Neural dynamics of food reward : the influence of body weight, cue exposure and attention

Chapter 6

Summary and general discussion

In the research presented in this dissertation, the influence of the type of attention (i.e., unbiased viewing without prior instructions versus focus on taste) on the neural processing of high-calorie palatable food cues was investigated in healthy-weight and overweight participants **(Chapter 2)**. Furthermore, the effect of food-cue palatability on brain reward activity in overweight and healthy-weight participants was examined **(Chapter 3)**. In addition, the effects of cue exposure with response prevention both on subjective craving for chocolate and on neural responses to chocolate pictures versus neutral pictures were measured over the course of a one-hour session **(Chapter 4)**. Finally, the predictive characteristics of both subjective craving and brain activation in response to chocolate cues on subsequent chocolate intake were investigated **(Chapter 5)**.

Research questions and summary of the main findings

The aim of the first functional magnetic resonance imaging (fMRI) study **(Chapter 2)** was to examine reward-related brain activity in overweight versus healthy-weight participants in response to high-calorie palatable food pictures in two conditions of attention. In a first condition participants viewed the pictures without prior instructions (*unbiased viewing*), while in a *taste imagination* condition participants were instructed to imagine the taste of the presented food pictures. We predicted that neural activation in brain reward regions would be greater in overweight participants than in healthy-weight ones and that this effect would be most pronounced during unbiased viewing, because the group difference during taste imagination might be less pronounced as all participants would be evaluating food palatability and might thus show resembling brain reward activity. To this end, an event-related design was used, in which palatable and unpalatable high-calorie and low-calorie food pictures were presented during these two conditions (unbiased viewing vs. taste imagination). Participants were satiated overweight and healthy-weight women.

A whole-brain analysis was conducted, testing the group (overweight vs. healthy weight) × condition (unbiased viewing vs. taste imagination) interaction on the neural response specifically to high-calorie palatable food stimuli. This analysis resulted in 14 functional regions of interest (fROIs) involved in food reward processing. Neural activation in these regions was greater in the overweight participants than in the healthy-weight ones during the taste imagination condition. During unbiased viewing, contrary to our expectations, the opposite pattern was observed: in the overweight participants the activation in reward regions was reduced compared to healthy-weight participants. This group × condition interaction was specific to high-calorie palatable food stimuli in all brain reward regions except for the left amygdala. This was apparent from group × condition interaction analyses on other types of food stimuli (i.e., high-calorie unpalatable and

low-calorie palatable). These interaction analyses resulted in clusters that did not overlap with the 14 found fROIs for the high calorie palatable foods, except for the left amygdala. Therefore the remaining 13 fROIs can be considered unique to high-calorie palatable food stimuli. The fROIs that resulted from the interaction analyses on the other stimulus types were not considered further.

So, high-calorie palatable food cues elicited a greater reward response in overweight people than in healthy-weight people, but only during taste imagination. The reduced reward activation during unbiased viewing in overweight as compared to healthy-weight people may reflect avoidance of processing of high-calorie palatable food stimuli in terms of how good they taste in overweight people, which is of course easier to achieve when the task does not require a focus on taste. Taken together, this pattern of activation might represent an ambivalence in the overweight group between desire for (in the taste imagination condition) and avoidance of (in the unbiased viewing condition) high-calorie palatable food stimuli.

In **Chapter 3** it was investigated if overweight participants were more responsive to taste than were healthy-weight participants, both on a neural and a subjective level. Therefore the data acquired in Chapter 2 were re-analysed after pooling responses to high-calorie and low-calorie stimuli. Further, only responses to palatable and to neutral food cues were taken into account. It was expected that group differences would be found on a neural level, but not in subjective reports. In response to palatable versus neutral food cues, overweight participants as compared to healthy-weight ones were expected to show more reward-related brain activation, and less inhibitory activation. This group difference was expected to be more pronounced during taste imagination than during unbiased viewing.

