their projected mother's choice correlated positively with dlPFC activation and the children chose healthier foods. Since an adult group was not included, no direct comparison between children and adults could be made. It remains unknown whether children can modify their own choice behavior and to what extent this is associated with changes in vmPFC and dlPFC activation. Children may not be able to utilize the dlPFC-vmPFC network to achieve healthier choice behavior as successfully as adults do, because of the relative immaturity of the PFC. Therefore, we aimed to examine the neural correlates of healthy food choice in children and how these differ from those in adults. Additionally, we aimed to determine whether health cues can modify choice behavior in children, and if so, how this affects vmPFC and dlPFC activation.

6.2   Methods

6.2.1   Participants

Children between 10-12 years old and their gender-matched parents were included in this study. Both normal-weight and overweight children and adults were included (BMI criteria children: standardized BMI score (SDS BMI) between -1.1 and 2.5; BMI criteria adults: between 18.5-37.5).

Table 6.1 Demographic variables per group

	Children (*n* =24, 17F)			Adults (*n* =28, 19F)		
	Mean	Range	SD	Mean	Range	SD
Age	10.8	10-12	0.76	43.9	32-52	3.80
(SDS) BMI[a]	0.30	-0.92-2.32	0.84	25.1	19.4-36.9	3.93
Tanner stage[b]	1.75	1-3	0.74			
Highest level of education				4.57	2-6	1.20

[a]BMI in kg/m^2 is reported for adults, BMI standard deviation score (SDS BMI) is reported for children.

[b]There was no significant difference in Tanner stage between girls and boys $t(22)$= -1.49, p=0.89.

Exclusion criteria were: in addition to the general MRI exclusion criteria, being left-handed, having an eating disorder, having a food allergy, following a diet (medically prescribed or for weight-loss), and having a gastro-intestinal disorder or a history of surgical or medical events that might significantly affect the study outcome. Additionally, regular smokers (>1 cigarette per day) or participants with a historical or current alcohol consumption of >28 units per week were excluded. Exclusion criteria were the same for children and adults. Thirty-two children and their thirty-two gender-matched parents enrolled in the study. Twelve participants were excluded from analysis, due to excessive head movement (two children) or because of a lack of variety in the choices in the food choice task (four adults and six children; see section 'Food choice fMRI task'). Twenty-four children and twenty-eight adults were included in the final analyses (for characteristics see Table 6.1).

6.2.2 Procedure

The procedures followed were in accordance with the ethical standards of the University Medical Center Utrecht and were approved by the Utrecht Medical Center Medical Ethical Committee. The study consisted of two sessions. During the first session, children were familiarized with the scan

protocol and the food choice task using a mock scanner. Using a mock scanner to train children decreases anxiety and increases data quality[155,156]. Participants were instructed to refrain from eating and drinking (except water) for two hours prior to the second session (the scan day). Parents and children were always scanned on the same day, and children were scanned first. Examinations usually took place in the morning (between 08:00-12:00 h). 3 child-parent pairs were scanned in the afternoon. Participants' height and weight were measured. After that they performed a food choice and a food viewing task while being scanned. We here focus on the food choice task, results of the food viewing task have been published elsewhere[184]. Afterwards, participants were asked to rate the foods from the food choice task (n=150) on their healthiness and tastiness on a five point scale in a computerized rating task. Children provided self-reported Tanner stages by indicating the best matching drawing showing external primary and secondary sex characteristics from a set of five (see Table 6.1).

6.2.3   Food choice fMRI task

This experiment used a food choice task adapted from Hare et al. 2011 (Figure 6.1). In this task participants are shown a picture of a food item for 2 s and are given 2 s to indicate whether they want to eat the food after the experiment by pressing a left (yes) or right (no) button with their right thumb, as[76]. 150 trials were presented. A random trial was selected as the trial that counted for real. Trials were separated by a variable inter-trial interval between 1.4 – 4.2 s. The sequence of trials was optimized and counterbalanced using the Optseq2 algorithm (https://surfer.nmr.mgh.harvard.edu/optseq/), which provides temporal jitter to increase signal discriminability[189]. Participants made choices in three different attention conditions. In the health condition they were asked to consider the healthiness of the food, in the taste condition they were asked to consider the taste of the food and in the natural condition they were asked to consider the food as a whole and choose naturally. Critically, the instructions emphasized that subjects should always choose what they

preferred, regardless of the condition. The attention condition was kept constant for 10 trials at a time, and the beginning of a new condition was announced with a 5 s instruction screen. After receiving task instructions, subjects completed 150 trials in the scanner; 50 in each condition. Each food was shown only once and the order of conditions was fully randomized for each subject. If subjects said either yes to less than 25% of the items or no to less than 25% of the items, their data were excluded from the analyses (n=10, 6 children). The excluded individuals did not differ from the included group in (SDS) BMI or age. Stimuli were presented on a screen which was viewed via a mirror on the head coil with use of the PRESENTATION software (Neurobehavioral Systems Inc., Albany, CA). Standardized food pictures from the Full4Health Image Collection were used[157]. The task was split up in 2 runs of 10 minutes with a 30 s break in between.
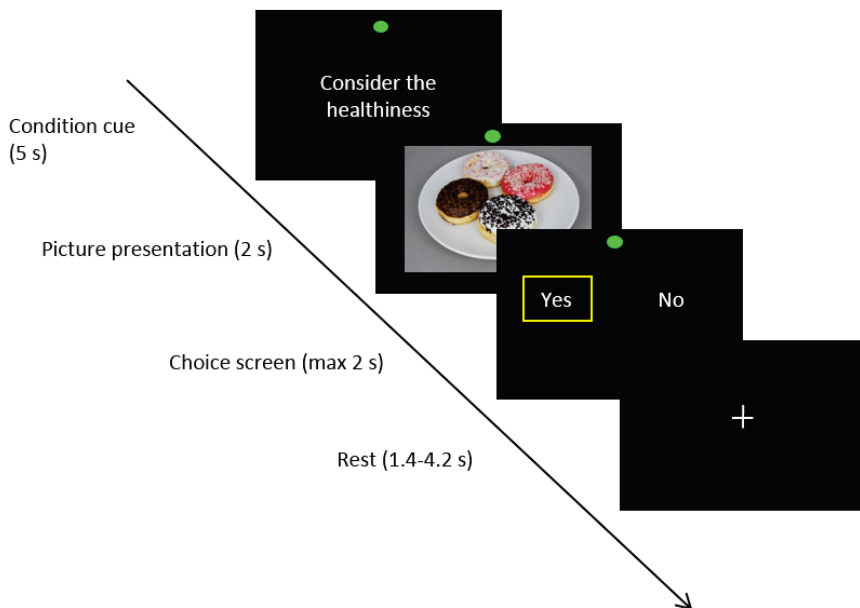

Figure 6.1 Trial structure of the food choice task.

6.2.4   Behavioral data analysis

For both groups, a mixed-effects logistic regression model was estimated per group with choice outcome (yes or no) as dependent variable and with health rating, taste rating, a dummy for health condition, a regressor for health condition interacted with health rating (HR*HC), a regressor for health condition interacted with taste rating (TR*HC), a dummy for taste condition, a regressor for taste condition interacted with health rating (HR*TC), and a regressor for taste condition interacted with taste rating (TR*TC) as predictors. Given the specification of the model the natural condition serves as baseline and health condition and taste condition measure differences from the natural condition. The same model was tested including group as a predictor to test the interaction between group and the other predictors.
Second, to gain insight in the choices made in each condition the choices were binned into four categories based on the health and taste ratings: unhealthy-untasty, healthy-untasty, unhealthy-tasty and healthy-tasty with healthy or tasty foods defined as being rated >3 on the healthiness or tastiness scale by that participant, and unhealthy or untasty foods defined as being rated <3 on the healthiness or tastiness scale. The percentage of 'yes' was then calculated and a repeated measures ANOVA was done with cue condition and category as within-subject factors and group as a between-subject factor.

Third, independent samples t-tests were done on the percentage of (un)healthy foods accepted overall to check for differences in the absolute amount of healthy and unhealthy foods accepted between children and adults.

In addition, a repeated-measures ANOVA was used to examine differences in reaction times in the HC and TC and the effect of group. A mixed-effects regression model was estimated with reaction time as dependent variable and taste rating and health rating as regressors per group, and with group added as predictor to look for differences between children and adults.

6.2.5   MRI data acquisition

MRI scanning was performed on a 3 Tesla scanner (Philips Achieva, Philips Healthcare, Best, The Netherlands), using an 8-channel SENSE head coil. A T_1-weighted structural image was acquired at a resolution of $1 \times 1 \times 1$ mm (repetition time (TR) = 8.4 ms, echo time (TE) = 3.8 ms, flip angle 8°, total scan duration = 284 s). The functional scan was a T_2*-weighted gradient echo 2D-echo planar imaging sequence (TR/TE = 1400/23 ms, flip angle = 72.5°, 30 axial slices, voxel size = $4 \times 4 \times 4$ mm).

6.2.6   fMRI data preprocessing

Data preprocessing and analysis was conducted with SPM12 (Wellcome Department of Imaging Neuroscience, London, United Kingdom) run with MATLAB R2015b (The Mathworks Inc, Natick, MA). After slice time correction using the middle slice as a reference, functional images were realigned to the first scan. A study-specific anatomical template was created using Diffeomorphic Anatomical Registration using Exponentiated Lie algebra (DARTEL,Ashburner[159]), and after co-registration DARTEL was used to normalize this template and the functional scans to MNI space (Montreal Neurological Institute–International Consortium for Brain Mapping). The data were then smoothed with an 8 mm full width at half maximum isotropic Gaussian kernel. The Volume Artefact tool from ArtRepair (http://cibsr.stanford.edu/tools/human-brain-project/artrepair-software.html) was used to detect and repair anomalously noisy volumes. Volumes that moved more than 1mm/TR were repaired. Based on this two children were excluded from the analysis because too many volumes (>30%) had to be repaired.

6.2.7   Subject level analyses

Data were high-pass filtered with a cutoff of 128 s and statistical maps were generated for each participant by fitting a boxcar function to the time series,

convolved with the canonical hemodynamic response function (HRF). To test for differences between children and adults in the basic choice process, first, we examined the neural correlates yes vs. no independent of condition. To test for effects of yes vs. no all the decision events (regressor 1; 2s) were modeled with yes (1) and no (0) as a parametric modulator, a regressor for health condition (regressor 2; modeled from the presentation of the condition instruction until the end of the block, 74s) and a regressor for taste condition (regressor 3; modeled from the presentation of the condition instruction until the end of the block, 74s) (Model 1). The following contrasts were calculated: (1) modulation of decision activation by yes and no response independent of condition, (2) effect of health condition on decision activation, (3) effect of taste condition on decision activation, (4) yes response independent of condition vs. rest, (5) no response independent of condition vs. rest. In all general linear models tested, condition cue (5 s), yes-no screen (2 s) and realignment parameters were modeled as regressors of no interest.

Second, a full model was estimated to look at the interaction of cue condition and rating (Model 2). This model had the following regressors: all decision events (regressor 1; 2s) with health (parametric modulator 1 of regressor 1) and taste rating (parametric modulator 2 of regressor 1) as parametric modulators, health condition (regressor 2; modeled from the presentation of the condition instruction until the end of the block, 74s), decision events in health condition (regressor 3; 2s) with taste rating (parametric modulator 1 of regressor 3) and health rating (parametric modulator 2 of regressor 3) as parametric modulators, taste condition (regressor 4; modeled from the presentation of the condition instruction until the end of the block, 74s), decision events in taste condition (regressor 5; 2s) with taste (parametric modulator 1 of regressor 5) and health rating (parametric modulator 2 of regressor 5) as parametric modulators. The following contrasts were calculated: (1) modulation of decision activation in natural condition by taste rating, (2) modulation of decision activation in natural condition by health rating, (3) modulation of decision activation in health condition by taste

rating, (4) modulation of decision activation in health condition by health rating, (5) modulation of decision activation in taste condition by health rating and (6) modulation of decision activation in taste condition by health rating. Note that because of the specification of this model contrast 3-6 denote the change in modulation by the ratings from the natural condition.

6.2.8   Group level analyses

To test for effects in a priori regions of interest (ROIs) a mask was generated using the Automated Anatomical Labeling (AAL) atlas as implemented in the Wake Forest University (WFU) Pickatlas toolbox[162,163]. ROIs were areas implicated in food decision-making: medial and lateral PFC, anterior cingulate cortex, and amygdala (all bilaterally). A single mask was created containing these areas (voxel count of the mask: 2007).

One-sample t-tests were used to examine within-group effects for the contrasts calculated in the first level analyses. Independent-samples t-tests were used to test for between-group differences. All t-tests were used to examine both sides (positive and negative) of effects. All analyses were repeated with gender and age (per group) added as covariates of no interest. A cluster level threshold of $p < 0.05$ corrected for multiple comparisons across ROI mask was derived using Monte Carlo simulations (10,000 iterations) of random noise distribution in the ROI mask using the 3dClustSim tool in AFNI version 16.2.07[112,113]. This approach combines an individual voxel probability threshold with a minimum cluster size to estimate the probability of a false positive. We used the 3DFWHMx tool in AFNI to estimate noise smoothness values of the data using the Auto-Correlation Function (ACF) based option. The resulting 2-sided threshold was $p < 0.001$ with a cluster extent $k \geq 6$ for the ROI mask.

6.2.9   Psychophysiological interaction

To explore differences between children and adults found in the previous analyses, a psychophysiological interaction (PPI) analysis was performed to identify regions exhibiting increased correlation during the health condition compared with the natural condition. The specific coordinate in the anterior cingulate/mPFC (MNI (-8, 40, 12)) was determined by the difference in modulation by health rating during health condition between adults and children. First, for each individual, the BOLD time-series within an 8-mm sphere centered on the mPFC ROI was extracted. Second, for each individual, a general linear model was estimated that included the following four regressors: interaction between neural activity in the mPFC and an indicator for health condition convolved with the canonical HRF, the indicator for health condition convolved with the HRF, the extracted timeseries from the mPFC, and an indicator for session. Single subject contrasts were calculated following estimation of the general linear model. Third, group-level contrast images were calculated based on the single-subject contrast values using one-sample t-tests and group differences were examined using independent-samples t-tests.

6.3   Results

6.3.1   Behavioral results

First, we examined the choice behavior of children and adults and the effects of health and taste ratings and the different conditions. The mixed-effects logistic regression model with choice outcome (yes vs. no) as dependent variable (see Figure 6.2) showed that in both children and adults there were effects of health rating in the natural condition (children: z = -2.8, p = 0.005; adults: z = 5.0, p = $6.4*10^{-7}$), taste rating in the natural condition (children: z = 20.3, p < $2*10^{-16}$; adults: z = 19.8, p < $2*10^{-16}$) and main effect of health condition (children: z = -2.4, p =0.015; adults: z = -4.6, p = $4.4*10^{-6}$). Thus, in the natural condition taste ratings predicted the acceptance of foods in both

children and adults and health ratings predicted acceptance of foods in adults but rejection of food in children. In the health condition both children and adults were less likely to accept foods. Taste condition did not have a main effect. In both children and adults there were significant interaction effects of health rating in the health condition (health rating*health condition; children: $z = 9.7$, $p < 2*10^{-16}$; adults: $z = 12.6$, $p < 2*10^{-16}$) and taste rating in the health condition (taste rating*health condition; children: $z = -7.7$, $p = 1.4*10^{-14}$; adults: $z = -4.7$, $p = 2.3*10^{-6}$). This shows that during health condition, both children and adults were more responsive to health features of the food than during natural condition, and less responsive to taste features. The interaction effect of health rating*group was significant ($z = 5.2$, $p = 2.1*10^{-7}$), with health rating being a positive predictor of choice in adults and a negative predictor of choice in children during natural condition. The taste and health rating of the foods presented in the choice task had a weak negative correlation in children (mean $r = -0.22$, SD 0.15) and a moderate positive correlation in adults (mean $r = 0.39$, SD 0.25). To examine whether the child-parent dyads were similar in their ratings we performed additional paired analyses. Since some children and adults had to be excluded (see Methods section 2.1) 22 child-parent dyads were included in analysis. In these dyads the children's health ratings correlated with those of their parents (mean $r = 0.73$, SD $= 0.12$). Children's taste ratings did not correlate with their parent's taste ratings (mean $r = 0.06$, SD $= 0.19$). The strength of the correlation between the taste or health ratings of children and their parents was not associated with any of the behavioral measures. Also, the correlation between the health and taste ratings per person was not correlated within child parent dyads (Intraclass correlation coefficient: 0.15, $p = 0.24$).

To see what kind of choices children and adults made in the cue conditions a repeated-measures ANOVA was performed to determine whether the percentage of saying yes to certain food categories (unhealthy-untasty, healthy-untasty, unhealthy-tasty and healthy- tasty) changed over conditions and whether this differed between children and adults. This repeated-

measures ANOVA (see Figure 6.3) showed a main effect for condition ($F(2,200) = 16.9$, $p < 0.001$) and category ($F(3,150) = 262.7$, $p < 0.001$) and an interaction effect for condition*food category ($F(6,300) = 37.6$, $p < 0.001$). Post-hoc tests showed that in the health condition less foods were accepted (41.8%) than in the natural (49.3%) and taste conditions (52.2%). Healthy-tasty foods were accepted the most (90.6%), followed by unhealthy-tasty (69.2%), healthy-untasty (19.2%) and unhealthy-untasty foods (12.2%). Healthy-untasty foods were accepted more often in the health condition (34.2%) than in the natural (11.6%) and taste conditions (11.7%) and unhealthy-tasty foods were accepted less often in the health condition (35.5%) than in the natural (83.5%) and taste conditions (88.7%).

Figure 6.2 Mean beta weights across subjects for each regressor in the mixed-effects logistic regression model. HR = health rating TR = taste rating HC = health condition TC = taste condition. * = regressor is significantly different from 0 at $p < 0.05$ in both groups # = significant interaction between group and regressor at $p < 0.001$. Error bars represent SEM.

There was no main effect of group, children (48.6%) and adults (47.0%) said yes to the same amount of foods over the task. There was no effect of group*condition, but there was an interaction effect of group*food category ($F(3,150) = 5.1$, $p = 0.002$). Post-hoc tests show that children accepted more unhealthy-tasty foods (76.7%) than adults (61.8%) did, and less healthy-tasty foods (children 85.1% and adults 96.0%). There was no interaction effect of group*condition*food category, meaning that the effect of condition on the food category acceptance did not differ between children and adults. There were no significant intraclass correlations between children and their parents for the percentage of acceptance of the different food categories.

Figure 6.3 Bar graph showing the percentage of the time subjects responded "yes" to eat the food as a function of taste– health combination and condition. * = significant difference between health condition and natural condition $p < 0.05$, *Group = interaction effect of group*food category $p < 0.05$. There were no interaction effects of group*condition. Error bars represent SEM.

Since the previous test was done using percentages, we furthermore tested whether children had a higher absolute number self-control challenges (healthy-untasty or unhealthy-tasty). Children had a higher number of healthy-untasty trials than adults over conditions (children M: 8.3 SD: 4.2 adults M: 3.6 SD: 3.2, $t(50) = 4.6$, $p < 0.001$) but there was no difference in the number of unhealthy-tasty foods (children M: 9.8 SD: 5.4, adults M: 8.3 SD: 5.2, $t(50) = 1.0$, $p = 0.32$). This means that the difference between children and adults in the amount of unhealthy-tasty foods accepted is not caused by a higher frequency of self-control trials in this category. Children did encounter more self- control trials of the healthy-untasty variety, but there was no difference in choice patterns between adults and children in this category. To examine the total amount of healthy and unhealthy choices made independent samples t-tests were performed and showed that over the entire task children accepted more unhealthy foods than adults ($t(50) = 4.2$, $p < 0.001$; children: M 54.8 SD 18.2, adults: M 35.8 SD 14.3) and less healthy foods than adults ($t(50) = -6.2$, $p < 0.001$; children: M 53.0 SD 4.1, adults: M 82.4 SD 13.7).

6.3.2   Neuroimaging results

6.3.2.1   Model 1: choice outcome and overall effect of health and taste condition

6.3.2.1.1   Choice outcome

First, we examined which areas showed more activation when accepting foods than rejecting foods independent of condition. In children yes vs. no positively modulated activation in the medial orbitofrontal cortex (vmPFC; Table 6.2). In adults yes vs. no positively modulated activation in the bilateral anterior cingulum (vmPFC). The independent-samples t-test showed that in adults there higher activation in the yes vs. no contrast in the right anterior cingulum and left superior frontal gyrus (dlPFC) (Figure 6.4).

Table 6.2 Yes vs. no independent of block

Brain region	Side	Cluster size	x	y	z	Z-value
Children						
Medial orbitofrontal cortex (vmPFC)	L/R	10	0	52	-8	3.54
Medial orbitofrontal cortex (vmPFC)	R		4	60	-4	3.19
Adults						
Anterior cingulum (vmPFC)	L	86	-4	44	0	5.46
Anterior cingulum	R		8	36	4	4.56
Adults > children						
Yes vs. No						
Anterior cingulum	R	6	16	40	20	3.70
Superior frontal gyrus (dlPFC)	L	12	-20	48	16	3.53
Superior frontal gyrus	L		-16	60	8	3.44
No children > adults						

Peaks listed are significant at the p < 0.05 level based cluster level corrections within an a priori set of regions of interest (individual voxel threshold = p < 0.001, cluster extent = 6 voxels, 4x4x4 mm voxels). L, Left; R, right.

To see whether the difference in activation in the left dlPFC was driven by the yes or the no response we examined the parameter estimates of the cluster in the dlPFC in contrast of yes vs. rest and no vs. rest (Figure 6.4). This analysis showed that the interaction effect of yes vs. no in children compared with adults in the dlPFC is driven by a greater deactivation of the dlPFC in children during yes vs. rest compared to no vs. rest, while in adults there was no dlPFC activation during yes vs. rest or no vs. rest.