The results contradicted our hypothesis when participants viewed the stimuli naturally without instructions (unbiased viewing): the response to palatable versus neutral food was smaller in overweight compared with healthy-weight participants in seven fROIs associated with reward. The opposite effect was found in three putative inhibitory fROIs: the response to palatable versus neutral food was larger in the overweight participants than in healthy-weight ones. Results were in line with our hypothesis during taste imagination. In this condition, in overweight compared with healthy-weight participants, seven reward-related fROIs were more active in response to palatable versus neutral food stimuli. These results show that when overweight participants view food stimuli naturally, their brain activation is very different from the activation when they focus on the taste of that food: in overweight people inhibitory processes are dominant during unbiased viewing, whereas reward-related processes are dominant during taste imagination. This study adds to the limited evidence-base that attention focus is highly relevant in the study of food reward and inhibition.

The study described in **Chapter 4** investigated the role of cue exposure with response prevention (CERP) on subjective craving and on the neural processing of choco-

late pictures versus neutral non-food pictures. The chocolate exposure group smelled chocolate, whereas the control group smelled a neutral control object (i.e., a wooden pencil). Cue exposure lasted one hour, during which participants were in the fMRI scanner. CERP was interrupted by seven short scanning sequences during which neutral and chocolate pictures were presented. In the exposure group, subjective chocolate craving was expected to increase until the middle of the session and from then on to decrease and extinguish at the end of the session. This craving curve was hypothesized to be mirrored by activation in brain reward regions.

As expected, a short exposure (30 min) caused an increase in subjective chocolate craving in the exposure group, which was mirrored by a corresponding increase in brain reward activation in the exposure group as compared to the control group. Unexpectedly, a long exposure (60 min) did not lead to the extinction of subjective craving in the experimental group, although craving had started to decrease at that point. On a neural level however, activation in regions of interest in the exposure group seemed to have extinguished after the long exposure, because activation levels returned to or fell below control group levels. These results indicate that for a short exposure, brain reward activation during CERP is linked to craving. Regarding the longer exposure, the decline in brain reward activation in the experimental group may be a precursor of a decrease in subjective craving.

The aim of the study in **Chapter 5** was to examine if brain regions could predict chocolate intake after participants had been either exposed to chocolate or to control stimuli during approximately one hour, and whether the variance in chocolate intake could be better explained by brain activation or by self-reported craving. Five brain regions in total correlated with subsequent chocolate intake. These consisted of two reward regions that correlated positively with intake in the exposure group, one of which was the right caudate. Further, two regions associated with cognitive control correlated negatively with intake in the control group. When the regression analysis was conducted with the exposure and the control group together, an additional region in the anterior prefrontal cortex correlated positively with chocolate intake. In all analyses, the intake variance explained by neural correlates was above and beyond the variance explained by self-reported craving. These results are in line with previous neuroimaging studies that showed that brain responses were a better predictor of subsequent behaviour than self-reported craving or intentions (Falk et al., 2010, 2011; Grüsser et al., 2004; Kosten et al., 2006). Therefore, our findings might provide a missing link by associating brain activation, previously shown to predict weight change, with short-term food intake.

General discussion and conclusions

Less reward activation during unbiased viewing in overweight than in healthy-weight people: an argument for attentional avoidance?

Both in **Chapters 2 and 3** it was found that, compared to healthy-weight participants, overweight participants showed more reward activation during taste imagination and less reward activation (and, additionally, in chapter 3 even inhibition) in the unbiased viewing condition. This difference between conditions shows how a focus of attention can modulate brain reward responses to food. The activation pattern during taste imagination was in line with our hypothesis and is thought to reflect a stronger motivation to approach or consume high-calorie palatable foods in overweight people, although participants were satiated.

A possible explanation for the reduced reward activation in overweight as compared to healthy-weight participants during unbiased viewing could be that during unbiased viewing, the overweight participants paid attention to health aspects, whereas the healthy-weight participants focused on the good taste of the high-calorie palatable foods. This focus on health may be due to higher scores of overweight participants on a measure of dietary restraint in this study as well as in previous studies (Herman & Polivy, 1980; Van Strien et al., 2007). Similar results were observed in studies with restrained versus unrestrained women, who showed attentional avoidance of high-calorie food (Veenstra et al., 2010), and in overweight participants versus healthy-weight participants, who showed a reduced maintenance of attention on food pictures (Werthmann et al., 2011). This avoidance may have been aided by the fact that participants were tested while satiated. Maybe this avoidance cannot be sustained under disinhibiting circumstances like depression or distraction (Boon et al., 2002; Roefs et al., 2012), which have been shown to lead to infraction of restrictive intake norms and to overconsumption (Herman & Polivy, 2007). Further, resources might become depleted over time by chronic self-regulation so that palatable, and often high-calorie, snack food becomes irresistible (Hofmann et al., 2007; Vohs & Heatherton, 2000).

An explanation of the supposed avoidance could be the activation of inhibitory regions, which indeed was found in **Chapter 3**. It is not clear why there was no sign of inhibitory activation in **Chapter 2**. Most likely this was due to the type of analysis that was conducted: In **Chapter 2** we only looked at high-calorie palatable stimuli and selected regions with an interaction between group and attention condition. In **Chapter 3**, both palatable and neutral food stimuli were taken into account and instead the interaction between group and stimulus type (palatable vs. neutral) was analysed.

The influence of cue exposure with response prevention (CERP)

In **Chapter 4** subjective craving for chocolate was found to increase after a short exposure to real chocolate, which was in accordance with our expectations. After a long exposure however, an extinction of subjective craving was not found, although a tendency towards a decrease in craving was significant at the end of the final prolonged exposure, which might have continued if the exposure had been even longer. Therefore it can be said that the CERP manipulation was not entirely successful, in that an extinction of subjective craving at the end of the session was not attained. This may have been due to the interruption of the olfactory exposure by six scan measurements, even though these measurements were short (only 5 min per scan). As discussed in **Chapter 5**, we suppose that as a result of this, chocolate intake in the exposure group was similar to that of the control group, although a smaller intake in the exposure group had been expected. If the CERP manipulation had been successful, this would probably have led to a decrease in chocolate intake in the exposure group, as would be expected from previous studies in which cue reactivity extinguished after a successful CERP (Van Gucht et al., 2008; Jansen, Broekmate, & Heymans, 1992; Jansen, Van den Hout, De Loof, Zandbergen, & Griez, 1989; Martinez-Mallén et al., 2007; Toro et al., 2003). This could be a subject of future studies. In **Chapter 5** it was also shown that the CERP manipulation was influential with respect to the predictive validity of neural correlates of chocolate craving on intake, because the brain regions that predicted subsequent intake were different for each group, both in location and in assumed functionality (reward in the exposure group versus inhibition in the control group).

The comparison of subjective craving ratings and brain reward activation **(Chapter 4)** shows that for a short exposure, the changes in brain reward activation during CERP were linked to changes in craving. Therefore, a short cue exposure can be considered effective in increasing both craving and brain reward activation. For a longer exposure, however, there was a disaccord between these two measures at the end of the session: brain reward activation levels of the exposed group returned back to control group levels in fROIs associated with reward, whereas subjective chocolate craving was still higher in the exposure group than in the control group. A stricter analysis confirmed these findings. We can conclude that CERP is an effective intervention for the reduction of brain reward activation as a form of food cue reactivity, even though subjective craving did not extinguish in this study.

Interesting in the context of cue exposure is a study on the prevalence of obesity in 41 occupational groups, among which foodservice employees (Caban et al., 2005). It was found that foodservice employees were in general less often obese than employees with other occupations. This was surprising to the author of a recent study (Pizam, 2013), but in the light of the exposure studies of this dissertation this could be inter-

preted as a continuous cue exposure to food and beverages, while eating and drinking often is not possible because either it is not allowed or there is no time for this in the foodservice industry. As a result, the association between the food and beverage cues and intake may be disrupted in these employees, leading to a lower prevalence of obesity in this occupational group.

Prediction by brain activation is better than prediction by subjective reports

The findings of **Chapter 5** were that the variance in chocolate intake after the cue exposure session could be better explained by brain activation to chocolate cues than by self-reported chocolate craving. This is in line with previous neuroimaging studies showing that brain responses were a better predictor of subsequent behaviour than self-reported craving or intentions (Falk et al., 2010, 2011; Grüsser et al., 2004; Kosten et al., 2006). The reason for this could be that introspection is limited (Nisbett & Wilson, 1977) and that self-reported craving may have become confounded by socially desirable answering tendencies (Schwarz & Oyserman, 2001).