6.3.2.1.2 *Overall effect of health and taste condition*

Second, we examined whether health or taste condition had an effect on the decision activation. In children and adults there were no areas found that were more active at the time of decision in health condition than natural condition, or taste condition than natural condition.

Figure 6.4 Left: Difference in modulation of choice activation by yes vs. no in the natural condition between children and adults. Right: Mean and SE of the parameter estimates of the cluster in the dlPFC (peak: MNI(-20, 48, 16)) for yes vs. rest and no vs. rest in children and adults. * denote significant differences: between children and adults in yes vs. rest, between children and adults in no vs. rest, and an interaction effect of choice outcome and age group. Peaks listed are significant at the $p < 0.05$ level based cluster level corrections within an a priori set of regions of interest (individual voxel threshold = $p < 0.001$, cluster extent = 6 voxels, 4x4x4 mm voxels).

When adding sex and age (per group) as covariates results of the analyses in Model 1 remain unchanged.

6.3.2.2 Model 2: effect of health ratings, taste ratings and health and taste conditions

6.3.2.2.1 Natural condition

In Model 2, which explores interactions between ratings and condition, we first examined the effects of health and taste ratings in the natural condition. In children health rating did not modulate brain activation in the natural condition. In adults, health rating negatively modulated choice activation in the bilateral superior frontal gyrus (dlPFC) (Table 6.3). There were no

significant differences between children and adults. In children taste rating positively modulated right medial orbitofrontal cortex (vmPFC) activation. In adults taste rating positively modulated activation in the anterior cingulum (vmPFC), and the right amygdala. There were no significant differences between children and adults in the modulation by ratings in the natural condition.

6.3.2.2.2   Health condition

Second, we looked at the how the effects of the ratings changed during health condition. During the health cue condition health rating negatively modulated the left anterior cingulum in children compared to the natural condition (Table 6.4, Figure 6.5). In adults health rating positively modulated activation in bilateral anterior cingulum compared to the natural condition (Table 6.4, Figure 6.5). The independent samples t-test showed that in the health cue condition, health rating modulated activation in the anterior cingulum stronger in adults than they did in children. Figure 6.6 illustrates that this difference is caused by negative modulation of left anterior cingulum activation by health rating compared to the natural condition in children and positive modulation of left anterior cingulum activation by health rating compared to the natural condition in adults. This area of the anterior cingulum dorsal to the vmPFC (MNI z>1) will be referred to as mPFC. To examine whether this difference between children and adults in the effect of health rating during health condition was related to the difference in correlation between health and taste ratings we repeated the analysis with the correlation for each person (using Fisher's transformation to approximate a normal distribution of the correlation coefficients) added as a covariate.

Table 6.3 Natural condition

Brain region	Side	Cluster size	x	y	z	Z-value
Children						
Modulation by taste rating (positive)						
Medial orbitofrontal cortex (vmPFC)	R	17	8	48	-4	3.83
Medial orbitofrontal cortex (vmPFC)	R/L		0	56	-8	3.65
No negative modulation by taste rating and no modulation by health rating						
Adults						
Modulation by health rating (negative)						
Superior frontal gyrus (dlPFC)	L	8	-12	28	40	4.12
Superior frontal gyrus (dlPFC)	R	7	16	28	36	3.96
No positive modulation by health rating						
Modulation by taste rating (positive)						
Amygdala	R	10	24	-8	-12	3.79
Anterior cingulum (vmPFC)	L	15	-4	52	0	3.59
Anterior cingulum	L/R		0	48	8	3.51
Anterior cingulum (vmPFC)	L		-4	60	-4	3.48
No negative modulation by taste rating						
Adults > children						
No differences in modulation by taste or health rating						

Peaks listed are significant at the p < 0.05 level based cluster level corrections within an a priori set of regions of interest (individual voxel threshold = p < 0.001, cluster extent = 6 voxels, 4x4x4 mm voxels). L, Left; R, right.

Table 6.4 Health condition

Brain region	Side	Cluster size	x	y	z	Z-value
Children						
Modulation by health rating (negative)						
Anterior cingulum (mPFC)	L	6	-8	40	12	3.77
No positive modulation by health rating and no modulation by taste rating						
Adults						
Modulation by health rating (positive)						
Anterior cingulum	L	6	-12	28	28	3.69
Anterior cingulum	R	6	8	40	20	3.48
Medial superior frontal gyrus	R	9	8	52	8	3.32
Anterior cingulum	R		-4	48	4	3.31
No negative modulation by health rating and no modulation by taste rating						
Adults > children						
Difference in modulation by health rating during health condition						
Anterior cingulum (mPFC)	L	35	-8	40	12	4.34
No effect of health condition on the modulation by taste						

Peaks listed are significant at the $p < 0.05$ level based cluster level corrections within an a priori set of regions of interest (individual voxel threshold = $p < 0.001$, cluster extent = 6 voxels, 4x4x4 mm voxels). L, Left; R, right.
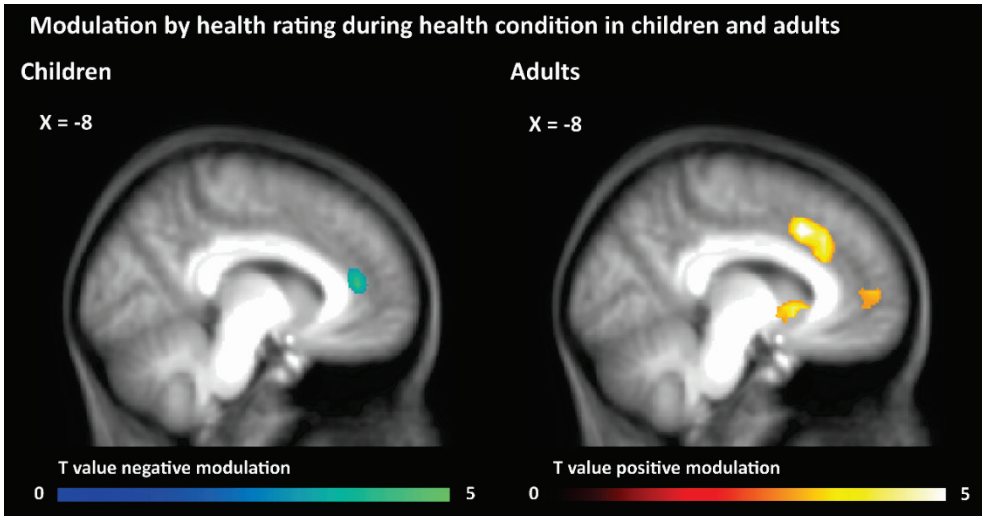
Figure 6.5 Modulation by health rating during health condition in children and adults. Peaks listed are significant at the *p* < 0.05 level based cluster level corrections within an a priori set of regions of interest (individual voxel threshold = *p* < 0.001, cluster extent = voxels 6, 4x4x4 mm voxels).
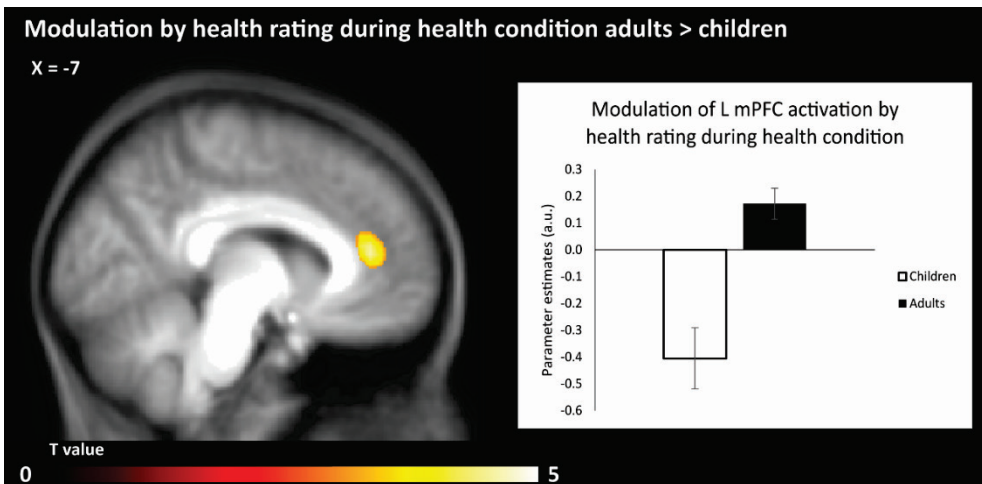

Figure 6.6 Difference in modulation by health rating during health condition between children and adults. Peaks listed are significant at the *p* < 0.05 level based cluster level corrections within an a priori set of regions of interest (individual voxel threshold = *p* < 0.001, cluster extent = 6 voxels, 4x4x4 mm voxels).

When controlling for TR*HR correlation the difference between children and adults in the mPFC remained significant; MNI(-8, -40, 12), Z=4.42, k=57. This means that the difference between children and adults in the modulation by health rating in health condition cannot be explained by the difference in correlation between health and taste ratings.

To examine whether the negative difference between the correlation with health ratings in the health condition and natural condition was caused by a more negative correlation with health ratings during the health condition or a less positive correlation during the health condition compared with the natural condition, we estimated an additional subject level model where the decision events in the three conditions were modeled separately (6.6 Supplementary material). Analysis of this model showed that children had a negative correlation between health ratings and activation in the mPFC cluster in the health condition, and a positive (but not statistically significant) correlation during the natural condition, while for adults the opposite is true (Figure S6.1).

6.3.2.2.3   Taste condition

Third, we looked at the how the effects of the ratings changed during taste condition. There were no differences in the effects of taste or health ratings between taste condition and natural condition. Furthermore, there were no differences between children and adults. When adding sex and age (per group) as covariates results of the analyses of Model 2 remain unchanged.

6.3.2.3   Effect of health condition on the functional connectivity of the mPFC

As a last step in our analyses, we further explored the difference found between children and adults in the modulation of the anterior cingulum (mPFC) by health rating during health condition, by examining the connectivity of this area in children and adults.

Table 6.5. Areas showing increased coupling (PPI) with mPFC during health condition

Brain region	Side	Cluster size	x	y	z	Z-value
Children > adults						
Anterior cingulum (vmPFC)	L	36	-4	44	0	5.17
Anterior cingulum	R		8	44	4	4.75
Adults > children						
Middle frontal gyrus (dlPFC)	L	6	-24	32	44	3.33

Peaks listed are significant at the $p < 0.05$ level based cluster level corrections within an a priori set of regions of interest (individual voxel threshold = $p < 0.001$, cluster extent = 6 voxels, 4x4x4 mm voxels). L, Left; R, right.

A PPI analysis was performed to assess the effect of the health cue condition on the connectivity of the mPFC seed and the difference between children and adults. In the health condition children showed higher connectivity within the anterior cingulum (higher connectivity between mPFC and vmPFC) compared to adults (Table 6.5), whereas adults had higher connectivity with the left middle frontal gyrus (dlPFC) compared to children. When adding sex and age (per group) as covariates results remain unchanged.

6.4   Discussion

In light of the rising prevalence of childhood obesity, we aimed to examine the neural correlates of food choice in children, and whether health cues can improve healthy choice behavior. This study builds on previous work in adults that showed that by considering the healthiness of foods during food choice, this aspect is incorporated in the value signal in the vmPFC, connectivity with dlPFC increases and individuals make healthier choices[81]. We examined whether this same pattern of changes in brain activation and behavior is found in children.

6.4.1 Food choice behavior

In both children and adults, tastiness was the strongest predictor of choice in the natural condition. This is in line with previous studies in children and adults[19,81,190]. In adults, the healthiness of the foods was a small but positive predictor of choice (similar to[81]), while in children it was a negative predictor of choice in the natural condition. For children the healthiness and tastiness of foods were negatively correlated, as was found by Lim, et al.[19]. When asked to consider the healthiness of the foods during choice, both children and adults made more healthy choices, i.e. healthiness became a stronger predictor for choice outcome. Nevertheless, even when considering healthiness, children accepted less healthy and a greater number of unhealthy foods than adults did. Thus, children prefer the taste of unhealthy foods and choose them more often and, although they improve the healthiness of their choices when considering health, they still do not choose as healthy as adults do.

6.4.2 Neural correlates of food choice independent of condition

We found that during food choice, children appear to rely on the same valuation system in the vmPFC that has been described in adults[78,80-85]. In both children and adults vmPFC activation was modulated by the tastiness of the food. The healthiness of the food did not affect children's brain activation in the natural condition. This is in accordance with Lim et al. 2016, who found that children's taste preferences were related to vmPFC activation, but found no effect of the healthiness of food on brain activation in children. Taken together, it appears that in general healthiness is not a relevant aspect of food choice for children. In our group of adults the healthiness of foods did not affect the vmPFC during the natural condition. However, we did find negative encoding of the healthiness of foods in the bilateral dlPFC. During food choice independent of attention condition, children had weaker dlPFC activation than adults during yes vs. no. This suggests that children have less

inhibitory activation during food choice than adults, in this area that encodes the healthiness of the food in adults but not children.

6.4.3 Changes in neural activation during food choice when considering healthiness

Even though children chose healthier foods when asked to consider the healthiness, healthiness was negatively encoded in the mPFC compared with the natural condition, i.e., the healthier the food, the lower the mPFC activation. The opposite was true for adults, who had positive encoding of the healthiness in the mPFC compared with the natural condition. This opposite pattern is remarkable since the effect of the health cue on the choice behavior was the same for children and adults. To elucidate this finding, we examined how the functional connections of this area in the mPFC changed in the natural condition. When children and adults considered the healthiness of the foods, differences in mPFC connectivity emerged: While in adults considering healthiness was associated with increased connectivity between mPFC and left dlPFC (as described by[80,81]), in children connectivity within mPFC/vmPFC was increased. This suggests that, in children, considering the healthiness of food does not lead to the changes in dlPFC-mPFC connectivity that have been associated with healthier choices in adults.

Although children improved the healthiness of their choices when considering health, the absolute number of healthy foods they accepted and unhealthy food they rejected remained significantly lower than in adults. Accordingly, they do not exhibit the same pattern of activation that adults do when considering the healthiness of foods, which may render them less successful. This may reflect developmental differences between children and adults in the neural processing of food choices overall and when attending to healthiness.

A recent study by Bruce, et al.[190] showed children had heightened vmPFC activation during food choice after watching food commercials and placed a higher emphasis on taste attributes of the food items. Future studies could examine whether watching commercials for healthy foods could have a similar effect on the emphasis placed on health attributes during food choice. The next step in this line of research would be to examine the role of weight status in the neural correlates of healthy food choice in children, to see whether there are neural differences in how lean and obese children make food choices.

Given the design of our task we could not pinpoint the exact moment of the decision. In our subject level models we assumed that the decision was made during the picture presentation, which is supported by the short reaction times (M 0.6s). We modeled the response screen separately to minimize the influences of motor activation due to the button press and differences between children and adults in reaction times. Modeling the response screen separately from the picture presentation will lead to collinearity of these two regressors which is a limitation of this approach that results in a higher a probability of type II errors. Binary choice outcome (yes/no) was used in this study instead of a 4 point scale as other studies have used[19,81]. As a consequence, information regarding the strength of choice could not be assessed, which is a limitation of this approach. However, we nevertheless decided to employ a binary choice paradigm to simplify the task for young children. Furthermore, because of the binary outcome of the choice task some participants had to be excluded because of a lack of variation in their data. This could lead to a bias, although we found no evidence that these individuals differed from the rest of our study population in age, (SDS) BMI and effect of health condition. In future studies in older children or adults a more continuous measure of valuation could be used to address these limitations.

6.5   Conclusion

Children appear to base their food choices on tastiness, and since they prefer unhealthy foods this leads to unhealthy choices. While they may employ the same basic neural circuitry as adults do during food choice, the attributes encoded might differ. Whereas in adults healthiness positively predicted choice when choosing naturally and was encoded positively in mPFC when considering health, healthiness negatively predicted choice in children when choosing naturally and was negatively encoded in the mPFC when asked to consider the healthiness. Children do improve their choice behavior when considering healthiness, but still choose less healthy than adults. Asking children to choose healthy appears to be asking them to go against their natural preference, while adults already appear to prefer healthier foods. Thus, this study suggests that it may be promising to develop interventions that heighten children's preference for healthy food, for example by increasing the habitual consumption of healthy foods from a young age, in addition to the current focus on increasing self-regulatory capacity and inhibitory control. Since food preference is largely learned during childhood[24,27], in children there is still an opportunity to encourage healthy preferences. In this way children could choose the foods they like and still choose healthy.

6.6   Supplementary material

6.6.1 Reaction times

There was no overall difference in the choice reaction times between children and adults (Children M = 607.4 ms; SD = 327.3. Adults M = 583.4 ms; SD 293.4, $F(1,55)$ = .08, p = .77). The effect of the health condition on reaction time differed in children and adults (interaction of group*health condition $F(1,71)$ = 6.61, p = .01). In children there was no effect of health condition on reaction time (natural condition: M = 608.7 ms; SD = 314.1, health condition: M = 630.7 ms; SD = 356.3, $F(1,46)$ = 1.75, p = .19), while adults reacted faster in health condition (natural condition: M = 607.1 ms; SD = 306.6, health condition: M = 573.5 ms; SD = 301.2, $F(1,54)$ = 9.43, p = .003). In children there was no significant effect of taste condition on reaction time (M = 585.8 ms; SD = 308.2, $F(1,46)$ = 1.60, p = .21), while adults reacted faster in taste condition (M = 569.5 ms; SD = 270.0, $F(1,54)$ = 11.7, p = .001). There was no interaction effect between taste condition and group ($F(1,71)$ = 0.82, p = .34). There was no relationship between taste or health ratings and reaction times in children (taste ratings: $t(3528)$ = 1.79, p = 0.07; health ratings: $t(3515)$ = -0.58, p = 0.56). Adults had shorter reaction times for foods that they rated as healthier, and longer reaction times for foods they rated as tastier (taste ratings: $t(4178)$ = 2.62, p = 0.009; health ratings: $t(4173)$ = -3.27, p = 0.001). There was no interaction effect of group*taste ratings or group*health ratings on reaction times. Note that the reaction time measured here is the time between the onset of the response screen and the moment of the button press. Since the food picture has been presented for 2 seconds before the response screen appears the decision has most likely already been made at this point. This should be kept in mind when interpreting the reaction time results.

6.6.2 Additional analysis of the effect of health ratings

To examine the correlation with health ratings in the separate blocks we have estimated an additional first level model, which had had the following regressors: decision events in the natural condition (regressor 1; 2s) with health (parametric modulator 1 of regressor 1) and taste rating (parametric modulator 2 of regressor 1) as parametric modulators, health condition (regressor 2; modeled from the presentation of the condition instruction until the end of the block, 74s), decision events in health condition (regressor 3; 2s) with taste rating (parametric modulator 1 of regressor 3) and health rating (parametric modulator 2 of regressor 3) as parametric modulators, taste condition (regressor 4; modeled from the presentation of the condition instruction until the end of the block, 74s), decision events in taste condition (regressor 5; 2s) with taste (parametric modulator 1 of regressor 5) and health rating (parametric modulator 2 of regressor 5) as parametric modulators. The following contrasts were calculated: (1) modulation of decision activation in natural condition by health rating, (2) modulation of decision activation in health condition by health rating. Because in this model the decision events in the natural condition and health condition do not overlap, contrast 1 and 2 give us the correlation of health ratings with activation independent of each other. We examined the activation in the mPFC cluster in contrast 1 and 2 for children and adults, see Figure S6.1 below.

Figure S6.1 Mean and SE of the parameter estimates of the cluster in the mPFC (peak: MNI(-8, 40, 12)) for correlation with health ratings in the natural condition and in the health condition in children and adults.

The results of this analysis show that children indeed have a negative correlation between health ratings and activation in the mPFC cluster in the health condition, and a positive (but not statistically significant) correlation during the natural condition, while for adults the opposite is true. Although children and adults do not differ in the correlation with health ratings in the natural and health condition, the interaction of natural vs. health and age group is where the difference between children and adults becomes apparent.

CHAPTER 7

DEVELOPMENT AND BODY MASS INVERSELY AFFECT CHILDREN'S BRAIN ACTIVATION IN INHIBITORY AREAS DURING FOOD CHOICE

van Meer, F., van der Laan, L. N., Eiben, G., Lissner, L., Wolters, M., Rach, S., Hermann, M., Erhard, P., Molnar, D., Orsi, G., Viergever, M. A., Adan, R. A., & Smeets, P. A. – On behalf of the I.Family Consortium

Submitted for publication

Abstract

Childhood obesity is a growing problem caused in part by unhealthy food choices. Food choices are based on a value signal encoded in the ventromedial prefrontal cortex. Self-control involves modulation of this signal by the dorsolateral prefrontal cortex (dlPFC). We determined the effects of development, body mass (BMI Cole score) and body mass history on the neural correlates of healthy food choice in children. 141 children (10-17y) performed a food choice task while being scanned with fMRI. During this task they considered the healthiness or the tastiness of the food or neither. Pubertal development correlated positively while body mass correlated negatively with dlPFC activation. Pubertal development, body mass and body mass change influenced the effect of health considerations on activation of areas involved in saliency. Younger children, children who gained weight and overweight children may be less sensitive to healthy eating interventions that rely on self-control or that call attention to health aspects of food.

7.1 Introduction

Childhood obesity is a growing problem[1]. In addition to a lack of physical activity, overconsumption is an important contributor to positive energy balance and thus weight gain[3]. Energy intake is determined by choices about when, how much and what to eat. To determine which factors may contribute to the development or maintenance of childhood obesity, we need to understand how these food choices come about in children, how this may change over development and how this is related to weight status.

Food choices are made in the brain, which integrates a multitude of neural and hormonal signals reflecting internal state and environmental factors[4]. In the decision-making process different aspects of the choice options are combined into a single value. This value reflects aspects relevant to the individual, such as taste, healthiness and the cost or effort required to obtain that food[88]. This assignment of value occurs in the ventromedial prefrontal cortex (vmPFC)[78-83]. Valuation activation in the vmPFC is strongly correlated with the tastiness of foods[80,81]. However, when dieters successfully make healthy choices, activity in the vmPFC is correlated with the healthiness of the foods, and vmPFC activity is modulated by the dorsolateral prefrontal cortex (dlPFC)[80]. Interestingly, when people who are not on a diet are asked to consider the healthiness of foods during their choice, their brain response and behavior mimics that of successful dieters: their vmPFC activation is correlated with the healthiness of the food, there is more connectivity with the dlPFC, and they make healthier choices[81]. This suggests that in adults, guiding attention towards health aspects facilitates healthier food choices by triggering dlPFC activation and enhancing connectivity between the dlPFC and vmPFC[81].

The neural mechanisms underlying food choice may be different in children since their prefrontal cortex (PFC) is not yet fully matured. The brain does not reach full maturity until 21 years of age and not all brain areas mature at the same rate. Between the age of 8 and the early 20s relatively larger changes

have been reported in the PFC compared with other brain regions (that mature earlier in development) for synaptogenesis[61], gray matter reduction[62], myelination increase[63], and resting level metabolism[64]. Areas in the PFC, such as the dlPFC, mediate the capacity to voluntarily inhibit desire for a short-term reward in favor of a (larger) long-term reward[65] and are thus important for self-control.

To our knowledge, there are only three studies on the neural correlates of food choice in children. These studies found that in children tastiness of foods greatly contributed to the decisions while healthiness did not[19,190,191]. In an earlier study we compared food choices between children (10-12 years) and adults and manipulated attention towards the health aspects of foods[191]. Overall, children chose fewer healthy foods than adults and had weaker dlPFC activation during choice. Furthermore, considering healthiness promoted healthier choices in both children and adults, but was accompanied by an opposing pattern of brain activation in the medial PFC. However, it remains unclear how these processes change as children develop and how this is related to body weight status.

The relationship between body mass and the neural correlates of food choice in children has not yet been examined to our knowledge. A small number of studies did examine brain responses to food cues in normal-weight and overweight children. Among several differences in neural activation in response to viewing foods[188], both higher and lower dlPFC activation has been reported in overweight compared with normal-weight children[11,71-73,152,184]. However, the age of the children examined varied greatly, which may explain the differences in findings, as pubertal development and weight may have independent or even interacting effects on the neural responses to food.

Body mass change rather than current body mass may have a stronger relationship with the neural correlates of food choice. Although a growing number of studies, mostly in adults, found that brain responses to food cues

can predict weight change (e.g.[11,12,17,192,193]), the effect of weight change (loss or gain) on brain responses to food has received less attention. After weight loss, adults had reduced precentral gyrus activation and increased inferior frontal gyrus (dlPFC) activation in response to food compared with non-food viewing[194]. Adolescents who gained body fat had a greater increase in putamen, precuneus and rolandic operculum activation in response to a milkshake cue[195]. Thus, weight loss may lead to higher activation in areas involved in self-control and lower activation in areas involved in reward processing while weight gain may lead to higher activation in the latter areas. We determined the effect of development, current body mass, and body mass history on the neural correlates of food choice in children, and examined whether these factors influence the effect of attending to the healthiness of food. We expected younger children, children with a higher body mass and children who gained weight to make fewer healthy choices and be less affected by considering the healthiness on their choice behavior. In line with this, we expected children further in pubertal development to have stronger activation in the dlPFC during food choice. Additionally, we expected children with a higher current body mass and children who gained weight to have less activation in the dlPFC and more activation in areas involved in reward processing, such as the striatum and the orbitofrontal cortex.

7.2 Results

7.2.1 Participants and procedures

141 children between 10 and 17 years (mean age: 13.4; 56.7% girls); see Table 7.1 for demographics) from the IDEFICS cohort were included in the study. In the IDEFICS baseline survey in 2007/2008, a population-based sample of 16,228 children aged 2 to 9.9 years from eight European countries was examined[21]. Follow-up examinations were conducted two years (IDEFICS) and six years later (I.Family study; 7105 children). The study design has been described in detail elsewhere[21].

Table 7.1 Demographic variables per center and total [a]

	Bremen (n =35, 18F)			Gothenburg (n =32, 19F)			Pecs (n =74, 43F)			Total (n =141, 80F)		
	Mean	Range	SD	Mean	Range	SD	Mean	Range	SD	Mean	Range	SD
Age	13.5	11-16	1.42	12.8	10-16	1.88	13.4	10-17	1.90	13.4	10-17	1.80
BMI Cole score	0.54	-0.99-2.87	0.93	0.29	-0.99-2.87	0.93	0.53	-2.83-3.03	1.14	0.48	-2.83-3.03	1.04
BMI Cole score change [b]	0.05	-0.17-0.27	0.09	0.04	-0.14-0.24	0.08	0.06	-0.21-0.39	0.14	0.05	-0.21-0.39	0.12
Tanner stage	1.96	1-3	0.53	1.81	1-3	0.71	2.06	1-3	0.73	1.98	1-3	0.69

[a] There were no statistically significant differences between the centers on the demographic variables.

[b] Difference in BMI Cole score between the scan day and the first measurement in the IDEFICS study divided by the time between measurements in years.

Children were instructed to refrain from eating and drinking (except water) for two hours prior to the scan session. During the scan session children made 150 food choices. For every food item they answered the question 'Would you like to eat this after the scan?' with 'yes' or 'no' using a button-box in three attention conditions: natural condition, health condition and taste condition. In the natural condition they were instructed to choose naturally, in the health condition they were instructed to consider the healthiness of the food and in the taste condition to consider the taste of the food (as in Hare, et al.[81]; see Figure 6.1 in Chapter 6). They were instructed that one choice would be selected and that they would receive the food of this choice if they said yes, and not receive it if they said no, independent of the condition the choice occurred in. After the scan they rated all food items on tastiness and healthiness (5-point scale).

7.2.2 Behavioral results

Before analyzing the fMRI data, we examined the food choice behavior. Four mixed-effects logistic regression models were estimated with choice outcome (yes or no; modeled as 1 and 0) as dependent variable and with health rating, taste rating, a dummy for health condition, a regressor for health condition interacted with health rating (HR*HC), a regressor for health condition interacted with taste rating (TR*HC), a dummy for taste condition, a regressor for taste condition interacted with health rating (HR*TC), and a regressor for taste condition interacted with taste rating (TR*TC) as predictors. Tanner stage, BMI Cole score (weight corrected for height, age and sex[196]), BMI Cole score change and two dummies for center were added as covariates. To assess weight change, the difference in BMI Cole score between the scan day and the first measurement in the IDEFICS study was calculated and divided by the time between measurements in years. The mean time between measurements was 7.24 years (SD 0.89).

To see which factors predicted choice outcome we assessed the effects of health and taste ratings and the different conditions controlled for Tanner stage, BMI Cole score and BMI Cole score change (Model 1, depicted as the green bars in Figure 7.1). There were positive effects of health ($b = 0.13$ $p = 1.76*10^{-7}$) and taste rating ($b = 1.46$, $p < 2*10^{-16}$) in the natural condition. There were significant interaction effects between health rating and health condition ($b = 0.30$, $p < 2*10^{-16}$), taste rating and health condition ($b = -0.39$ $p < 2*10^{-16}$), health rating and taste condition ($b = -0.11$ $p = 0.002$) and taste rating and taste condition ($b = 0.14$ $p = 0.004$). This means that overall children adhered to the condition instructions; when asked to consider the healthiness of the foods they chose more based on healthiness and less on taste, when asked to consider the taste of the foods they chose more based on taste and less based on healthiness, and when choosing naturally they chose mostly based on taste but healthiness predicted choice as well.

Since our main interests were the effects of development, body mass and body mass change, the next three models examined interactions between a covariate of interest (Tanner stage, BMI Cole score or BMI Cole score change) and the task- related predictors (Model 1) while controlling for the other covariates.

There was a main effect of Tanner stage on choice outcome (Figure 7.1, blue bars; b = -0.81, p = 0.0008), meaning that more physically mature children accepted foods less often. There were interactions between Tanner stage and taste rating in the natural condition (b = 0.19, p = 0.0001) and Tanner stage and health rating in the health condition (b = 0.10, p = 0.045). This indicates that more physically mature children were more responsive to health features during the health condition than less physically mature children. Additionally, taste was a stronger predictor of acceptance in the natural condition for children further in development, which was an unexpected finding.

There was no main effect of BMI Cole score on choice outcome (Figure 7.1, orange bars). However, there was an interaction effect between BMI Cole score and taste rating in the natural condition (b = -0.09, p = 0.009). This indicates that the taste rating of the accepted food was lower for children with a higher BMI Cole score, which is again not something that we had hypothesized.

There was a main effect of BMI Cole score change on choice outcome (Figure 7.1, yellow bars; b = 2.75, p = 0.035) which indicates that children with a higher positive weight change accepted foods more often than children who gained less weight or lost weight. There was an interaction effect between BMI Cole score change and taste rating in the natural condition (b = -1.12, p < $3.4*10^{-5}$) and BMI Cole score change and health rating in the health condition (b = -0.64, p = 0.015) and taste rating in the health condition (b = 0.74, p = 0.030). This indicates that in the natural condition the taste rating of the accepted food was lower for children with a higher positive weight

change. This is in line with the findings regarding development and body weight. Furthermore, children who gained more weight were less responsive to health features during health condition and more responsive to taste features during health condition than those who gained less weight or lost weight.

To examine the unexpected relationship between Tanner stage, BMI Cole score and BMI Cole score change and the strength of the effect of taste ratings on choice outcome in the natural condition we further examined the health and taste ratings of the food pictures. The taste and health rating of the foods presented in the choice task had an average weak positive correlation in children (mean r=0.15, SD 0.33). The average taste rating of the foods in the choice task (mean average rating 3.81, SD 0.42) was weakly negatively correlated with Tanner stage (r=-0.17, p=0.05), which indicates that children who were more physically mature liked the foods less. This may partially explain the negative relationship between Tanner stage and choice outcome, and between Tanner stage and taste ratings of accepted foods in the natural condition. The taste and health rating correlation per child did not correlate with Tanner stage (r=0.01, p=0.90).

Figure 7.1 Mean beta weights across participants for each regressor in the mixed-effects logistic regression model with Tanner stage, BMI Cole score and BMI Cole score change and center as covariates. Green bars: model with choice outcome as dependent variable controlled for Tanner stage, BMI Cole score and BMI Cole score change. Blue bars: model with choice outcome as dependent variable, interactions with Tanner stage modeled controlled for BMI Cole score and BMI Cole score. Orange bars: model with choice outcome as dependent variable, interactions with BMI Cole score modeled controlled for Tanner stage and BMI Cole score change. Yellow bars: model with choice outcome as dependent variable, interactions with BMI Cole score change modeled controlled for Tanner stage and BMI Cole score. HR = health rating TR = taste rating HC = health condition TC = taste condition. * = regressor is significantly different from 0 at $p < 0.05$. Error bars represent SE.

7.2.3 Imaging results

7.2.3.1 Choice outcome

To examine the effect of choice outcome (yes vs. no) and the effects of health cue condition and taste cue condition we estimated a subject level model with a regressor for choice event, a parametric modulator for yes/no, and a regressor for health cue condition and taste cue condition. Similar to the behavioral results, we first analyzed the overall neural responses during the food choice task by examining which areas showed more activation when accepting foods than rejecting foods independent of attention condition. To do so we performed a one-sample t-test with Tanner stage, BMI Cole score, BMI Cole score change and center as covariates on the group level. This test showed that yes > no positively modulated activation in the right precentral gyrus, right middle cingulum, left cerebellum, right calcarine sulcus, the medial orbital part of the superior frontal gyrus (vmPFC), right middle occipital gyrus/middle temporal gyrus, left supramarginal gyrus, left middle temporal gyrus and left middle frontal gyrus (dlPFC; Table 7.2). This demonstrates the involvement of the vmPFC and dlPFC in food choice in children.

Tanner stage correlated positively with brain activation in the contrast of yes > no in the left triangular part of the inferior frontal gyrus (dlPFC) and the left lingual gyrus (Figure 7.2). In this model BMI Cole score was negatively correlated with yes>no activation in the right transverse temporal gyrus/insula and the left triangular part of the inferior frontal gyrus (dlPFC). Thus, children with a higher BMI Cole score had weaker activation in the dlPFC. BMI Cole score change was positively correlated with yes>no activation in the bilateral calcarine sulcus/lingual gyrus (Figure 7.3). Thus, children with a higher positive weight change had stronger activation in areas involved in visual processing.

Table 7.2 Brain regions with significant activation in, or correlation with, yes vs. no contrast of the food choice task independent of condition

Brain region	Side	Cluster size	x	y	z	Z-score[a]
Precentral gyrus	R	1893	36	-21	54	Inf
Postcentral gyrus	R		42	-27	51	Inf
Postcentral gyrus	R		33	-33	57	Inf
Middle cingulum	R	1157	9	-21	45	Inf
Middle cingulum	R		6	-9	51	Inf
Middle cingulum	R		6	-3	45	Inf
Cerebellum 6	L	296	-6	-63	-12	Inf
Cerebellum 4-5	L		-9	-51	-15	Inf
Lingual gyrus	L		-6	-75	-3	7.59
Calcarine sulcus	R	109	12	-90	6	7.51
Medial orbital superior frontal gyrus	L	389	-12	39	-6	7
Medial orbital superior frontal gyrus	R/L		0	45	-9	6.74
Olfactory	R		3	12	-6	6.54
Middle occipital gyrus	R	297	42	-69	27	6.63
Middle temporal gyrus	R		57	-51	-3	6.14
Middle temporal gyrus	R		51	-54	3	5.81
Supramarginal gyrus	L	110	-63	-39	39	5.91
Supramarginal gyrus	L		-66	-24	24	3.45
Middle temporal gyrus	L	41	-63	-6	-9	4.69
Middle temporal gyrus	L		-54	-9	-15	4.41
Middle frontal gyrus	L	99	-27	27	39	4.64
Middle frontal gyrus	L		-21	12	51	3.98
Positive correlation with Tanner stage						
Inferior frontal gyrus triangular part	L	30	-36	12	24	4.38
Lingual gyrus	L/R	40	0	-57	12	3.52
Lingual gyrus	L		-9	-54	3	3.46
Negative correlation with BMI Cole score						
Transverse temporal gyrus	R	52	48	-12	6	4.40
Insula	R		42	-9	-9	3.33

Table 7.2 continued

Brain region	Side	Cluster size	x	y	z	Z-score[a]
Insula	R	60	42	6	-3	4.08
Superior temporal pole	R		51	9	-9	3.78
Insula	R		42	6	6	3.35
Inferior frontal gyrus triangular part	L	43	-45	36	27	3.86
Inferior frontal gyrus triangular part	L		-45	33	9	3.63
Middle frontal gyrus	L		-39	36	21	3.61
Positive correlation with BMI Cole score change						
Calcarine sulcus	R	121	24	-66	9	4.16
Lingual gyrus	R		24	-54	3	3.89
Lingual gyrus	R		9	-54	3	3.88
Calcarine sulcus	L	79	-24	-66	9	3.95
Lingual gyrus	L		-15	-57	0	3.85
Cerebellum 4-5	L		-6	-57	0	3.62

[a] Infinite Z score is due to the P value being so small that the Z score is effectively infinite.

Figure 7.2 Correlation of Tanner stage and BMI Cole score with modulation of choice activation by yes vs. no independent of condition. Blue circle denotes negative correlation with BMI Cole score and yellow circle denotes positive correlation with Tanner stage. Peaks listed are significant at $p < 0.05$ based cluster level corrections (individual voxel threshold $p = 0.001$, cluster extent threshold k = 30 voxels, 3x3x3 mm voxels).
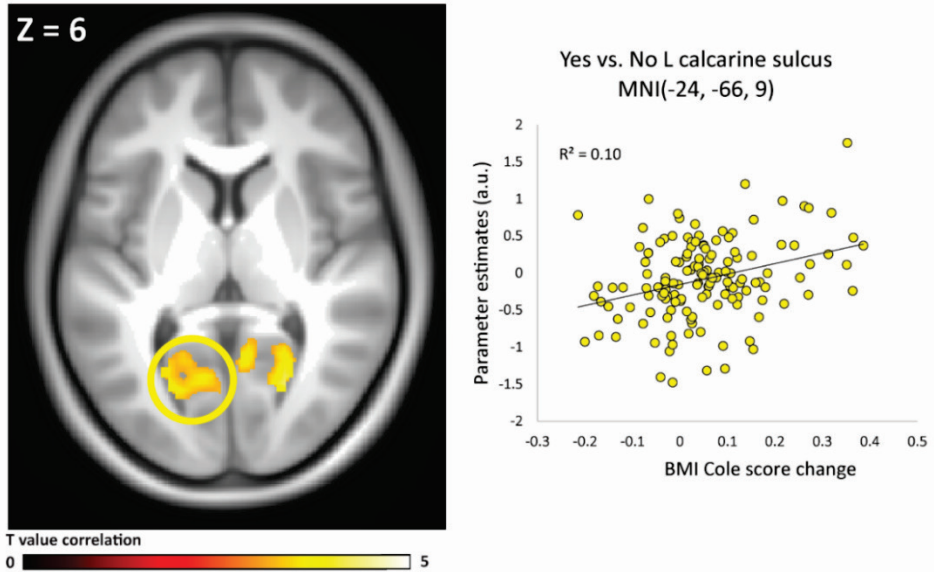
Figure 7.3 Correlation of weight (BMI Cole score) change with modulation of choice activation by yes vs. no independent of condition. BMI Cole score change is in BMI Cole score points per year. Yellow circle denotes positive correlation with BMI Cole score change. Peaks listed are significant at p < 0.05 based cluster level corrections (individual voxel threshold p = 0.001, cluster extent threshold k = 30 voxels, 3x3x3

7.2.3.2 Effect of health condition

To examine the effect of the health cue condition on the neural response to food choice we performed a one-sample t-test on the effect of health cue condition on choice with Tanner stage, BMI Cole score, BMI Cole score change and center as covariates. When considering the healthiness of the food during choice, children had more activation in the medial lingual gyrus/calcarine sulcus/superior occipital gyrus, and the left supplementary motor area/superior frontal gyrus (dlPFC) compared with the natural choice condition (Table 7.3). There was a negative correlation between the effect of health condition and Tanner stage in the bilateral calcarine sulcus and the medial lingual gyrus/cerebellum in this model. Also, there was a positive

correlation between the effect of health condition and BMI Cole score in the cerebellum. Thus, children with a higher BMI Cole score and who are less developmentally mature have higher activation in the cerebellum (Figure 7.4). Additionally, children who were less developmentally mature had stronger activation in areas involved in visual processing. Finally, there was a positive correlation between the effect of health condition and BMI Cole score change in the left inferior parietal gyrus, which means that children with a higher positive weight change had stronger activation in this area.

7.2.3.3 Effect of taste condition

Finally, we performed a one-sample t-test on the effect of taste cue condition on the neural response to food choice (again with Tanner stage, BMI Cole score, BMI Cole score change and center as covariates). We found no overall effects of taste condition, which suggest that when choosing naturally children mainly consider the taste of foods. There was a negative correlation between the effect of taste condition and BMI Cole score in the right middle frontal gyrus (dlPFC; Table 7.4). Thus, children with a higher BMI Cole score had weaker dlPFC activation during the taste compared to the natural condition. There were no correlations between the effect of taste condition and BMI Cole score change or Tanner stage in this model.

Table 7.3 Brain regions with significant activation in, or correlation with, health condition vs. natural condition contrast of the food choice task

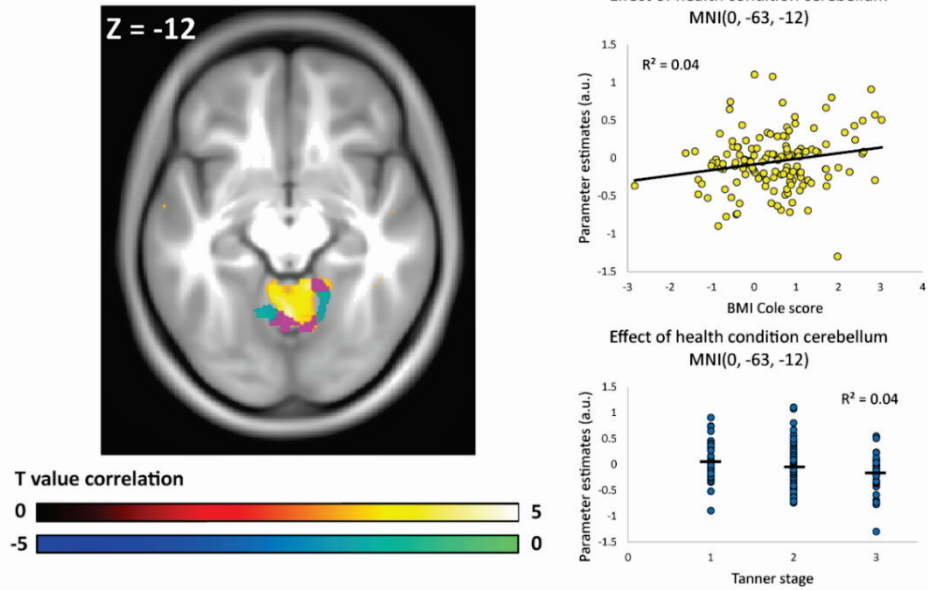| Brain region	Side	Cluster size	x	y	z	Z-score
Lingual gyrus	R	223	9	-87	-6	7.35
Calcarine sulcus	L		-6	-87	-9	6.93
Superior occipital gyrus	L		-9	-96	3	5.58
Supplemental motor area	L	125	-6	12	51	5.51
Superior frontal gyrus (dlPFC)	L		-12	33	54	5.44
Superior frontal gyrus (dlPFC)	L		-12	18	57	4.69
Negative correlation with Tanner stage						
Calcarine sulcus	R	36	21	-54	12	4.42
Lingual gyrus	R		15	-54	0	3.12
Lingual gyrus	R	115	15	-48	-9	4.15
Cerebellum 4-5	L		-6	57	-6	4.02
Vermis 6	R/L		0	-63	-12	3.68
Calcarine sulcus	L	33	-6	-66	15	3.23
Calcarine sulcus	L		-18	-72	21	3.43
Positive correlation with BMI Cole score						
Cerebellum	R	179	9	-45	-15	4.8
Vermis	R/L		0	-57	-12	4.59
Cerebellum	R		9	-66	-12	3.84
Positive correlation with BMI Cole score change						
Inferior parietal gyrus	L	43	-30	-45	45	4.08
Inferior parietal gyrus	L		-36	-51	54	3.49

Figure 7.4 Correlation of Tanner stage and BMI Cole score with the effect of health condition on choice activation. Purple voxels denote overlap between correlation with Tanner stage and BMI Cole score. Peaks listed are significant at p < 0.05 based cluster level corrections (individual voxel threshold p = 0.001, cluster extent threshold k = 30 voxels, 3x3x3 mm voxels).

Table 7.4 Brain regions with significant activation in, or correlation with, taste condition vs. natural condition contrast of the food choice task

Brain region	Side	Cluster size	x	y	z	Z-score
Negative correlation with BMI Cole score						
Middle frontal gyrus	R	43	42	48	15	4.22
Middle frontal gyrus	R		39	45	24	3.74

135

Additionally, there were no correlations with BMI Cole score, BMI Cole score change or Tanner stage and the effect of taste and health ratings on brain activation in the different conditions (see 7.5 Supplementary material for the model specification and results).

7.3 Discussion

In this study, we determined the effect of development, current body mass, and body mass history on the neural correlates of food choice in children, and whether these factors influence the effect of attending to the healthiness of food. We showed that children in an earlier pubertal stage or with greater weight gain had a smaller effect of considering the healthiness of food on their choice behavior. In line with this, children in an earlier developmental stage and children with a higher BMI had weaker activation in the dlPFC during food choice. Pubertal development, current BMI and BMI change influenced the effect of health considerations on activation in the cerebellum, visual processing areas and the inferior parietal gyrus. Our findings suggest that younger children and children who are (becoming) overweight have less activation in cognitive control areas during food choice, and are less responsive to attention manipulations intended to promote healthier choices.

Our behavioral analyses showed that children in an earlier pubertal stage and children who gained weight accepted more foods during the food choice task. Furthermore, children in an earlier pubertal stage and children who gained weight chose less healthy foods when considering the healthiness of the foods. In children in an earlier pubertal stage, children with higher BMI and with greater weight gain, taste ratings were less predictive of choice in the natural condition. The effect of developmental stage could be partially explained by the fact that there was a negative correlation between pubertal stage and average taste rating of the food. Furthermore, children who are developmentally younger or have a higher weight gain may discriminate less on taste; their taste criterion for saying yes may have been lower. This sheds

a different light on our findings regarding the smaller effect of the health cue in these children as well, since this could be caused by a less discriminative choice style overall in children with higher weight gain and/or in an earlier developmental stage.

We then examined the effect of pubertal development on the neural responses to food choice and found that children in a higher pubertal stage had stronger dlPFC activation in response to yes than no during food choice. This is in line with differences observed between children and adults in our previous study[191] and previous work that has found an increase in dlPFC activation and better performance during a task with choices involving a trade-off between immediate and delayed rewards and stronger vmPFC-dlPFC activation as a function of age[197]. To our knowledge, this is the first study to examine neural responses to food choice over pubertal development.

Additionally, children in later pubertal stages had increased activation in the lingual gyrus independent of condition. However, when considering the healthiness, children in later pubertal stages had less activation in the lingual gyrus and calcarine sulcus. Activation in these visual processing areas has consistently been found in food vs. non-food viewing, both in children and adults[8,70]. Furthermore, higher activation in these areas has been found when viewing high vs. low calorie food choice options[76], food vs. non-food logos and food vs. non-food commercials[198,199]. Since in all these instances the food stimuli were matched on visual properties these differences have been interpreted as reflecting differences in saliency[8,199], e.g. how much attention a stimulus attracts and how relevant it is. This would suggest that while for older children food is more salient in the natural condition, their saliency activation decreases in the health condition, while there is no such decrease in younger children. This is reflected in the choice behavior; children in an earlier pubertal stage chose less discriminately in the natural condition and do not show the same shift towards more healthy and less tasty food choices in the health condition.

During yes vs. no choices there was stronger activation in the dorsal cerebellum. Furthermore, dorsal cerebellum activation was positively correlated with both developmental stage and BMI during the health condition. Among other functions, the cerebellum has been shown to be involved in saliency and reward processing, in a meta-analysis on drug craving[200]. In line with this, the dorsal cerebellum has previously been found in a food choice study where it was more activated in response to high vs. low calorie choice options[76]. There is a growing interest in involvement of the cerebellum in cognitive function and emotion processing although its precise role is not yet clear[201]. Here it may the case that children in an earlier developmental stage and children with a higher BMI do not show the same decrease in saliency related activation in in the health condition as the other children. However, since we had no hypotheses about the cerebellum and it is not often found in decision-making studies we wish to be careful with our interpretation. More studies should be done to confirm our findings and to determine the role of the cerebellum in food choice.

We also examined the relationship between brain responses and body mass. DlPFC activation was not only related to developmental stage, but to body mass (BMI Cole score) as well. Children with a higher body mass had weaker activation in an area in the left dlPFC during food choice. This is in line with our previous study in which children with a higher BMI had lower dlPFC activation in response to watching unhealthy food pictures[184] and a study that found lower dlPFC activation in children with a higher BMI in response to palatable foods in a go/no-go task[152] (although the opposite has been found as well, see[71-73]). This suggests that children with a higher body mass engage this area involved in cognitive control less during food choice.

There was a negative correlation between current body mass and middle insula activation during food choice. The middle insula is involved in interoception[202]. In a meta-analysis about the difference between normal-weight and overweight adults the latter had less middle insula activation in

response to food images[10]. However a systematic review describes the opposite[9]. Food cue studies in children have found a positive correlation between BMI and middle insula activation[11,73] as did a study in adolescent girls using a food go/no-go task[152]. However, a recent study showed that middle insula activation is very task-dependent; when participants made judgements about the color of pictures there was more middle insula activation in food compared with non-food pictures, but when participants made judgements about the edibility of pictured objects there was no difference between food and non-food stimuli in the middle insula[203]. In summary, children with a higher body mass may have less activation in the middle insula during food choice, possibly due to lessened interoceptive awareness. Since insula activation seems very task-dependent, future studies should look further into this association.

Finally, we examined the correlation between weight history and neural responses to food choice. Children with greater weight gain had stronger activation in the bilateral calcarine sulcus/lingual gyrus, independent of condition. This could be due to a higher saliency of food for children who gained weight. This supports the previous finding that adolescents who gain body fat have higher activation in reward related areas[195] during food anticipation. Additionally, a correlation between lingual gyrus activation and BMI was found for adolescents when looking at food compared with non-food commercials[193]. Taken together, foods may be more salient to children who have gained weight, and this was accompanied with a less discriminative choice style. When considering the healthiness of foods, children with a greater positive weight change had increased inferior parietal gyrus activation. The inferior parietal gyrus is part of the decision-making network, and encodes subjective value[204]. It has been found to be consistently active during reward anticipation and salience in a meta-analysis[205], and its activation was found to be higher during the presentation of a product that was chosen later compared to products that were not chosen[13]. This could mean that for children who gained weight, activation in the part of the decision-making network that deals with the value, rewarding properties and

salience of food does not decrease or may even increase in response to health considerations. This was accompanied with a lower number of healthy choices for children who had gained weight. The incentive-sensitization theory of obesity[13,14] states that after repeated overeating episodes, conditioning occurs which leads to hyper-responsivity of regions that encode incentive salience of food cues[14]. Thus, perhaps as children repeatedly overeat and as consequence of that gain weight, they may become more attentive to foods. Our results suggest that this increased salience of foods may hamper the positive effects of attending to the healthiness of foods.

With cross-sectional measurements of body mass it is not possible to disentangle effects caused by the body's state itself or by the eating behavior that caused it. Since body mass change is caused by a positive or negative energy balance, it may be more directly related to diet than current body mass is. Therefore, future studies should examine the effects of body mass change on the neural correlates at food choice, to learn more about the possible mechanisms that drive weight gain.

We did not find a relationship between pubertal development, current body mass or body mass change and brain activation related to the health or taste ratings of the foods in the three conditions. This mirrors a study in adults where in a food choice task no differences were found between normal and overweight adults in the correlation between taste and health ratings and the neural correlates of food choice[206]. It seems that although there are differences in the basic yes vs. no choices and in the main effects of condition, the relative effects of the ratings on choice activation and on the interaction with health or taste condition are unrelated to pubertal development, current body mass or body mass change.

Our findings that developmentally younger children and children with a higher body mass have less activation in self-control areas support previous findings that reduced executive function predicts overweight in children[207,208]. This may mean that children who need help the most i.e.

younger children and children who are gaining weight or are already overweight, may be least susceptible to health interventions. In particular, weight loss interventions that rely on the ability of children to exhibit self-control, or interventions that steer attention towards health aspects of food, may be less effective in these children. Different types of interventions, for example based more on adaptations of the obesogenic environment, such as limiting the availability of options for unhealthy behavior, may bypass the need for self-control[209], and could thus be a more effective. Alternatively, interventions that are aimed at improving self-control in children may also positively affect their dietary choices[210]. Moreover, the indications of altered salience of food that was found in children earlier in development, children with a higher body mass and children who have gained weight, could possibly be targeted with tasks aimed to change implicit reactions to food to make them less salient[211].

To conclude, in children in earlier pubertal stages and children who have gained weight the positive effect of considering the healthiness of foods on their choices is smaller. Furthermore, children in earlier pubertal stages and children with a higher body mass have less activation in an area important for self-control during food choice. Pubertal development, current body mass and body mass change influence the effect of health considerations on brain areas involved in saliency. Thus, the effectiveness of interventions that rely on self-control or that call attention to health aspects of food may be lower in younger children, children who are gaining weight and overweight children.

7.4 Experimental procedures

7.4.1 Participants

The children included were part of the IDEFICS cohort which was followed-up during the I.Family study. In the IDEFICS (Identification and prevention of dietary- and lifestyle-induced health effects in children and infants) baseline

survey in 2007/2008, a population-based sample of 16,228 children aged 2 to 9.9 years from eight European countries (Belgium, Cyprus, Estonia, Germany, Hungary, Italy, Spain, Sweden) was examined. Follow-up examinations were conducted two years (IDEFICS) and six years (I.Family study; 7105 children) later; the study design has been described in detail elsewhere[21]. A subsample of 192 out of these 7105 children in I.Family centers in Hungary, Germany and Sweden were scanned with fMRI. Care was taken to prioritize the inclusion of overweight children and children who had gained weight to ensure enough variation in the sample. For the current analyses, data of 141 children was available.

Children were included if they matched MRI inclusion criteria. Exclusion criteria were, in addition to the general MRI exclusion criteria, being left-handed, having an eating disorder, having a food allergy, following a diet (medically prescribed or to lose weight), and having a gastro-intestinal disorder or a history of surgical or medical events that might significantly affect the study outcome. All children provided assent and their parents provided written informed consent before participation, as approved by the Scientific and Research Ethics Committee of the Medical Research Council of Pécs (TUKEB), the Ethics Committee of the University of Bremen and the Regional Ethics Committee of the University of Gothenburg. The data of 51 children could not be used for analysis, because of excess movement (n=11), a missing or incomplete log file of the choice task (n=22), missing food picture ratings (n=4), missing baseline weight and height (n=4) and lack of variety in the choices in the food choice task (n=10; see section 'Food choice fMRI task'). This leaves a final sample of 141 children (see Table 7.1 for demographics).

7.4.2 Procedure

Prior to the scan, children were familiarized with the procedure and the tasks through movie clips and a practice version of the task. Participants were instructed to refrain from eating and drinking (except water) for two hours

prior to the scan session. Participants' height and weight were measured. To assess weight change the difference in BMI Cole score (weight corrected for height, age and sex,[196]) between the scan day and the first measurement in the IDEFICS study was calculated and divided by the time between measurements in years. The mean time between measurements was 7.24 years (SD 0.89). Over the whole sample the mean BMI Cole score change was 0.05 BMI Cole score points per year (SD 0.12).

Subsequently they performed a food choice and a food viewing task while being scanned. Afterwards, participants were asked to rate the healthiness and tastiness of the foods from the food choice task (n=150) on a five point scale in a computerized rating task.

7.4.3 Food choice fMRI task

This experiment used a food choice task adapted from Hare et al.[81] (see Figure 6.1 in Chapter 6). In this task participants are shown a picture of a food item for 2 s and are given 2 s to indicate whether they wanted to eat the food after the experiment by pressing a left (yes) or right (no) button with their left or right thumb, as in[76]. 150 trials were presented. A trial was selected as the trial for which after the scan the child would receive the food if they said yes, or not would not receive the food if they said no. Trials were separated by a variable inter-trial interval between 1.4 – 4.2 s. The sequence of trials was optimized and counterbalanced using the Optseq2 algorithm (https://surfer.nmr.mgh.harvard.edu/optseq/), which provides temporal jitter to increase signal discriminability[189]. Participants made choices in three different attention conditions. In the health condition they were asked to consider the healthiness of the food, in the taste condition they were asked to consider the taste of the food and in the natural condition they were asked to consider the food as a whole and choose naturally. Critically, the instructions emphasized that participants should always choose what they preferred, regardless of the condition. The attention condition was kept constant for 10 consecutive trials, and the beginning of a new condition was

announced with a 5-s instruction screen. To remind children about which condition they were in a different colored dot was shown per condition, dark blue for natural condition, green for health condition and orange for taste condition. After receiving task instructions, participants completed 150 trials in the scanner; 50 in each condition. Each food was shown only once and the order of conditions was fully randomized for each participant. If participants said either yes to less than 10% of the items or no to less than 10% of the items, their data were excluded from the analyses (n=10). Stimuli were presented on a screen which was viewed via a mirror on the head coil or with goggles with use of the PRESENTATION software (Neurobehavioral Systems Inc., Albany, CA). Standardized food pictures from the Full4Health Image Collection were used[157]. The task was split up in 2 runs of 10 minutes with a 30 s break in between.

7.4.4 Behavioral data analysis

Four mixed-effects logistic regression models were estimated with choice outcome (yes or no) as dependent variable and with health rating, taste rating, a dummy for health condition, a regressor for health condition interacted with health rating (HR*HC), a regressor for health condition interacted with taste rating (TR*HC), a dummy for taste condition, a regressor for taste condition interacted with health rating (HR*TC), and a regressor for taste condition interacted with taste rating (TR*TC) as predictors. Given the specification of the model the natural condition served as baseline and health condition and taste condition measured differences from the natural condition. Tanner stage, BMI Cole score, BMI Cole score change and two dummies for center were added as covariates. The first model examined task effects controlled for the covariates. The other three models examined interactions between a covariate of interest (Tanner stage, BMI Cole score or BMI Cole score change) and the task- related predictors while controlling for the other covariates.

7.4.5 MRI data acquisition

MRI scanning was performed in the three centers on 3 tesla MRI scanners (Germany: Siemens Skyra; Hungary: Siemens Trio, Siemens AG, Erlangen, Germany; Sweden: GE Discovery MR750w, GE Healthcare Systems, Milwaukee, USA), using a 32-channel head coil (Germany, Sweden) or a 12-channel head coil (Hungary). A T_1-weighted structural image was acquired at a resolution of $1 \times 1 \times 1$ mm with 176 sagittal slices and a field of view of 256x256 (Germany: repetition time (*TR)* = 1900 ms, echo time (*TE)* = 2.07 ms, flip angle 9°; Hungary: TR = 2530 ms, TE = 3.37 ms, flip angle 7° ; Sweden: TR = 6.928 ms, TE = 2.53 ms, flip angle 7°). The functional scan was a T_2*-weighted gradient echo 2D-echo planar imaging sequence (TR/TE = 2000/30 ms, flip angle = 76°, 36 axial slices, voxel size = $3 \times 3 \times 3$ mm, at all sites).

7.4.6 fMRI data preprocessing

Data preprocessing and analysis was conducted with SPM12 (Wellcome Department of Imaging Neuroscience, London, United Kingdom) run with MATLAB R2015b (The Mathworks Inc, Natick, MA). After slice time correction using the middle slice as a reference, functional images were realigned to the first scan. After grey and white matter segmentation, study-specific anatomical template was created using Diffeomorphic Anatomical Registration using Exponentiated Lie algebra (DARTEL)[159], and after co-registration DARTEL was used to normalize this template and the functional scans to MNI space (Montreal Neurological Institute–International Consortium for Brain Mapping). The data were then smoothed with a 6 mm full width at half maximum isotropic Gaussian kernel. The Volume Artefact tool from ArtRepair (http://cibsr.stanford.edu/tools/human-brain-project/artrepair-software.html) was used to detect and repair anomalously noisy volumes. Volumes that moved more than 1mm/TR were repaired. 11 children were excluded from the analysis because too many volumes (>25%) had to be repaired.

7.4.7 Subject level analyses

Data were high-pass filtered with a cutoff of 128 s and statistical maps were generated for each participant by fitting a boxcar function to the time series, convolved with the canonical hemodynamic response function (HRF). First, we examined the neural correlates yes vs. no independent of condition. To test for effects of yes vs. no all the decision events (regressor 1; 2s) were modeled with yes and no as a parametric modulator, a regressor for health condition (regressor 2; modeled from the presentation of the condition instruction until the end of the block, 74s) and a regressor for taste condition (regressor 3; modeled from the presentation of the condition instruction until the end of the block, 74s). In this model, condition cue (regressor 4; 5 s), yes-no screen (regressor 5; 2 s) and realignment parameters were modeled as regressors of no interest. Parametric modulators were orthogonalized. The following contrasts were calculated: 1) decision events modulated by yes vs. no, 2) health condition effect, and 3) taste condition effect. Note that, given the specification of the model, contrasts 2 and 3 measure the change in average activity with respect to the natural control condition.

A second first-level model aimed to measure the effects of healthiness and tastiness ratings and their interactions with the conditions was estimated and is described in 7.5 Supplementary material.

7.4.8 Group level analyses

One-sample t-tests were used to examine effects for the contrasts calculated in the first level analyses. Tanner stage, BMI Cole score and BMI Cole score change were added in the same model as covariates. Two dummy variables for center were added as covariates of no interest.

The analysis was confined to gray matter with a gray matter mask (made by thresholding the mean of the DARTEL gray matter segmentations at a

probability of 0.5). A cluster level threshold of $p < 0.05$ corrected for multiple comparisons across the mask volume was derived using Monte Carlo simulations (10,000 iterations) of random noise distribution in the ROI mask using the 3dClustSim tool in AFNI version 16.2.07[112,113]. This approach combines an individual voxel probability threshold with a minimum cluster size to estimate the probability of a false positive. We used the 3DFWHMx tool in AFNI to estimate noise smoothness values of the data using the Auto-Correlation Function (ACF) option. The resulting 2-sided threshold was $p < 0.001$ with a cluster extent $k \geq 30$.

7.5 Supplementary material

7.5.1 Effects of taste and health ratings in the different conditions

As a last step in our imaging analyses we estimated another subject level model to examine the effect of taste and health ratings and the effects of health cue condition and taste cue condition. This model contained regressors for decision events with taste and health ratings as parametric modulators in the different conditions (see Subject level analysis below for details). The outcomes of this model largely replicate findings from previous studies using this task and model (see Table S7.1-S7.5)[191,212]. In this group of children (controlling for Tanner stage, BMI Cole score, BMI Cole score change and center) we find positive modulation by health rating during the health condition in the right opercular part of the inferior frontal gyrus and right middle frontal gyrus (dlPFC) and negative modulation by health rating in the left angular gyrus. There were no correlations with Tanner stage, BMI Cole score, BMI Cole score change and taste or health ratings in the different conditions.

7.5.2 Subject level analysis

A full model was estimated to look at the interaction of cue condition and rating (Model 2). This model had the following regressors: all decision events (regressor 1; 2s) with health (parametric modulator 1 of regressor 1) and taste rating (parametric modulator 2 of regressor 1) as parametric modulators, health condition (regressor 2; modeled from the presentation of the condition instruction until the end of the block, 74s), decision events in health condition (regressor 3; 2s) with taste rating (parametric modulator 1 of regressor 3) and health rating (parametric modulator 2 of regressor 3) as parametric modulators, taste condition (regressor 4; modeled from the presentation of the condition instruction until the end of the block, 74s), decision events in taste condition (regressor 5; 2s) with taste (parametric modulator 1 of regressor 5) and health rating (parametric modulator 2 of

regressor 5) as parametric modulators. The following contrasts were calculated: (1) modulation of decision activation in natural condition by taste rating, (2) modulation of decision activation in natural condition by health rating, (3) modulation of decision activation in health condition by taste rating, (4) modulation of decision activation in health condition by health rating, (5) modulation of decision activation in taste condition by health rating and (6) modulation of decision activation in taste condition by health rating. Note that because of the specification of this model, contrasts 3-6 denote the change in modulation by the ratings from the natural condition.

7.5.3 Imaging results

There were no correlations with Tanner stage, BMI Cole score or BMI Cole score change and any of the contrasts from model 2. There was no effect of taste rating in the health condition, the other effects are listed in the tables below.

Table S7.1 Effect of taste rating in natural condition

Brain region	Side	Cluster size	x	y	z	Z-score[a]
Positive effect of taste rating in natural condition						
Precentral gyrus	R	311	36	-21	54	Inf
Postcentral gyrus	R		42	-27	51	7.34
Postcentral gyrus	R		33	-36	57	5.73
Middle cingulum	R	226	6	-12	51	5.96
Posterior cingulum	L		-3	-33	33	4.58
Rolandic operculum	R	141	42	-21	21	5.29
Posterior insula	R		39	-12	15	3.99
Middle occipital gyrus	L	77	-39	-75	33	4.98
Middle temporal gyrus	L		-42	-63	15	3.52
Lingual gyrus	L	69	-15	-69	-9	4.94
Cerebellum 6	L		-15	-60	-12	4.22
Precuneus	L		-9	-51	-15	3.55
Calacarine sulcus	R	37	12	-90	3	4.55
Medial orbital superior frontal gyrus	L/R	59	0	42	-6	4.15
Medial orbital superior frontal gyrus	L		-6	39	-12	3.74
Medial orbital superior frontal gyrus	R		3	54	-6	3.18
Inferior parietal gyrus	L	42	-51	-45	48	4.07
Inferior parietal gyrus	L		-45	-51	45	4.03
Middle frontal gyrus	L	44	-24	15	57	3.98
Superior frontal gyrus	L		-21	24	42	3.74
Precuneus	R	111	15	-57	24	3.87
Precuneus	R		6	-63	27	3.75
Cuneus	L		-15	-57	21	3.63
Negative effect of taste rating in natural condition						
Postcentral gyrus	L	200	-39	-21	51	Inf
Postcentral gyrus	L		-51	-21	51	7.74
Postcentral gyrus	L		-36	-33	57	5.42
Cerebellum 4 5	R	174	15	-54	-18	6.31
Cerebellum 4 5	R		21	-48	-21	5.17
Cerebellum 4 5	R		9	-60	-9	4.91

Table S.7.1 continued

Brain region	Side	Cluster size	x	y	z	Z-score[a]
Supramarginal gyrus	L	32	-51	-24	21	4.8
Rolandic operculum	L		-42	-24	21	3.9

[a] Infinite Z score is due to the P value being so small that the Z score is effectively infinite.

Table S7.2 Effect of health rating in natural condition

Brain region	Side	Cluster size	x	y	z	Z-score
Positive effect of health rating in natural condition						
Middle temporal gyrus	L	62	-54	-69	9	4.3
Middle temporal gyrus	L		-54	-69	18	4.14
Middle temporal gyrus	L		-57	-63	0	3.4
Precuneus	L/R		0	-60	42	3.69
Precuneus	R		3	-60	33	3.66
Negative effect of health rating in natural condition						
Inferior occipital gyrus	R	190	27	-93	-6	6.72
Middle occipital gyrus	R		30	-78	15	5.05
Middle occipital gyrus	R		33	-78	15	4.02
Inferior occipital gyrus	L	107	-15	-96	-6	6.69
Middle occipital gyrus	L		-30	-87	3	4.46
Middle occipital gyrus	L		-27	-96	0	4.26
Insula	R	108	42	21	-6	4.44
Insula	R		36	9	-6	4.32
Inferior frontal gyrus triangular part	R		51	24	3	3.46
Precentral gyrus	L	63	-51	-3	48	4.38
Postcentral gyrus	L		-57	-3	39	3.46

Table S7.3 Effect of health rating in health condition

Brain region	Side	Cluster size	x	y	z	Z-score
Positive effect of health rating in health condition						
Inferior occipital gyrus	L	75	-15	-96	-6	6.27
Calcarine sulcus	L		-12	-87	0	5.06
Fusiform gyrus	L		-24	-81	-6	3.73
Calcarine sulcus	R	114	15	-93	0	5.53
Calcarine sulcus	R		24	-93	3	4.84
Lingual gyrus	R		24	-90	-9	4.8
Inferior frontal gyrus opercular part	R	115	45	12	21	5.2
Inferior frontal gyrus opercular part	R		51	15	27	4.56
Precentral gyrus	R	51	36	-18	54	4.1
Postcentral gyrus	R		33	-33	57	3.86
Postcentral gyrus	R		30	-27	51	3.54
Middle frontal gyrus	R	50	42	42	18	3.67
Inferior frontal gyrus triangular part	R		48	33	9	3.55
Inferior frontal gyrus triangular part	R		48	42	9	3.47
Negative effect of health rating in health condition						
Angular gyrus	L	49	-42	-60	24	4.09
Middle temporal gyrus	L		-54	-66	21	3.65

Table S7.4 Positive effect of health rating in taste condition

Brain region	Side	Cluster size	x	y	z	Z-score
Fusiform gyrus	R	77	30	-78	-9	4.61
Lingual gyrus	R		21	-78	-9	4.15
Inferior occipital gyrus	R		42	-75	-12	3.76
Middle frontal gyrus	R	49	33	51	24	3.72
Middle frontal gyrus	R		27	48	18	3.68
Middle frontal gyrus	R		36	42	18	3.44

Table S7.5 Negative effect of taste rating in taste condition

Brain region	Side	Cluster size	x	y	z	Z-score
Inferior parietal gyrus	L	41	-51	-48	48	3.99
Inferior parietal gyrus	L		-39	-57	51	3.31
Middle temporal gyrus	L	30	-54	-48	24	3.62
Angular gyrus	L		-48	-54	27	3.43
Middle temporal gyrus	L		-51	-45	12	3.32

CHAPTER 8

SUMMARY AND DISCUSSION

8.1 Summary

In this thesis we aimed to examine the neural processes underlying healthy eating behavior in normal- and overweight children and adults.

We started by synthesizing the existing literature regarding the effect of weight status and age on food decision-making in **Chapter 2**. The behavioral studies included in this review showed that in particular lower self-control ability may have an adverse effect on food choice in children and adults with overweight and obesity. Neuroimaging studies included in the review showed that overweight and obese individuals have altered neural responses to food in brain areas related to reward, self-control and interoception. We concluded that more research into the neural correlates of eating behavior may provide better insight in the effects of age and weight on the food decision-making process and provide targets for healthy eating interventions, which may be tuned to different subgroups like children or dieters.

Next, to identify the areas that have been most consistently reported to respond to food cues in children we performed a meta-analysis on children's neural responses to food and examined how these relate to those in adults in **Chapter 3**. We found that the brain areas most consistently activated in children by food viewing are part of the appetitive brain network and largely overlap with those found in adults, although there are some indications that children may not activate areas important for cognitive control. There was a relatively low concurrence across studies in most brain areas, likely due to between study variability, the wide age range in children, and the small number of studies, which limited to what extent the findings can be interpreted.

In **Chapter 4**, we compared brain responses to healthy and unhealthy foods between children and adults and examined how they relate to weight status.

We found that unhealthy foods might elicit more attention, both in children and in adults, as witnessed by activation in visual processing areas. Children had stronger activation while viewing unhealthy compared to healthy foods in areas involved in reward, motivation and memory. Furthermore, children activated the precentral gyrus, involved in motivation, stronger than adults did in response to unhealthy foods. Finally, children with a higher BMI had less activation in the dorsolateral prefrontal cortex (dlPFC), an area involved in inhibition, in response to unhealthy foods. This suggests children may be more likely to indulge when confronted with tempting food cues, especially when they are overweight.

In Chapter 4 we showed differences between preteen children and adults in the brain responses to healthy and unhealthy foods, but what happens to children's brain responses to food over adolescence remained unknown. Therefore, in **Chapter 5** we examined the effect of pubertal development on healthy and unhealthy food cue reactivity. Furthermore, this study assessed the effect of weight status and differences between children and adults. We found that activation in response to unhealthy foods in the precentral gyrus, involved in motivation, was negatively related to pubertal development. Adults had stronger activation in response to unhealthy foods than children in the dlPFC. Children, but not adults, with a higher BMI had lower dlPFC activation. Taken together, these findings suggest that activation in response to unhealthy food cues in areas involved in motivation declines over adolescence and that activation in areas involved in cognitive control in older children does not yet reach the level seen in adults.

In **Chapter 6**, we examined the neural correlates of food choice in children, and how considering healthiness affects neural activity during food decision-making and choice behavior. Furthermore, we examined differences between children and adults. We found that considering healthiness can promote healthier choices in both children and adults. However, in adults this was accompanied by a positive correlation between the perceived healthiness of foods and brain activation in the medial prefrontal cortex,

while in children there was a negative correlation between the perceived healthiness of foods and brain activation in this area. The overall lower absolute number of healthy choices in children suggests that they may not yet be geared to modify their choices away from their natural tendency to choose unhealthy tasty foods.

Subsequently, in **Chapter 7** we examined the effects of pubertal development, weight status and weight status history on the neural correlates of healthy food choice in children. In children earlier in pubertal development and children who gained weight the positive effect of considering the healthiness of foods on their choices was smaller. In addition, pubertal development was positively associated with dlPFC activation while weight status was negatively associated with dlPFC activation during choice. Pubertal development was negatively, and body mass and body mass change were positively related to activation when attending to the food's healthiness in areas involved in saliency, such as visual processing areas (lingual gyrus and calcarine sulcus), the cerebellum and inferior parietal gyrus. These findings suggest that the effectiveness of interventions that rely on self-control or that call attention to health aspects of food may be lower in younger children, children who gained weight and overweight children.

8.2 Discussion

8.2.1 Differences in neural processing of foods related to age and pubertal stage

As the first objective of this thesis we determined how the neural processes underlying healthy eating behavior develop over adolescence, and how they differ between children and adults. We found that there are differences between children and adults in the brain response to both healthy food viewing and choice, and that these differences may change over pubertal development. Our results suggest that younger children early in pubertal

development have a stronger response in the precentral gyrus while viewing unhealthy foods than adults, but that this difference diminishes over adolescence. When considering healthiness during food choice, in developmentally younger children there is a smaller decrease of activation in visual processing areas and areas involved in encoding salience (such as the calcarine sulcus, lingual gyrus and cerebellum) than there is in more developmentally mature children. Children had a weaker response in the dlPFC during food choice than adults, and this may improve over adolescence. In response to unhealthy food viewing children again had weaker dlPFC responses than adults, although in this case there were no indications that this improves over adolescence. Our study in Chapter 4 showed no differences in dlPFC activation in response to viewing unhealthy foods between children and adults. However, this could have been due to lower power because of the smaller sample size. The effects of differences in age and pubertal stage on the neural responses to food choice go hand in hand with the effects on their food choice behavior. Children make less healthy choices than adults and children earlier in pubertal development show a smaller effect of considering healthiness on their choice behavior. Thus, as children develop over adolescence their motivational response towards unhealthy foods may decline. Their response in inhibitory areas such as the dlPFC may increase over adolescence, particularly during food choice, although adults still activate this area more than children do. This could be due to the fact that the dlPFC does not fully mature until about 21 years of age[64]. The changes in brain response over pubertal development and the differences between children and adults are reflected in a change towards healthier choices as children mature, and a healthier choice style in adults. It may seem that the issue of different brain responses and associated behavior resolves itself over time as children grow up. However, if this leads to unhealthy eating habits or overweight during childhood, it can have far reaching consequences in adulthood, since dietary patterns mostly persist from adolescence into adulthood[213] and there is a heightened chance for an overweight child to become an overweight adult[2,214].

8.2.2 Differences in neural processing of foods related to weight status

The second objective of this thesis was to determine how body mass influences the neural processes underlying healthy eating behavior. Furthermore, we examined the effect of body mass history and to what extent the effect of body mass is age dependent. Children with a higher body weight for their height, age and gender had different neural processing of food than children with a lower body weight, while we found no evidence of such differences in adults. The association that we found between BMI and food-related brain responses is mostly in the dlPFC. Both in response to viewing unhealthy food and during food choice children with a higher BMI had a lower response in areas in the dlPFC. In addition to these differences in inhibitory areas we found lower middle insula activation during food choice in children with a higher body weight. Interestingly, in none of our studies did we find an effect of BMI on the neural processing of foods in adults. In Chapter 5 we should have had enough power to detect associations with BMI in adults as well as in children. We suggest that developmental differences may explain the different association with BMI in children compared with adults. Perhaps, when the dlPFC matures and functions optimally, it is less under the influence of other factors such as BMI. Another possible explanation of this finding is that differences in brain response related to BMI are not so much caused by the body mass itself but by the diet (positive energy balance) that caused it. Overweight adults could have gained weight at any point in their life, and have had a relatively stable level of overweight for a prolonged period prior to the study. Therefore, their diet at the moment of measurement might not differ much from that of normal-weight individuals with a stable weight. Children, on the other hand, have had less time to become overweight, and chances are larger that the current diet of an overweight child is more similar to a diet that would lead to weight gain. Thus, in children the association between eating behavior and BMI may be stronger, and this could explain why their brain responses in response to food cues and food choice are related to BMI while those of adults are not.

Our findings in children are consistent with previous studies in adults that compared brain responses to foods and non-foods in obese vs. normal-weight individuals and found reduced activation in the left dlPFC in obese individuals[10]. However, previous studies in overweight and obese children have reported both higher dlPFC activation (in response to food vs. non-food cues and anticipation for consumption)[71-73] and lower dlPFC activation (in response to palatable food in a go/no-go task)[152]. These different findings could be due to the different contrasts that were examined (food compared with non-food pictures, high calorie food compared with non-food pictures and in our case unhealthy compared with healthy foods pictures). The food vs. non-food contrast for example, is used to assess how individuals respond towards foods in general, irrespective of healthiness or calorie content. We have shown that dlPFC activation depends on the healthiness of the food cues, since self-control activation may be triggered in response to unhealthy foods but not to healthy foods. Therefore, it makes sense that comparing high calorie, generally regarded as unhealthy foods, with non-foods, comparing mixed high and low calorie foods with non-foods or comparing high calorie foods with low calorie (i.e. unhealthy vs. healthy) foods leads to different dlPFC findings. The age dependent effect of BMI on dlPFC activation during food viewing, which we identified in Chapter 5, could explain differences between studies as well. These differences in dlPFC response to food viewing may be predictive of real life behavior, as stronger left dlPFC activation predicted greater success in a weight loss program[17]. Furthermore, people who successfully maintained a healthy weight after weight loss had a stronger bilateral dlPFC response than obese people[215] and weaker activation in this area when obese women make choices between long-term vs. short-term rewards predicted future weight gain[186]. Our finding that children with a higher body mass had weaker brain responses related to cognitive control may increase their risk of weight gain, and hinder weight loss in children. In adults we did not find an effect of body mass on brain responses to food, which may be due to an age-dependent effect of body mass, or a less direct link between body mass and eating behavior in adults.

To our knowledge, we were the first to examine the effect of weight history (average 7 years) on the neural correlates of food choice and on food choice behavior. With cross-sectional measurements of body mass it is not possible to disentangle effects caused by the body's state itself or by the positive energy balance that caused it. Body mass change is caused by a positive or negative energy balance. Therefore, body mass change over a recent time period may be more directly related to diet than current body mass is. Furthermore, by combining weight history and current BMI, it is possible to infer more about the possible mechanisms that drive weight gain. We have shown that weight gain is related to stronger activation in visual processing areas during food choice, and to a smaller decrease of inferior parietal gyrus activation when considering healthiness. Behaviorally, children who had gained weight accepted more foods, and considering healthiness during food choice did not change their food choice behavior towards healthier choices as much as it did for children who had lost weight or whose weight remained stable. Thus, to children who have gained weight food may be more visually salient during choice. In addition, they were less selective in their choices (i.e. they accepted foods already at a lower level of tastiness). In children that lost weight or remained stable, activation in an area involved in encoding salience decreased when they were considering the healthiness of foods during choice. This decrease did not occur in children who gained weight. This was accompanied with a lower number of healthy choices for children who had gained weight. These findings can be interpreted in light of the incentive-sensitization theory of obesity[216,217]. This theory states that after repeated overeating episodes, conditioning occurs which leads to hyper-responsivity of regions that encode incentive salience of food cues[217]. Thus, as children repeatedly overeat and as consequence of that gain weight, they may become more attentive to cues that are associated with eating, such as food images, and this may be accompanied by a less selective choice style. Our results suggest that this increased salience of food cues may hamper the positive effects of attending to the healthiness of foods, since the brain responses in an area that encodes salience did not decrease in children who have gained weight, and they did not make as many healthy choices as

children who have lost weight or who remained stable. Longitudinal studies that measure the brain responses to food and food choice over time as children's weight changes could shed more light on the mechanisms behind weight gain in children.

8.2.3 Methodological considerations

The two paradigms used to measure the neural processing of food that have been used in this thesis each have their strengths and weaknesses. Food viewing paradigms have by far been used most, which means that new studies looking at food cue reactivity have a rich set of studies that they can compare their results with. However, the results of these studies have only moderate consistency as has been shown in Chapter 3 and other meta-analyses[8,70]. This could be due to a number of factors, such as different paradigms, stimuli, study populations and fasting time[8,70]. Furthermore, Pohl et al.[203] showed that brain activation in response to viewing food pictures depended on the type of instructions participants were given. Most studies use a 'passive viewing' instruction, like we did, with only the instruction to 'attend to the pictures because a food picture recall task will be done at the end of the session'. Since this task requires no response such as button presses, it may be less engaging than more active paradigms. Additionally, the fact that participants are not performing a task means that there is no behavioral data to support interpretation. This means that care should be taken not to over-interpret the results of food viewing studies in isolation of other evidence. However, as an upside, a growing number of studies has shown that brain responses to food viewing in areas related to reward and areas related to cognitive control can predict food choice[14] and future weight outcomes[11-13,15-17]. This suggests that the neural response to food cues is a useful indicator of vulnerability for weight gain or the chance on persistent weight loss.

In contrast to food viewing paradigms, food choice tasks have a behavioral component, which greatly aids interpretation. There are quite a number of

different tasks, such as single or dual food choice paradigms[13,74-81], willingness to pay for different foods[82-85], and auction paradigms[86]. This multitude of paradigms used in the field can hamper between study comparisons. In most of these studies, ratings (e.g. liking, healthiness, caloric content) for the different foods are collected before, after, or during the task. The availability of such ratings enables quantifying the relative influence of these factors on the choice outcome or neural response during choice. This makes food choice tasks valuable instruments to determine how food decisions come to pass in different groups of people. A downside of food choice tasks is that as participants are aware they are taking part in a study on healthy food behavior, social desirability may influence their food choice behavior. To our knowledge, only one study has directly linked the neural responses during a food choice task to real-life behavior. Medic et al.[206] performed a food choice fMRI study in normal-weight and overweight participants, followed by a buffet meal. The correlation between health ratings and vmPFC activation predicted the proportion of healthy foods consumed at the buffet in both normal-weight and overweight individuals. However, although the brain responses related to the tastiness and healthiness of the foods did not differ between the groups, overweight individuals ate a higher proportion unhealthy foods during the buffet. This underlines the importance of complementing neural measures with more naturalistic measures, such as food intake. Future food choice studies should add such eating behavior measures, if possible.

8.2.4 Future directions

Even though this work was part of a longitudinal cohort study, participants were only scanned once, so all the MRI measurements in this thesis were cross-sectional in nature. This means that causality cannot be inferred. A strength of this work is that we were able to include longitudinal body mass data to assess weight change, instead of just body mass at one time point. This allowed studying the effects of body mass change on the neural correlates of food choice and food choice behavior independent of current

body mass. Nevertheless, longitudinal MRI studies, where children are scanned repeatedly over adolescence or during a weight loss intervention, could provide more information regarding cause and effect. However, truly proving causality is challenging. Correlation over time cannot rule out that an additional variable explains both factors. An experimental design would give the strongest evidence of causation[218]. However, not all cause-effect relationships are easily experimented with. For example, manipulating body weight over a period of time and measuring brain responses has been proven feasible and may be easier than doing the reverse. Several studies have measured brain responses before and after weight loss interventions[17,219,220], and have shown changes in brain responses before and after weight loss in areas involved in reward and cognitive control. Even with these repeated fMRI measurements it is hard to comment on causality. If a certain brain response persists after weight loss, this does not necessarily mean it was there before weight gain. For example, formerly obese individuals differed from a group of lean individuals but not from a group of currently obese individuals in their insula response when tasting and consuming a meal[221]. However, this does not make the effects of being obese irreversible, as endocrine functioning can take years to normalize, if it even does so completely[222]. Studies where a weight gain intervention would be randomly assigned could shed more light on the neural adaptations to increasing fat and body mass, but setting ethical issues aside, willing subjects might be hard to find.

Attempts are being made to examine the reverse association; to manipulate brain responses over a period of time while measuring body mass. In a proof-of-concept study real-time fMRI feedback has been used to increase brain activation associated with healthy choices (vmPFC-dlPFC functional connectivity) in overweight and obese subjects[223]. Several studies have used repetitive transcranial magnetic stimulation (rTMS) and transcranial direct-current stimulation (tDCS) to stimulate dlPFC activation. Thus far, only single-session effects have been examined; most studies show a decrease in food craving, but the effects of dlPFC stimulation on food intake were inconsistent

and transient (see[224] for a review). Future studies in these emerging fields will prove whether fMRI feedback and rTMS and tDCS can be used to promote weight loss or prevent weight gain. Furthermore, molecular imaging techniques such as positron emission tomography (PET) could allow future studies to further examine body mass-related brain changes on a molecular scale, i.e. to assess brain metabolism and neurotransmitter functioning. In conclusion, enough open questions remain for future studies, but it remains to be seen whether a causal relationship between age, development, body mass, and brain responses can be established.

In addition to the use of longitudinal and experimental designs, the field would greatly benefit from the use of standardized paradigms and stimuli to aid between-study comparisons. The food pictures developed for the studies in this thesis are freely available for research purposes[157], as are different sets of food pictures suitable for neuroimaging such as[225] and[226]. Comparable study design additionally allows for data pooling, so that research questions for which there was not enough power in the original studies can be answered, or different populations of interest can be compared. Furthermore, replication studies using the same methods in different groups of participants, as we have done in Chapters 4 and 5 and Chapters 6 and 7, are necessary to test the robustness of findings. Lastly, using appropriately large sample sizes reduces the odds of false positive findings and inflated effect sizes in neuroscience[227].

8.2.5 Implications

In this thesis we identified several neural vulnerability factors that explain why children, in particular those who are overweight, may be more susceptible to engage in unhealthy eating behavior. In Chapter 7 we additionally show that children in earlier pubertal stages, children that have gained weight and children with a higher body weight are less responsive to health considerations during food choice. This suggests that the children who need help the most may be least susceptible to health interventions. In

particular weight loss interventions that rely on the ability of children to exert self-control, or interventions that steer attention towards health aspects of food, may be less effective in these children. Interventions that are aimed at improving self-control in children may positively affect their dietary choices[210]. Different types of interventions, based on adaptations of the obesogenic environment, such as limiting the availability of options for unhealthy behavior, may bypass the need for self-control[209]. These types of interventions would also be in line with our findings in regard to the brain response to viewing unhealthy foods. Instead of targeting children with marketing for unhealthy foods, why not protect them from things that are bad for their health, as we do with alcohol and cigarettes? In our current society, people's biological, psychological, social, and economic vulnerabilities are being triggered by the obesogenic environment, such that their ability to act in their long-term self-interest, i.e. staying healthy, is being undermined[228]. Government regulation in combination with efforts of industry and society, rather than trying to intervene at the level of individuals or their environments in isolation, may give the best approach to turn the tide on the childhood obesity epidemic. Because of the large scale of this type of intervention and the competing interests of the stakeholders involved, e.g. governments, food industry and consumers, this will not be an easy solution or quick fix. Moreover, regulatory action that is not supported by the general public and food industry has a large chance of being repealed (e.g. the large soda ban in New York[229] and the fat tax in Denmark[230]). Thus, the greatest challenge for the future may be to get the public opinion on board with such measures, which will make it in the best interest of food industry to follow suit.

8.3 Conclusion

Children had weaker brain responses related to cognitive control than adults when viewing unhealthy foods and when making food choices. Children who are overweight had even weaker responses in this area. This pattern of brain

activation was accompanied by more unhealthy choices in children. Taken together, children in general and overweight children in particular may be more vulnerable to unhealthy foods in their environment and less able to resist unhealthy choice options. The results presented in this thesis make a strong case for decreasing the marketing of unhealthy foods directed at children and adapting the food environment to promote healthier choices.

REFERENCES

1   Wang, Y. & Lobstein, T. I. M. Worldwide trends in childhood overweight and obesity. *Int. J. Pediatr. Obes.* **1**, 11-25, (2006).

2   Styne, D. M. Childhood and adolescent obesity: prevalence and significance. *Pediatr. Clin. North Am.* **48**, 823-854, (2001).

3   Blundell, J. E. & Cooling, J. Routes to obesity: phenotypes, food choices and activity. *Br. J. Nutr.* **83**, S33-S38, (2000).

4   Smeets, P. A., Charbonnier, L., van Meer, F., van der Laan, L. N. & Spetter, M. S. Food-induced brain responses and eating behaviour. *Proc. Nutr. Soc.* **71**, 511-520, (2012).

5   Frank, S. *et al.* Processing of food pictures: Influence of hunger, gender and calorie content. *Brain Res.* **1350**, 159-166, (2010).

6   LaBar, K. S. *et al.* Hunger selectively modulates corticolimbic activation to food stimuli in humans. *Behav. Neurosci.* **115**, 493, (2001).

7   Siep, N. *et al.* Hunger is the best spice: an fMRI study of the effects of attention, hunger and calorie content on food reward processing in the amygdala and orbitofrontal cortex. *Behav. Brain Res.* **198**, 149-158, (2009).

8   Van der Laan, L. N., De Ridder, D. T. D., Viergever, M. A. & Smeets, P. A. M. The first taste is always with the eyes: A meta-analysis on the neural correlates of processing visual food cues. *Neuroimage* **55**, 296-303, (2011).

9   Pursey, K. *et al.* Neural Responses to Visual Food Cues According to Weight Status: A Systematic Review of Functional Magnetic Resonance Imaging Studies. *Front. Nutr.* **1**, (2014).

10   Brooks, S. J., Cedernaes, J. & Schiöth, H. B. Increased Prefrontal and Parahippocampal Activation with Reduced Dorsolateral Prefrontal and Insular Cortex Activation to Food Images in Obesity: A Meta-Analysis of fMRI Studies. *PLoS One* **8**, e60393, (2013).

11   Yokum, S., Ng, J. & Stice, E. Attentional Bias to Food Images Associated With Elevated Weight and Future Weight Gain: An fMRI Study. *Obesity* **19**, 1775-1783, (2011).

12   Demos, K. E., Heatherton, T. F. & Kelley, W. M. Individual differences in nucleus accumbens activity to food and sexual images predict weight gain and sexual behavior. *J. Neurosci.* **32**, 5549-5552, (2012).

13   Van der Laan, L. N., De Ridder, D. T. D., Viergever, M. A. & Smeets, P. A. M. Appearance Matters: Neural Correlates of Food Choice and Packaging Aesthetics. *PLoS One* **7**, e41738, (2012).

14   Mehta, S. *et al.* Regional brain response to visual food cues is a marker of satiety that predicts food choice. *Am. J. Clin. Nutr.* **96**, 989-999, (2012).

15   Lawrence, N. S., Hinton, E. C., Parkinson, J. A. & Lawrence, A. D. Nucleus accumbens response to food cues predicts subsequent snack consumption in women and increased body mass index in those with reduced self-control. *Neuroimage* **63**, 415-422, (2012).

16   Killgore, W. *et al.* Cortico-limbic responsiveness to high-calorie food images predicts weight status among women. *Int. J. Obes.* **37**, 1435-1442, (2013).

17   Murdaugh, D. L., Cox, J. E., Cook III, E. W. & Weller, R. E. fMRI reactivity to high-calorie food pictures predicts short-and long-term outcome in a weight-loss program. *Neuroimage* **59**, 2709-2721, (2012).

18   Bruce, A. S., Martin, L. E. & Savage, C. R. Neural correlates of pediatric obesity. *Prev. Med.* **52, Supplement**, S29-S35, (2011).

19   Lim, S.-L. *et al.* The child brain computes and utilizes internalized maternal choices. *Nat Commun* **7**, (2016).

20   Casey, B., Giedd, J. N. & Thomas, K. M. Structural and functional brain development and its relation to cognitive development. *Biol. Psychol.* **54**, 241-257, (2000).

21   Ahrens, W. *et al.* Cohort Profile: The transition from childhood to adolescence in European children–how I. Family extends the IDEFICS cohort. *Int. J. Epidemiol.*, dyw317, (2016).

22   Wansink, B. & Sobal, J. Mindless Eating: The 200 Daily Food Decisions We Overlook. *Environ. Behav.* **39**, 106-123, (2007).

23   Nijs, I. M., Muris, P., Euser, A. S. & Franken, I. H. Differences in attention to food and food intake between overweight/obese and normal-weight females under conditions of hunger and satiety. *Appetite* **54**, 243-254, (2010).

24   Berridge, K. C. Food reward: Brain substrates of wanting and liking. *Neurosci. Biobehav. Rev.* **20**, 1-25, (1996).

25   Mela, D. J. Determinants of Food Choice: Relationships with Obesity and Weight Control. *Obes. Res.* **9**, 249S-255S, (2001).

26   Dressler, H. & Smith, C. Food choice, eating behavior, and food liking differs between lean/normal and overweight/obese, low-income women. *Appetite* **65**, 145-152, (2013).

27   Cox, D. N., Hendrie, G. A. & Carty, D. Sensitivity, hedonics and preferences for basic tastes and fat amongst adults and children of differing weight status: A comprehensive review. *Food Qual. Prefer.* **48, Part B**, 359-367, (2016).

28   Skinner, J. D., Carruth, B. R., Bounds, W. & Ziegler, P. J. Children's food preferences: a longitudinal analysis. *J. Am. Diet. Assoc.* **102**, 1638-1647, (2002).

29   de Wild, V. W. T., de Graaf, C. & Jager, G. Effectiveness of flavour nutrient learning and mere exposure as mechanisms to increase toddler's intake and preference for green vegetables. *Appetite* **64**, 89-96, (2013).

30   Boyland, E. J. & Halford, J. C. G. Television advertising and branding. Effects on eating behaviour and food preferences in children. *Appetite* **62**, 236-241, (2013).

31   Brown, K., McIlveen, H. & Strugnell, C. Nutritional awareness and food preferences of young consumers. *Nutrition & Food Science* **30**, 230-235, (2000).

32   Lumbers, M. & Raats, M. in *The Psychology of Food Choice* Vol. 3 *Frontiers in Nutritional Science* (eds Richard Shepherd & Monique Raats) 289 (CABI, 2006).

33   Schiffman, S. & Graham, B. Taste and smell perception affect appetite and immunity in the elderly. *Eur. J. Clin. Nutr.* **54**, S54, (2000).

34   MacLeod, C., Mathews, A. & Tata, P. Attentional bias in emotional disorders. *J. Abnorm. Psychol.* **95**, 15, (1986).

35   Mogg, K., Bradley, B. P., Hyare, H. & Lee, S. Selective attention to food-related stimuli in hunger: are attentional biases specific to emotional and psychopathological states, or are they also found in normal drive states? *Behav. Res. Ther.* **36**, 227-237, (1998).

36   Castellanos, E. H. *et al.* Obese adults have visual attention bias for food cue images: evidence for altered reward system function. *Int. J. Obes.* **33**, 1063-1073, (2009).

37   Werthmann, J. *et al.* Can(not) take my eyes off it: Attention bias for food in overweight participants. *Health Psychol.* **30**, 561-569, (2011).

38   Stroop, J. R. Studies of interference in serial verbal reactions. *J. Exp. Psychol.* **18**, 643, (1935).

39   Braet, C. & Crombez, G. Cognitive Interference Due to Food Cues in Childhood Obesity. *J. Clin. Child Adolesc. Psychol.* **32**, 32-39, (2003).

40   Wenzlaff, R. & Stultz, C. *A new method of assessing attentional bias in depression* in *Washington, DC: In Meeting of the American Psychological Society.* (1998).

41   Soetens, B. & Braet, C. Information processing of food cues in overweight and normal weight adolescents. *Br. J. Health Psychol.* **12**, 285-304, (2007).

42   Werthmann, J. *et al.* Food through the child's eye: An eye-tracking study on attentional bias for food in healthy-weight children and children with obesity. *Health Psychol.* **34**, 1123-1132, (2015).

43   Theeuwes, J., Atchley, P. & Kramer, A. F. Attentional control within 3-D space. *J. Exp. Psychol. Hum. Percept. Perform.* **24**, 1476, (1998).

44   Junghans, A. F., Hooge, I. T., Maas, J., Evers, C. & De Ridder, D. T. UnAdulterated—Children and adults' visual attention to healthy and unhealthy food. *Eating Behaviors* **17**, 90-93, (2015).

45   Weller, R. E., Cook, E. W., Avsar, K. B. & Cox, J. E. Obese women show greater delay discounting than healthy-weight women. *Appetite* **51**, 563-569, (2008).

46   Gunstad, J. *et al.* Elevated body mass index is associated with executive dysfunction in otherwise healthy adults. *Compr. Psychiatry* **48**, 57-61, (2007).

47   Cserjési, R., Luminet, O., Poncelet, A.-S. & Lénárd, L. Altered executive function in obesity. Exploration of the role of affective states on cognitive abilities. *Appetite* **52**, 535-539, (2009).

48   Nederkoorn, C., Smulders, F. T. Y., Havermans, R. C., Roefs, A. & Jansen, A. Impulsivity in obese women. *Appetite* **47**, 253-256, (2006).

49   Mostofsky, S. H. & Simmonds, D. J. Response inhibition and response selection: two sides of the same coin. *J. Cogn. Neurosci.* **20**, 751-761, (2008).

50   Fillmore, M. T. & Rush, C. R. Polydrug abusers display impaired discrimination-reversal learning in a model of behavioural control. *Journal of psychopharmacology* **20**, 24-32, (2006).

51   Logan, G. D. in *Inhibitory processes in attention, memory, and language* (eds Dale Dagenbach & Thomas H Carr) Ch. xiv, 189-239 (Academic Press, 1994).

52   Mazur, J. E. An adjusting procedure for studying delayed reinforcement. *Commons, ML.; Mazur, JE.; Nevin, JA*, 55-73, (1987).

53   Mischel, W., Ebbesen, E. B. & Raskoff Zeiss, A. Cognitive and attentional mechanisms in delay of gratification. *J. Pers. Soc. Psychol.* **21**, 204, (1972).

54   Robbins, T. W., Weinberger, D., Taylor, J. & Morris, R. Dissociating executive functions of the prefrontal cortex [and discussion]. *Philosophical Transactions of the Royal Society B: Biological Sciences* **351**, 1463-1471, (1996).

55   Casey, B. Beyond simple models of self-control to circuit-based accounts of adolescent behavior. *Annu. Rev. Psychol.* **66**, 295-319, (2015).

56   Barkin, S. L. The relationship between executive function and obesity in children and adolescents: a systematic literature review. *J. Obes.* **2013**, (2013).

57   Braet, C., Claus, L., Verbeken, S. & Van Vlierberghe, L. Impulsivity in overweight children. *Eur. Child Adolesc. Psychiatry* **16**, 473-483, (2007).

58   Cserjési, R., Molnár, D., Luminet, O. & Lénárd, L. Is there any relationship between obesity and mental flexibility in children? *Appetite* **49**, 675-678, (2007).

59   Schlam, T. R., Wilson, N. L., Shoda, Y., Mischel, W. & Ayduk, O. Preschoolers' Delay of Gratification Predicts their Body Mass 30 Years Later. *J. Pediatr.*, (2012).

60   Green, L., Myerson, J. & Ostaszewski, P. Discounting of delayed rewards across the life span: age differences in individual discounting functions. *Behav. Processes* **46**, 89-96, (1999).

61   Huttenlocher, P. R. & Dabholkar, A. S. Regional differences in synaptogenesis in human cerebral cortex. *J. Comp. Neurol.* **387**, 167-178, (1997).

62   Sowell, E. R., Thompson, P. M., Holmes, C. J., Jernigan, T. L. & Toga, A. W. In vivo evidence for post-adolescent brain maturation in frontal and striatal regions. *Nat. Neurosci.* **2**, 859-861, (1999).

63   Giedd, J. N. *et al.* Brain development during childhood and adolescence: a longitudinal MRI study. *Nat. Neurosci.* **2**, 861-863, (1999).

64   Booth, J. R. *et al.* Neural development of selective attention and response inhibition. *Neuroimage* **20**, 737-751, (2003).

65   Watanabe, J. *et al.* The human prefrontal and parietal association cortices are involved in NO-GO performances: an event-related fMRI study. *Neuroimage* **17**, 1207-1216, (2002).

66   Sowell, E. R. *et al.* Mapping cortical change across the human life span. *Nat. Neurosci.* **6**, 309-315, (2003).

67   Dagher, A. Functional brain imaging of appetite. *Trends Endocrinol. Metab.* **23**, 250-260, (2012).

68   Schachter, S. Obesity and Eating. *Science* **161**, 751-756, (1968).

69   Kennedy, J. & Dimitropoulos, A. Influence of feeding state on neurofunctional differences between individuals who are obese and normal weight: a meta-analysis of neuroimaging studies. *Appetite* **75**, 103-109, (2014).

70   van Meer, F., van der Laan, L. N., Adan, R. A. H., Viergever, M. A. & Smeets, P. A. M. What you see is what you eat: An ALE meta-analysis of the neural correlates of food viewing in children and adolescents. *Neuroimage* **104**, 35-43, (2015).

71   Davids, S. *et al.* Increased dorsolateral prefrontal cortex activation in obese children during observation of food stimuli. *Int. J. Obes.* **34**, 94-104, (2010).

72   Bruce, A. S. *et al.* Obese children show hyperactivation to food pictures in brain networks linked to motivation, reward and cognitive control. *Int. J. Obes.* **34**, 1494-1500, (2010).

73   Stice, E., Spoor, S., Bohon, C., Veldhuizen, M. G. & Small, D. M. Relation of reward from food intake and anticipated food intake to obesity: a functional magnetic resonance imaging study. *J. Abnorm. Psychol.* **117**, 924-935, (2008).

74   Grabenhorst, F., Schulte, F. P., Maderwald, S. & Brand, M. Food labels promote healthy choices by a decision bias in the amygdala. *Neuroimage*, (2013).

75   van der Laan, L. N., De Ridder, D. T., Charbonnier, L., Viergever, M. A. & Smeets, P. A. Sweet lies: neural, visual, and behavioral measures

reveal a lack of self-control conflict during food choice in weight-concerned women. *Front. Behav. Neurosci.* **8**, (2014).

76   van der Laan, L. N., de Ridder, D. T., Viergever, M. A. & Smeets, P. A. Activation in inhibitory brain regions during food choice correlates with temptation strength and self-regulatory success in weight-concerned women. *Front. Neurosci.* **8**, (2014).

77   Charbonnier, L., van der Laan, L. N., Viergever, M. A. & Smeets, P. A. M. Functional MRI of Challenging Food Choices: Forced Choice between Equally Liked High- and Low-Calorie Foods in the Absence of Hunger. *PLoS One* **10**, e0131727, (2015).

78   Litt, A., Plassmann, H., Shiv, B. & Rangel, A. Dissociating Valuation and Saliency Signals during Decision-Making. *Cereb. Cortex* **21**, 95-102, (2011).

79   Lim, S.-L., O'Doherty, J. P. & Rangel, A. The Decision Value Computations in the vmPFC and Striatum Use a Relative Value Code That is Guided by Visual Attention. *J. Neurosci.* **31**, 13214-13223, (2011).

80   Hare, T. A., Camerer, C. F. & Rangel, A. Self-control in decision-making involves modulation of the vmPFC valuation system. *Science* **324**, 646-648, (2009).

81   Hare, T. A., Malmaud, J. & Rangel, A. Focusing Attention on the Health Aspects of Foods Changes Value Signals in vmPFC and Improves Dietary Choice. *J. Neurosci.* **31**, 11077-11087, (2011).

82   Chib, V. S., Rangel, A., Shimojo, S. & O'Doherty, J. P. Evidence for a Common Representation of Decision Values for Dissimilar Goods in Human Ventromedial Prefrontal Cortex. *J. Neurosci.* **29**, 12315-12320, (2009).

83   Plassmann, H., O'Doherty, J. P. & Rangel, A. Appetitive and Aversive Goal Values Are Encoded in the Medial Orbitofrontal Cortex at the Time of Decision Making. *J. Neurosci.* **30**, 10799-10808, (2010).

84   Plassmann, H., O'Doherty, J. & Rangel, A. Orbitofrontal Cortex Encodes Willingness to Pay in Everyday Economic Transactions. *J. Neurosci.* **27**, 9984-9988, (2007).

85   Hare, T. A., O'Doherty, J., Camerer, C. F., Schultz, W. & Rangel, A. Dissociating the Role of the Orbitofrontal Cortex and the Striatum in the Computation of Goal Values and Prediction Errors. *J. Neurosci.* **28**, 5623-5630, (2008).

86   Linder, N. S. *et al.* Organic labeling influences food valuation and choice. *Neuroimage* **53**, 215-220, (2010).

87   Bettman, J. R., Luce, M. F. & Payne, J. W. Constructive consumer choice processes. *Journal of consumer research* **25**, 187-217, (1998).

88   Rangel, A. Regulation of dietary choice by the decision-making circuitry. *Nat. Neurosci.* **16**, 1717-1724, (2013).

89   Kang, M. J., Rangel, A., Camus, M. & Camerer, C. F. Hypothetical and Real Choice Differentially Activate Common Valuation Areas. *J. Neurosci.* **31**, 461-468, (2011).

90   Thorndike, A. N., Sonnenberg, L., Riis, J., Barraclough, S. & Levy, D. E. A 2-phase labeling and choice architecture intervention to improve healthy food and beverage choices. *Am. J. Public Health* **102**, 527-533, (2012).

91   Enax, L., Hu, Y., Trautner, P. & Weber, B. Nutrition labels influence value computation of food products in the ventromedial prefrontal cortex. *Obesity* **23**, 786-792, (2015).

92   Barnard, N. D. *et al.* Dietary and lifestyle guidelines for the prevention of Alzheimer's disease. *Neurobiol. Aging* **35, Supplement 2**, S74-S78, (2014).

93   Huerta, C. I., Sarkar, P. R., Duong, T. Q., Laird, A. R. & Fox, P. T. Neural bases of food perception: Coordinate-based meta-analyses of neuroimaging studies in multiple modalities. *Obesity* **22**, 1439-1446, (2014).

94   Holsen, L. M. *et al.* Neural mechanisms underlying food motivation in children and adolescents. *Neuroimage* **27**, 669-676, (2005).

95   Killgore, W. D. & Yurgelun-Todd, D. A. Body mass predicts orbitofrontal activity during visual presentations of high-calorie foods. *Neuroreport* **16**, 859-863, (2005).

96   Cascio, C. J. *et al.* Response of neural reward regions to food cues in autism spectrum disorders. *J. Neurodev. Disord* **4**, (2012).

97   Holsen, L. M. *et al.* Neural Mechanisms Underlying Hyperphagia in Prader-Willi Syndrome. *Obesity* **14**, 1028-1037, (2006).

98   Stice, E., Yokum, S., Bohon, C., Marti, N. & Smolen, A. Reward circuitry responsivity to food predicts future increases in body mass: moderating effects of DRD2 and DRD4. *Neuroimage* **50**, 1618-1625, (2010).

99   Casey, B. J. *et al.* Behavioral and neural correlates of delay of gratification 40 years later. *Proc. Natl. Acad. Sci. U. S. A.* **108**, 14998-15003, (2011).

100 Killgore, W. D. & Yurgelun-Todd, D. A. Developmental changes in the functional brain responses of adolescents to images of high and low-calorie foods. *Dev. Psychobiol.* **47**, 377-397, (2005).

101 Rubia, K. *et al.* Functional frontalisation with age: mapping neurodevelopmental trajectories with fMRI. *Neurosci. Biobehav. Rev.* **24**, 13-19, (2000).

102 Andreyeva, T., Kelly, I. R. & Harris, J. L. Exposure to food advertising on television: associations with children's fast food and soft drink consumption and obesity. *Econ. Hum. Biol.* **9**, 221-233, (2011).

103 Termini, R. B., Roberto, T. & Hostetter, S. Food Advertising and Childhood Obesity: A Call to Action for Proactive Solutions. *Minnesota Journal of Law, Science & Technology* **12**, 619-651, (2011).

104 Powell, L. M., Schermbeck, R. M. & Chaloupka, F. J. Nutritional Content of Food and Beverage Products in Television Advertisements Seen on Children's Programming. *Childhood Obesity* **9**, 524-531, (2013).

105 Eickhoff, S. B., Bzdok, D., Laird, A. R., Kurth, F. & Fox, P. T. Activation likelihood estimation meta-analysis revisited. *Neuroimage* **59**, 2349-2361, (2012).

106 Eickhoff, S. B. *et al.* Co-activation patterns distinguish cortical modules, their connectivity and functional differentiation. *Neuroimage* **57**, 938-949, (2011).

107 Eickhoff, S. B. *et al.* Coordinate-based activation likelihood estimation meta-analysis of neuroimaging data: A random-effects approach based on empirical estimates of spatial uncertainty. *Hum. Brain Mapp.* **30**, 2907-2926, (2009).

108 Turkeltaub, P. E. *et al.* Minimizing within-experiment and within-group effects in activation likelihood estimation meta-analyses. *Hum. Brain Mapp.* **33**, 1-13, (2012).

109 Sabatinelli, D. *et al.* Emotional perception: Meta-analyses of face and natural scene processing. *Neuroimage* **54**, 2524-2533, (2011).

110 Simmonds, D. J., Pekar, J. J. & Mostofsky, S. H. Meta-analysis of Go/No-go tasks demonstrating that fMRI activation associated with

response inhibition is task-dependent. *Neuropsychologia* **46**, 224-232, (2008).

111   Rubinstein, M. L., Luks, T. L., Dryden, W. Y., Rait, M. A. & Simpson, G. V. Adolescent Smokers Show Decreased Brain Responses to Pleasurable Food Images Compared With Nonsmokers. *Nicotine & Tobacco Research* **13**, 751-755, (2011).

112   Cox, R. W. AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. *Comput. Biomed. Res.* **29**, 162-173, (1996).

113   Forman, S. D. *et al.* Improved assessment of significant activation in functional magnetic resonance imaging (fMRI): use of a cluster-size threshold. *Magn. Reson. Med.* **33**, 636-647, (1995).

114   Beaver, J. D. *et al.* Individual differences in reward drive predict neural responses to images of food. *J. Neurosci.* **26**, 5160-5166, (2006).

115   Cornier, M.-A. *et al.* The Effects of Overfeeding on the Neuronal Response to Visual Food Cues in Thin and Reduced-Obese Individuals. *PLoS One* **4**, e6310, (2009).

116   Cornier, M.-A., Von Kaenel, S. S., Bessesen, D. H. & Tregellas, J. R. Effects of overfeeding on the neuronal response to visual food cues. *Am. J. Clin. Nutr.* **86**, 965-971, (2007).

117   Führer, D., Zysset, S. & Stumvoll, M. Brain Activity in Hunger and Satiety: An Exploratory Visually Stimulated fMRI Study. *Obesity* **16**, 945-950, (2008).

118   Killgore, W. D. S. *et al.* Cortical and limbic activation during viewing of high- versus low-calorie foods. *Neuroimage* **19**, 1381-1394, (2003).

119   Malik, S., McGlone, F., Bedrossian, D. & Dagher, A. Ghrelin modulates brain activity in areas that control appetitive behavior. *Cell Metab.* **7**, 400-409, (2008).

120   Malik, S., McGlone, F. & Dagher, A. State of expectancy modulates the neural response to visual food stimuli in humans. *Appetite* **56**, 302-309, (2011).

121   Miller, J. L. *et al.* Enhanced activation of reward mediating prefrontal regions in response to food stimuli in Prader–Willi syndrome. *J. Neurol. Neurosurg. Psychiatry* **78**, 615-619, (2007).

122   Rothemund, Y. *et al.* Differential activation of the dorsal striatum by high-calorie visual food stimuli in obese individuals. *Neuroimage* **37**, 410-421, (2007).

123   Schienle, A., Schäfer, A., Hermann, A. & Vaitl, D. Binge-Eating Disorder: Reward Sensitivity and Brain Activation to Images of Food. *Biol. Psychiatry* **65**, 654-661, (2009).

124   Simmons, W. K., Martin, A. & Barsalou, L. W. Pictures of Appetizing Foods Activate Gustatory Cortices for Taste and Reward. *Cereb. Cortex* **15**, 1602-1608, (2005).

125   Smeets, P. A. M., Kroese, F. M., Evers, C. & de Ridder, D. T. D. Allured or alarmed: Counteractive control responses to food temptations in the brain. *Behav. Brain Res.* **248**, 41-45, (2013).

126   Uher, R., Treasure, J., Heining, M., Brammer, M. J. & Campbell, I. C. Cerebral processing of food-related stimuli: Effects of fasting and gender. *Behav. Brain Res.* **169**, 111-119, (2006).

127   Albrecht, J. *et al.* The neuronal correlates of intranasal trigeminal function—an ALE meta-analysis of human functional brain imaging data. *Brain research reviews* **62**, 183-196, (2010).

128   Brooks, S. J. *et al.* Exposure to subliminal arousing stimuli induces robust activation in the amygdala, hippocampus, anterior cingulate, insular cortex and primary visual cortex: a systematic meta-analysis of fMRI studies. *Neuroimage* **59**, 2962-2973, (2012).

129   Gottfried, J. A., O'Doherty, J. & Dolan, R. J. Encoding predictive reward value in human amygdala and orbitofrontal cortex. *Science* **301**, 1104-1107, (2003).

130   Padoa-Schioppa, C. & Assad, J. A. The representation of economic value in the orbitofrontal cortex is invariant for changes of menu. *Nat. Neurosci.* **11**, 95-102, (2008).

131   Elliott, R., Dolan, R. J. & Frith, C. D. Dissociable functions in the medial and lateral orbitofrontal cortex: evidence from human neuroimaging studies. *Cereb. Cortex* **10**, 308-317, (2000).

132   Kringelbach, M. L. The human orbitofrontal cortex: linking reward to hedonic experience. *Nature reviews. Neuroscience* **6**, 691-702, (2005).

133   Gottfried, J. A. & Dolan, R. J. The nose smells what the eye sees: crossmodal visual facilitation of human olfactory perception. *Neuron* **39**, 375-386, (2003).

134   Veldhuizen, M. G. *et al.* Identification of human gustatory cortex by activation likelihood estimation. *Hum. Brain Mapp.* **32**, 2256-2266, (2011).

135   Killgore, W. D. & Yurgelun-Todd, D. A. Positive affect modulates activity in the visual cortex to images of high calorie foods. *Int. J. Neurosci.* **117**, 643-653, (2007).

136   Fan, J., McCandliss, B. D., Sommer, T., Raz, A. & Posner, M. I. Testing the efficiency and independence of attentional networks. *J. Cogn. Neurosci.* **14**, 340-347, (2002).

137   Lang, P. J. *et al.* Emotional arousal and activation of the visual cortex: an fMRI analysis. *Psychophysiology* **35**, 199-210, (1998).

138   Paus, T. Primate anterior cingulate cortex: where motor control, drive and cognition interface. *Nature Reviews Neuroscience* **2**, 417-424, (2001).

139   Hoogendam, J. M., Kahn, R. S., Hillegers, M. H. J., Van Buuren, M. & Vink, M. Different developmental trajectories for anticipation and receipt of reward during adolescence. *Dev. Cogn. Neurosci.* **6**, 113-124, (2013).

140   Bunge, S. A., Dudukovic, N. M., Thomason, M. E., Vaidya, C. J. & Gabrieli, J. D. E. Immature Frontal Lobe Contributions to Cognitive Control in Children: Evidence from fMRI. *Neuron* **33**, 301-311, (2002).

141   Van Leijenhorst, L. *et al.* What motivates the adolescent? Brain regions mediating reward sensitivity across adolescence. *Cereb. Cortex* **20**, 61-69, (2010).

142   Somerville, L. H. & Casey, B. Developmental neurobiology of cognitive control and motivational systems. *Curr. Opin. Neurobiol.* **20**, 236-241, (2010).

143   Stice, E., Yokum, S., Blum, K. & Bohon, C. Weight gain is associated with reduced striatal response to palatable food. *J. Neurosci.* **30**, 13105-13109, (2010).

144   Frankort, A. *et al.* The Craving Stops Before You Feel It: Neural Correlates of Chocolate Craving During Cue Exposure with Response Prevention. *Cereb. Cortex* **24**, 1589-1600, (2014).

145   Bennett, C. M. & Miller, M. B. How reliable are the results from functional magnetic resonance imaging? *Ann. N. Y. Acad. Sci.* **1191**, 133-155, (2010).

146   Gorgolewski, K. J., Storkey, A. J., Bastin, M. E., Whittle, I. & Pernet, C. Single subject fMRI test–retest reliability metrics and confounding factors. *Neuroimage* **69**, 231-243, (2013).

147   Luna, B., Padmanabhan, A. & O'Hearn, K. What has fMRI told us about the development of cognitive control through adolescence? *Brain Cogn.* **72**, 101, (2010).

148   Schlaggar, B. L. *et al.* Functional Neuroanatomical Differences Between Adults and School-Age Children in the Processing of Single Words. *Science* **296**, 1476-1479, (2002).

149   Hertz-Pannier, L. & Noulhiane, M. in *fMRI*   197-211 (Springer, 2013).

150   Ng, M. *et al.* Global, regional, and national prevalence of overweight and obesity in children and adults during 1980–2013: a systematic analysis for the Global Burden of Disease Study 2013. *The Lancet* **384**, 766-781, (2014).

151   Linné, Y., Barkeling, B., Rössner, S. & Rooth, P. Vision and eating behavior. *Obes. Res.* **10**, 92-95, (2002).

152   Batterink, L., Yokum, S. & Stice, E. Body mass correlates inversely with inhibitory control in response to food among adolescent girls: An fMRI study. *Neuroimage* **52**, 1696-1703, (2010).

153   di Pellegrino, G., Magarelli, S. & Mengarelli, F. Food pleasantness affects visual selective attention. *The Quarterly Journal of Experimental Psychology* **64**, 560-571, (2010).

154   Silvers, J. A. *et al.* Curbing Craving: Behavioral and Brain Evidence That Children Regulate Craving When Instructed to Do So but Have Higher Baseline Craving Than Adults. *Psychol. Sci.* **25**, 1932-1942, (2014).

155   Bie, H. A. *et al.* Preparing children with a mock scanner training protocol results in high quality structural and functional MRI scans. *Eur. J. Pediatr.* **169**, 1079-1085, (2010).

156   Durston, S. *et al.* Magnetic resonance simulation is effective in reducing anxiety related to magnetic resonance scanning in children. *J. Am. Acad. Child Adolesc. Psychiatry* **48**, 206, (2009).

157   Charbonnier, L., van Meer, F., van der Laan, L. N., Viergever, M. A. & Smeets, P. A. Standardized food images: A photographing protocol and image database. *Appetite* **96**, 166-173, (2016).

158   Drewnowski, A. The Nutrient Rich Foods Index helps to identify healthy, affordable foods. *Am. J. Clin. Nutr.* **91**, 1095S-1101S, (2010).

159   Ashburner, J. A fast diffeomorphic image registration algorithm. *Neuroimage* **38**, 95-113, (2007).

160   Mazaika, P., Whitfield-Gabrieli, S., Reiss, A. & Glover, G.*Artifact repair for fMRI data from high motion clinical subjects* in *annual meeting of the Organization for Human Brain Mapping.*   (2007).

161   Mazaika, P. *ArtRepair Instructions (v3, Mar. 2009)* <http://cibsr.stanford.edu/tools/human-brain-project/artrepair-software/artrepairinstructions.html> (2009).

162   Maldjian, J. A., Laurienti, P. J., Kraft, R. A. & Burdette, J. H. An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. *Neuroimage* **19**, 1233-1239, (2003).

163   Tzourio-Mazoyer, N. *et al.* Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage* **15**, 273-289, (2002).

164   Papies, E. K. Tempting food words activate eating simulations. *Front. Psychol.* **4**, 838, (2013).

165   Corbetta, M. & Shulman, G. L. Control of goal-directed and stimulus-driven attention in the brain. *Nature reviews. Neuroscience* **3**, 201-215, (2002).

166   Wallner-Liebmann, S. *et al.* Insulin and Hippocampus Activation in Response to Images of High-Calorie Food in Normal Weight and Obese Adolescents. *Obesity* **18**, 1552-1557, (2010).

167   Wittmann, B. C. *et al.* Reward-Related fMRI Activation of Dopaminergic Midbrain Is Associated with Enhanced Hippocampus-Dependent Long-Term Memory Formation. *Neuron* **45**, 459-467, (2005).

168   Kirsch, P. *et al.* Anticipation of reward in a nonaversive differential conditioning paradigm and the brain reward system:: an event-related fMRI study. *Neuroimage* **20**, 1086-1095, (2003).

169   Geliebter, A. *et al.* Responsivity to food stimuli in obese and lean binge eaters using functional MRI. *Appetite* **46**, 31-35, (2006).

170   Tiggemann, M. Body image across the adult life span: stability and change. *Body Image* **1**, 29-41, (2004).

171   Carter, C. S. & Van Veen, V. Anterior cingulate cortex and conflict detection: an update of theory and data. *Cognitive, Affective, & Behavioral Neuroscience* **7**, 367-379, (2007).

172   Fregni, F. *et al.* Transcranial direct current stimulation of the prefrontal cortex modulates the desire for specific foods. *Appetite* **51**, 34-41, (2008).

173   Menon, V., Adleman, N. E., White, C. D., Glover, G. H. & Reiss, A. L. Error-related brain activation during a Go/NoGo response inhibition task. *Hum. Brain Mapp.* **12**, 131-143, (2001).

174   Martens, M. J. *et al.* Increased sensitivity to food cues in the fasted state and decreased inhibitory control in the satiated state in the overweight. *Am. J. Clin. Nutr.*, (2013).

175   Stice, E., Spoor, S., Bohon, C. & Small, D. Relation between obesity and blunted striatal response to food is moderated by TaqIA A1 allele. *Science* **322**, 449-452, (2008).

176   Hofmann, J., Ardelt-Gattinger, E., Paulmichl, K., Weghuber, D. & Blechert, J. Dietary restraint and impulsivity modulate neural responses to food in adolescents with obesity and healthy adolescents. *Obesity*, n/a-n/a, (2015).

177   Lobstein, T. *et al.* Child and adolescent obesity: part of a bigger picture. *The Lancet* **385**, 2510-2520, (2015).

178   Pledge, E. Monitoring report. *EU Pledge*, (2013).

179   Peeler, C., Kolish, E., Enright, M. & Burke, C. The children's food & beverage advertising initiative in action. *A Report On Compliance And Implementation During 2009*, (2010).

180   Swinburn, B. *et al.* Strengthening of accountability systems to create healthy food environments and reduce global obesity. *The Lancet* **385**, 2534-2545, (2015).

181   Bryden, A., Petticrew, M., Mays, N., Eastmure, E. & Knai, C. Voluntary agreements between government and business—a scoping review of the literature with specific reference to the Public Health Responsibility Deal. *Health Policy* **110**, 186-197, (2013).

182   Hawkes, C. & Harris, J. L. An analysis of the content of food industry pledges on marketing to children. *Public Health Nutr.* **14**, 1403-1414, (2011).

183   Galbraith-Emami, S. & Lobstein, T. The impact of initiatives to limit the advertising of food and beverage products to children: a systematic review. *Obes. Rev.* **14**, 960-974, (2013).

184   van Meer, F. *et al.* Developmental differences in the brain response to unhealthy food cues: an fMRI study of children and adults. *Am. J. Clin. Nutr.* **104**, 1515-1522, (2016).

185   Ahrens, W. *et al.* The IDEFICS cohort: design, characteristics and participation in the baseline survey. *Int. J. Obes.* **35**, S3-S15, (2011).

186   Kishinevsky, F. I. *et al.* fMRI reactivity on a delay discounting task predicts weight gain in obese women. *Appetite* **58**, 582-592, (2012).

187   Westerterp, K. R. & Speakman, J. R. Physical activity energy expenditure has not declined since the 1980s and matches energy expenditures of wild mammals. *Int. J. Obes.* **32**, 1256-1263, (2008).

188   van Meer, F., Charbonnier, L. & Smeets, P. A. M. Food Decision-Making: Effects of Weight Status and Age. *Curr. Diab. Rep.* **16**, 1-8, (2016).

189   Dale, A. M. Optimal experimental design for event-related fMRI. *Hum. Brain Mapp.* **8**, 109-114, (1999).

190   Bruce, A. S. *et al.* The Influence of Televised Food Commercials on Children's Food Choices: Evidence from Ventromedial Prefrontal Cortex Activations. *J. Pediatr.* **177**, 27-32. e21, (2016).

191   van Meer, F., Van der Laan, L. N., Viergever, M. A., Adan, R. & Smeets, P. A. Considering healthiness promotes healthier choices but modulates medial prefrontal cortex differently in children compared with adults. *Neuroimage*, (under review).

192   Winter, S. R., Yokum, S., Stice, E., Osipowicz, K. & Lowe, M. R. Elevated reward response to receipt of palatable food predicts future weight variability in healthy-weight adolescents. *Am. J. Clin. Nutr.* **105**, 781-789, (2017).

193   Yokum, S., Gearhardt, A. N., Harris, J. L., Brownell, K. D. & Stice, E. Individual differences in striatum activity to food commercials predict weight gain in adolescents. *Obesity* **22**, 2544-2551, (2014).

194   Rosenbaum, M., Sy, M., Pavlovich, K., Leibel, R. L. & Hirsch, J. Leptin reverses weight loss–induced changes in regional neural activity responses to visual food stimuli. *J. Clin. Invest.* **118**, 2583-2591, (2008).

195   Stice, E. & Yokum, S. Gain in Body Fat Is Associated with Increased Striatal Response to Palatable Food Cues, whereas Body Fat Stability Is Associated with Decreased Striatal Response. *J. Neurosci.* **36**, 6949-6956, (2016).

196 Cole, T. J. & Lobstein, T. Extended international (IOTF) body mass index cut-offs for thinness, overweight and obesity. *Pediatr. Obes.* **7**, 284-294, (2012).

197 Steinbeis, N., Haushofer, J., Fehr, E. & Singer, T. Development of Behavioral Control and Associated vmPFC–DLPFC Connectivity Explains Children's Increased Resistance to Temptation in Intertemporal Choice. *Cereb. Cortex* **26**, 32-42, (2016).

198 Bruce, A. S. *et al.* Brain responses to food logos in obese and healthy weight children. *J. Pediatr.* **162**, 759-764. e752, (2013).

199 Gearhardt, A. N., Yokum, S., Stice, E., Harris, J. L. & Brownell, K. D. Relation of obesity to neural activation in response to food commercials. *Soc. Cogn. Affect. Neurosci.* **9**, 932-938, (2014).

200 Moulton, E. A., Elman, I., Becerra, L. R., Goldstein, R. Z. & Borsook, D. The Cerebellum and Addiction: Insights Gained from Neuroimaging Research. *Addict. Biol.* **19**, 317-331, (2014).

201 E, K.-H., Chen, S.-H. A., Ho, M.-H. R. & Desmond, J. E. A meta-analysis of cerebellar contributions to higher cognition from PET and fMRI studies. *Hum. Brain Mapp.* **35**, 593-615, (2014).

202 Avery, J. A. *et al.* Major depressive disorder is associated with abnormal interoceptive activity and functional connectivity in the insula. *Biol. Psychiatry* **76**, 258-266, (2014).

203 Pohl, T. M., Tempelmann, C. & Noesselt, T. How task demands shape brain responses to visual food cues. *Hum. Brain Mapp.*, (2017).

204 Levy, D. J. & Glimcher, P. W. The root of all value: a neural common currency for choice. *Curr. Opin. Neurobiol.*, (2012).

205 Liu, X., Hairston, J., Schrier, M. & Fan, J. Common and distinct networks underlying reward valence and processing stages: a meta-analysis of functional neuroimaging studies. *Neurosci. Biobehav. Rev.* **35**, 1219-1236, (2011).

206 Medic, N. *et al.* The presence of real food usurps hypothetical health value judgment in overweight people. *eneuro*, ENEURO. 0025-0016.2016, (2016).

207 Reyes, S., Peirano, P., Peigneux, P., Lozoff, B. & Algarin, C. Inhibitory control in otherwise healthy overweight 10-year-old children. *Int. J. Obes.* **39**, 1230-1235, (2015).

208 Wirt, T., Schreiber, A., Kesztyüs, D. & Steinacker, J. M. Early life cognitive abilities and body weight: cross-sectional study of the

association of inhibitory control, cognitive flexibility, and sustained attention with BMI percentiles in primary school children. *J. Obes.* **2015**, (2015).

209   Marteau, T. M., Hollands, G. J. & Fletcher, P. C. Changing Human Behavior to Prevent Disease: The Importance of Targeting Automatic Processes. *Science* **337**, 1492-1495, (2012).

210   Stautz, K., Pechey, R., Couturier, D.-L., Deary, I. J. & Marteau, T. M. Do Executive Function and Impulsivity Predict Adolescent Health Behaviour after Accounting for Intelligence? Findings from the ALSPAC Cohort. *PLoS One* **11**, e0160512, (2016).

211   Folkvord, F., Veling, H. & Hoeken, H. Targeting implicit approach reactions to snack food in children: Effects on intake. *Health Psychol.* **35**, 919, (2016).

212   Cherodath, S. & Singh, N. C. The influence of orthographic depth on reading networks in simultaneous biliterate children. *Brain Lang.* **143**, 42-51, (2015).

213   Mikkilä, V., Räsänen, L., Raitakari, O. T., Pietinen, P. & Viikari, J. Consistent dietary patterns identified from childhood to adulthood: The Cardiovascular Risk in Young Finns Study. *Br. J. Nutr.* **93**, 923-931, (2007).

214   Guo, S. S., Wu, W., Chumlea, W. C. & Roche, A. F. Predicting overweight and obesity in adulthood from body mass index values in childhood and adolescence. *The American Journal of Clinical Nutrition* **76**, 653-658, (2002).

215   McCaffery, J. M. *et al.* Differential functional magnetic resonance imaging response to food pictures in successful weight-loss maintainers relative to normal-weight and obese controls. *Am. J. Clin. Nutr.* **90**, 928-934, (2009).

216   Robinson, T. E. & Berridge, K. C. The psychology and neurobiology of addiction: an incentive–sensitization view. *Addiction* **95**, 91-117, (2000).

217   Burger, K. S. & Stice, E. Variability in reward responsivity and obesity: evidence from brain imaging studies. *Current drug abuse reviews* **4**, 182, (2011).

218   Parascandola, M. & Weed, D. L. Causation in epidemiology. *J. Epidemiol. Community Health* **55**, 905-912, (2001).

219   Bruce, A. S. *et al.* A comparison of functional brain changes associated with surgical versus behavioral weight loss. *Obesity* **22**, 337-343, (2014).

220   Deckersbach, T. *et al.* Pilot randomized trial demonstrating reversal of obesity-related abnormalities in reward system responsivity to food cues with a behavioral intervention. *Nutr. Diabetes* **4**, e129, (2014).

221   DelParigi, A. *et al.* Persistence of abnormal neural responses to a meal in postobese individuals. *Int. J. Obes.* **28**, 370-377, (2004).

222   Ochner, C. N., Barrios, D. M., Lee, C. D. & Pi-Sunyer, F. X. Biological mechanisms that promote weight regain following weight loss in obese humans. *Physiol. Behav.* **120**, 106-113, (2013).

223   Spetter, M. S. *et al.* Volitional regulation of brain responses to food stimuli in overweight and obese subjects: A real-time fMRI feedback study. *Appetite* **112**, 188-195, (2017).

224   Val-Laillet, D. *et al.* Neuroimaging and neuromodulation approaches to study eating behavior and prevent and treat eating disorders and obesity. *NeuroImage: Clinical* **8**, 1-31, (2015).

225   Blechert, J., Meule, A., Busch, N. A. & Ohla, K. Food-pics: an image database for experimental research on eating and appetite. *Front. Psychol.* **5**, (2014).

226   Miccoli, L. *et al.* Affective Pictures and the Open Library of Affective Foods (OLAF): Tools to Investigate Emotions toward Food in Adults. *PLoS One* **11**, e0158991, (2016).

227   Button, K. S. *et al.* Power failure: why small sample size undermines the reliability of neuroscience. *Nature reviews. Neuroscience* **14**, 365-376, (2013).

228   Roberto, C. A. *et al.* Patchy progress on obesity prevention: emerging examples, entrenched barriers, and new thinking. *The Lancet* **385**, 2400-2409, (2015).

229   Barnhill, A. & King, K. F. Ethical agreement and disagreement about obesity prevention policy in the United States. *International journal of health policy and management* **1**, 117, (2013).

230   Bødker, M., Pisinger, C., Toft, U. & Jørgensen, T. The rise and fall of the world's first fat tax. *Health Policy* **119**, 737-742, (2015).

SAMENVATTING

De prevalentie van obesitas bij kinderen neemt bijna overal ter wereld toe. De kans dat een kind met overgewicht een volwassene met overgewicht wordt is veel groter dan deze kans voor een kind met een normaal gewicht. Daarom is preventie van groot belang. Gewichtstoename, en dus overgewicht en obesitas, wordt grotendeels veroorzaakt door overconsumptie, wat gedreven wordt door voedselkeuzes. Deze beslissingen over wat, wanneer en hoeveel te eten, worden gemaakt in de hersenen. De hersenen integreren de neurale en hormonale signalen die de interne toestand van het lichaam en de omgeving reflecteren. Het is van cruciaal belang om te begrijpen hoe de hersenen op voedsel in de omgeving reageren en hoe voedselkeuzes in de hersenen worden gemaakt, zodat de neurale processen die ten grondslag liggen aan ongezond eetgedrag opgehelderd kunnen worden. Deze kennis kan nieuwe benaderingen bieden voor het voorkomen van obesitas bij kinderen en voor interventies gericht op het stimuleren van een gezond eetpatroon.

Functionele Magnetische Resonantie Imaging (fMRI) is een niet-invasieve onderzoekstechniek die het mogelijk maakt om te meten welke delen van de hersenen actief worden wanneer een bepaalde taak wordt uitgevoerd. In het domein van voedsel-gerelateerde hersenreacties is fMRI vooral gebruikt om hersenresponsen op voedselprikkels en tijdens voedselkeuze te onderzoeken. Van deze aspecten zijn de neurale reacties op voedselprikkels, zoals de aanblik, de geur en de smaak van voedsel, het meest onderzocht. De meeste fMRI studies laten foto's van voedsel aan deelnemers zien. De manier waarop de hersenen reageren op afbeeldingen van voedsel varieert binnen en tussen individuen. Sommige hersengebieden reageren bijvoorbeeld anders op (bepaalde soorten) voedsel tijdens honger dan tijdens verzadiging. Ook zijn er verschillen gevonden tussen mensen met overgewicht en mensen met een normaal gewicht in de reactie op voedsel in hersengebieden die betrokken zijn bij beloning, zelfbeheersing en interoceptie. Interessant genoeg is gebleken dat interindividuele variatie in de hersenrespons op voedselprikkels, met name in gebieden betrokken bij beloning en cognitieve controle, toekomstige gewichtstoename bij vrouwelijke adolescenten en

volwassenen, voedselkeuze, snackgedrag, lichaamsgewicht en succes in een afvalprogramma kan voorspellen. Ondanks het wereldwijde probleem van obesitas bij kinderen is er slechts een handvol studies uitgevoerd die de neurale reactiviteit op voedsel bij kinderen heeft onderzocht. Bovendien zijn er nauwelijks studies die kinderen en volwassenen direct hebben vergeleken. Gezien het verband tussen hersenreacties op voedselprikkels en toekomstige gewichtsuitkomsten is het belangrijk om te weten hoe deze hersenreacties zich ontwikkelen als kinderen ouder worden.

Naast de hersenresponsen op voedselprikkels hebben we ook onderzoek gedaan naar voedselkeuze. Het maken van voedselkeuzes lijkt meer op echt eetgedrag en daarom is het relevant om te onderzoeken hoe deze keuzes tot stand komen in de hersenen. De neurale respons tijdens voedselkeuze zou mogelijk kunnen verklaren wat ervoor zorgt dat gezonde keuzes gemakkelijk te maken zijn voor sommige personen, maar moeilijker voor anderen.

Onze verwachting was dat voedsel-gerelateerde hersenactivatie bij kinderen zou verschillen van die van volwassenen, aangezien de hersenen van kinderen nog in ontwikkeling zijn. Dit geldt in het bijzonder voor de prefrontale cortex (PFC), een van de hersengebieden die als laatste rijpt en die betrokken is bij de controle van gedrag en de remming van impulsen.

Het doel van dit proefschrift was het onderzoeken van de neurale reacties op het bekijken van gezond en ongezond voedsel en de neurale reacties tijdens voedselkeuze, bij kinderen en volwassenen van normaal gewicht en met overgewicht.

in **Hoofdstuk 2** hebben we de bestaande literatuur over het effect van de gewichtsstatus en leeftijd op voedselkeuzes gesynthetiseerd. De gedragsstudies in dit overzichtsartikel laten zien dat in het bijzonder een lager vermogen tot zelfcontrole een nadelig effect kan hebben op de voedselkeuze bij kinderen en volwassenen met overgewicht en obesitas. fMRI studies opgenomen in dit artikel toonden aan dat personen met

overgewicht en obesitas andere neurale reacties hebben op voedsel in hersengebieden die betrokken zijn bij beloning, zelfcontrole en interoceptie, dan personen van normaal gewicht. We concluderen dat meer onderzoek naar de neurale responsen op eetgedrag beter inzicht kan geven in de effecten van leeftijd en gewicht op het voedselkeuzeproces. Dit zou tevens handvatten kunnen bieden voor interventies om gezond eten te stimuleren, die afgestemd zouden kunnen worden op verschillende subgroepen zoals kinderen en mensen die willen afvallen.

in **Hoofdstuk 3** hebben we een meta-analyse uitgevoerd op de neurale responsen op voedsel in kinderen en deze vergeleken met die in volwassenen, om de gebieden te identificeren die het meest consistent reageren op voedselprikkels bij kinderen. We vonden dat de hersengebieden die het meest consistent geactiveerd werden bij kinderen tijdens het bekijken van eten, deel uitmaken van het eetlust-gerelateerde hersennetwerk. Deze gebieden overlappen grotendeels met de gebieden die bij volwassenen gevonden zijn, hoewel er enkele aanwijzingen waren dat kinderen gebieden belangrijk voor cognitieve controle minder activeren. In de meeste hersengebieden was er relatief weinig overlap tussen studies, waarschijnlijk door de variatie tussen studies, het brede leeftijdsbereik van de onderzochte kinderen en het kleine aantal studies, wat de mate waarin de bevindingen gegeneraliseerd kunnen worden beperkt.

In **Hoofdstuk 4** vergeleken we hersenresponsen op gezond en ongezond voedsel tussen kinderen en volwassenen en onderzochten we hoe deze betrekking hebben op de gewichtsstatus. We vonden dat ongezond voedsel meer aandacht trekt, zowel bij kinderen als bij volwassenen, zoals bleek uit de activatie van visuele hersengebieden. Kinderen hadden sterkere reacties tijdens het kijken naar ongezond vergeleken met gezond voedsel in gebieden die betrokken zijn bij beloning, motivatie en geheugen. Bovendien activeerden kinderen de precentrale gyrus, die betrokken is bij motivatie, sterker dan volwassenen in reactie op ongezond voedsel. Tenslotte reageerden kinderen met een hogere BMI minder sterk op ongezond voedsel

in de dorsolaterale prefrontale cortex (dlPFC), een gebied wat bij zelfcontrole betrokken is. Dit suggereert dat kinderen meer kans hebben om toe te geven aan hun verlangens wanneer ze geconfronteerd worden met verleidelijke voedselprikkels, vooral als ze overgewicht hebben.

In Hoofdstuk 4 lieten we de verschillen zien tussen kinderen en volwassenen in de hersenreacties op gezond en ongezond voedsel, maar konden we niet bekijken wat hiermee gebeurt tijdens adolescentie. Daarom hebben we in **Hoofdstuk 5** het effect van puberteitsontwikkeling op de hersenreacties op gezonde en ongezonde voedselcues onderzocht. Bovendien bekeken we in deze studie het effect van de gewichtsstatus en de verschillen tussen kinderen en volwassenen. We vonden dat activatie in reactie op ongezond voedsel in de precentrale gyrus, die betrokken is bij motivatie, negatief was gerelateerd aan puberteitsontwikkeling. Volwassenen hadden sterkere reacties op ongezond voedsel dan kinderen in de dlPFC. Kinderen, maar niet volwassenen, met een hogere BMI hadden lagere dlPFC activatie. Samengenomen suggereren deze bevindingen dat de activatie in reactie op ongezonde voedselprikkels in motivatiegebieden afneemt tijdens de puberteitsontwikkeling. Bovendien lijkt de activatie in gebieden die betrokken zijn bij cognitieve controle bij oudere kinderen nog niet het niveau van volwassenen te bereiken.

In **Hoofdstuk 6** hebben we de neurale respons tijdens voedselkeuze bij kinderen onderzocht en hoe het overwegen van de gezondheid de neurale activiteit tijdens de voedselkeuze en voedselkeuzegedrag beïnvloedt. Daarnaast hebben we de verschillen tussen kinderen en volwassenen onderzocht. We vonden dat aandacht besteden aan de gezondheid tijdens keuze gezondere keuzes bevordert bij zowel kinderen als volwassenen. Bij volwassenen ging dit echter gepaard met een positieve correlatie tussen de waargenomen gezondheid van voedsel en hersenactivatie in de mediale prefrontale cortex, terwijl er bij kinderen een negatieve correlatie was tussen de waargenomen gezondheid van voedsel en hersenactivatie in dit gebied.

Het lagere aantal gezonde keuzes bij kinderen suggereert dat ze nog niet in staat zijn af te wijken van hun neiging om ongezond, lekker eten te kiezen.

Vervolgens hebben we in **Hoofdstuk 7** de effecten van puberteitsontwikkeling, gewichtsstatus en gewichtsverandering op de neurale correlaten van gezonde voedingskeuzes bij kinderen onderzocht. Bij kinderen vroeger in de puberteitsontwikkeling en kinderen die aangekomen waren was het positieve effect van het overwegen van de gezondheid van voedsel op hun keuzes kleiner. Bovendien was puberteitsontwikkeling positief geassocieerd met dlPFC activatie, terwijl de gewichtsstatus negatief was geassocieerd met dlPFC activatie tijdens de keuze. Activatie in onder meer visuele verwerkingsgebieden (linguale gyrus en calcarine sulcus), het cerebellum en de inferieure pariëtale gyrus was negatief gerelateerd aan puberteitsontwikkeling en positief gerelateerd aan lichaamsmassa en verandering van lichaamsgewicht. Deze bevindingen suggereren dat de effectiviteit van interventies die zich richten op zelfcontrole of die aandacht vragen voor de gezondheidsaspecten van voedsel, lager zou kunnen zijn bij jongere kinderen, kinderen die zijn aangekomen en kinderen met overgewicht.

Samenvattend hadden kinderen verminderde hersenreacties gerelateerd aan zelfcontrole vergeleken met volwassenen bij het bekijken van ongezond voedsel en bij het maken van voedselkeuzes. Kinderen met overgewicht hadden zelfs nog lagere responsen in dit gebied. Dit patroon van hersenactivatie ging in kinderen gepaard met meer ongezonde keuzes. Derhalve kunnen kinderen over het algemeen en kinderen met overgewicht in het bijzonder, kwetsbaar zijn voor ongezond voedsel in hun omgeving en minder in staat zijn om ongezonde keuzemogelijkheden te weerstaan. De resultaten die in dit proefschrift worden gepresenteerd vormen een sterk argument voor het verminderen van de marketing van ongezonde voedingsmiddelen gericht op kinderen en het aanpassen van de voedselomgeving om gezondere keuzes te bevorderen.

ACADEMIC ACHIEVEMENTS

Journal publications

1 **van Meer, F.**, van der Laan, L. N., Viergever, M. A., Adan, R. A., & Smeets, P. A. (2017). Considering healthiness promotes healthier choices but modulates medial prefrontal cortex differently in children compared with adults. NeuroImage, 159, 325-333.

2 **van Meer, F.**, van der Laan, L. N., Charbonnier, L., Viergever, M. A., Adan, R. A., & Smeets, P. A. (2016). Developmental differences in the brain response to unhealthy food cues: an fMRI study of children and adults. The American Journal of Clinical Nutrition, 104, 1515-1522.

3 Sultson, H., **van Meer, F.**, Sanders, N., van Elburg, A. A., Danner, U. N., Hoek, H. W., Adan, R.A. & Smeets, P. A. (2016). Associations between neural correlates of visual stimulus processing and set-shifting in ill and recovered women with anorexia nervosa. Psychiatry Research: Neuroimaging, 255, 35-42.

4 **van Meer, F.,** Charbonnier, L., & Smeets, P. A. M. (2016). Food Decision-Making: Effects of Weight Status and Age. Current Diabetes Reports, 16, 1-8.

5 Charbonnier, L., **van Meer, F.**, van der Laan, L. N., Viergever, M. A., & Smeets, P. A. (2016). Standardized food images: A photographing protocol and image database. Appetite, 96, 166-173.

6 Sanders, N., Smeets, P. A., van Elburg, A. A., Danner, U. N., **van Meer, F.,** Hoek, H. W., & Adan, R. A. (2015). Altered food cue processing in chronically ill and recovered women with Anorexia Nervosa. Frontiers in Behavioral Neuroscience, 9, 46.

7 **van Meer, F.,** van der Laan, L. N., Adan, R. A., Viergever, M. A., & Smeets, P. A. (2015). What you see is what you eat: An ALE meta-analysis of the neural correlates of food viewing in children and adolescents. NeuroImage, 104, 35-43.

8 Dingemans, A. E., Danner, U. N., Donker, J. M., Aardoom, J. J., **van Meer, F.,** Tobias, K., van Elburg, A.A. & van Furth, E. F. (2014). The effectiveness of cognitive remediation therapy in patients with a severe or enduring

eating disorder: a randomized controlled trial. Psychotherapy and Psychosomatics, 83, 29-36.

9 Danner, U. N., Evers, C., Sternheim, L., **van Meer, F.,** van Elburg, A. A., Geerets, T. A., Breteler, L.M.T. & de Ridder, D. T. (2013). Influence of negative affect on choice behavior in individuals with binge eating pathology. Psychiatry research, 207, 100-106.

10 Smeets, P. A., Charbonnier, L., **van Meer, F.,** van der Laan, L. N., & Spetter, M. S. (2012). Food-induced brain responses and eating behaviour. The Proceedings of the Nutrition Society, 71, 511-520.

11 Danner, U. N., Sanders, N., Smeets, P. A. M., **van Meer, F.,** Adan, R. A., Hoek, H. W., & van Elburg, A. A. (2012). Neuropsychological weaknesses in anorexia nervosa: Set-shifting, central coherence, and decision making in currently ill and recovered women. International Journal of Eating Disorders, 45, 685-694.

Conference abstracts (first author)

1 van Meer, F., van der Laan, L. N., Eiben, G., Lissner, L., Wolters, M., Rach, S., Hermann, M., Erhard, P., Molnar, D., Orsi, G., Viergever, M. A., Adan, R. A., & Smeets, P. A. Associations between body weight, development and brain responses to unhealthy foods, Society for the Study of Ingestive Behavior meeting, 2017.

2 van Meer, F., van der Laan, L. N., Eiben, G., Lissner, L., Wolters, M., Rach, S., Hermann, M., Erhard, P., Molnar, D., Orsi, G., Viergever, M. A., Adan, R. A., & Smeets, P. A. The effect of development, body weight and body weight change on brain responses during food choice in children, Society for the Study of Ingestive Behavior meeting, 2017.

3 van Meer, F., van der Laan, L. N., Eiben, G., Lissner, L., Wolters, M., Rach, S., Hermann, M., Erhard, P., Molnar, D., Orsi, G., Viergever, M. A., Adan, R. A., & Smeets, P. A. The effect of development, body weight and body weight change on brain responses during food choice in children, Netherlands Association for the Study of Obesity, 2017.

4   van Meer, F., van der Laan, L. N., Charbonnier, L., Viergever, M. A., Adan, R. A., & Smeets, P. A. Considering health aspects during food choice modulates medial PFC activation in children and promotes healthier choices, Society for the Study of Ingestive Behavior meeting, 2016.

5   van Meer, F., van der Laan, L. N., Charbonnier, L., Viergever, M. A., Adan, R. A., & Smeets, P. A. Considering health aspects during food choice modulates medial PFC activation in children and promotes healthier choices, Dutch Neuroscience meeting, 2016.

6   van Meer, F., van der Laan, L. N., Charbonnier, L., Viergever, M. A., Adan, R. A., & Smeets, P. A. The neural correlates of healthy and unhealthy food viewing and food choice in children and adults, 1st Leipzig International Meeting for Interdisciplinary Obesity Research, 2015.

7   van Meer, F., van der Laan, L. N., Charbonnier, L., Viergever, M. A., Adan, R. A., & Smeets, P. A. The neural correlates of healthy and unhealthy food viewing and food choice in children and adults, Organization for Human Brain Mapping, 2015.

8   van Meer, F., van der Laan, L. N., Charbonnier, L., Viergever, M. A., Adan, R. A., & Smeets, P. A. The neural correlates of healthy and unhealthy food viewing and food choice in children and adults, Dutch Neuroscience meeting, 2015.

9   van Meer, F., van der Laan, L. N., Charbonnier, L., Viergever, M. A., Adan, R. A., & Smeets, P. A. The neural correlates of healthy and unhealthy food viewing and food choice in children and adults, British Feeding and Drinking Group, 2015.

10   van Meer, F., van der Laan, L. N., Charbonnier, L., Adan, R. A., Viergever, M. A., & Smeets, P. A. What you see is what you eat: An ALE meta-analysis of neural correlates of food viewing in children, Organization for Human Brain Mapping, 2014.

11   van Meer, F., van der Laan, L. N., Charbonnier, L., Adan, R. A., Viergever, M. A., & Smeets, P. A. What you see is what you eat: An ALE meta-analysis of neural correlates of food viewing in children, Endo-Neuro-Psycho meeting, 2014.

12   van Meer, F., Smeets, P.A., Danner, U.N., Adan, R.A., van den Hout, M.A. Imaging mental imagery in anorexia nervosa, Eating Disorders Research Society, 2012.

ABOUT THE AUTHOR

Floor van Meer was born on August 17th 1986 in Heidelberg, Germany. She completed her Psychology bachelor at Utrecht University. During her master Clinical and Health Psychology at the same university she completed her thesis and internship at Altrecht Eating Disorders Rintveld. She finished her MSc-thesis on neuropsychological weaknesses in chronic Anorexia Nervosa patients, as part of a larger fMRI study of brain responses to food stimuli and relationships with cognitive functioning in AN. After her MSc degree she worked as a research assistant on different projects with Rintveld and the Experimental Psychopathology department of the Utrecht University. In 2012 she started as a PhD candidate at the Nutritional Neuroscience lab, part of the Image Sciences Institute of the University Medical Center Utrecht. The results of the work during her PhD are described in this thesis.