Real food is a stronger cue than the image of that food

In **Chapter 4** it was found that the smell of real chocolate (during exposures) was more effective in increasing chocolate craving than the sight of chocolate pictures (during brain scans). This was indicated by a higher average of the six craving ratings *after* as compared with *before* each exposure to real chocolate in the chocolate exposure group. An opposite pattern was found in the control group: average chocolate craving ratings were lower after than before the pencil exposure, which indicated that the sight of chocolate pictures during the scan runs was more effective in increasing chocolate craving than the smell of a pencil. This is in line with previous literature, in that craving elicited by a real food cue and by mental imagery of that food cue are related (Kavanagh et al., 2005; Tiggemann & Kemps, 2005). Our findings in the chocolate exposure group add to this literature by indicating that the perception of real food is a stronger cue than the image of that food with its accompanying imagined smell and taste.

Methodological issues

Methodological issues are described in the discussion of every chapter, but the most important, as well as general issues, will be mentioned in the following.

Choice of the design: event-related versus blocked

The experiment described in **Chapters 2 and 3** made use of an event-related design. This type of design is not very common in neuroimaging studies on food reward processing. The majority of studies in this field used a blocked design (e.g., Bruce et al., 2010; Killgore et al., 2003; Martens et al., 2013; Martin et al., 2010; McCaffery et al., 2009; Murdaugh, Cox, Cook, & Weller, 2012; Rothemund et al., 2007; Stoeckel et al., 2008). The choice of our design may be the reason why the results of the studies described in **Chapters 2 and 3** were partly contrary to our expectations and to previous research. For example, in **Chapter 3** we found an activation of inhibitory control regions and a lack of activation of reward regions in overweight participants during unbiased (passive) viewing. The majority of studies on food reward with a condition of passive viewing without instructions found the opposite, that is, more activation in reward regions in overweight compared with healthy-weight participants (e.g., Bruce et al., 2010; Martens et al., 2013; Murdaugh, Cox, Cook, & Weller, 2012; Rothemund et al., 2007; Stoeckel et al., 2008). The reason for this discrepancy could be the type of design: a blocked design in the previous studies versus an event-related design in our study. In a blocked design, multiple palatable food stimuli are shown consecutively. Therefore, craving for the shown food could be stronger in this type of design than in our event-related design in which stimuli of different categories are mixed. Even in a condition of passive viewing without instructions, a blocked design may result in a stronger build-up of craving because of the grouped presentation of high-calorie palatable foods. This would overrule any natural inhibitory response to a single stimulus and this may be the reason why no such responses were found in the majority of food reward studies.

Because in an event-related design the reward value of individual food stimuli is assessed, the measurement of responses to food stimuli in an event-related design gives, in our opinion, more ecologically valid results than measurement in a blocked design. This type of design seems to be closer to reality than a blocked design, because in real life people also view stimuli of different categories almost simultaneously or consecutively (e.g., a food stimulus next to a pair of scissors and a picture postcard on a colourful table cloth). In a blocked design one can only measure the brain activity in response to a group of stimuli. Such settings also occur in real life (e.g., a buffet dinner table, or the supermarket corridor with shelves full of snack food), but less often, because food intake takes mostly place at home.

Measurement of neural responses during satiation instead of hunger

Both experiments **(Chapters 2 to 5)** have been conducted with participants who had eaten lunch before they were tested. We chose to test satiated instead of hungry participants because the excess of energy intake in obesity is at least partly due to eating in the absence of hunger, during which hedonic drives override homeostatic ones (Berthoud, 2011; Fisher & Birch, 2002; Zheng et al., 2009). Therefore we expected that the difference in neural food reward processing between healthy-weight and overweight participants would be found primarily in a state of satiation. Together with the event-related (instead of blocked) design, this may have contributed to our findings of less reward activation in overweight versus healthy-weight participants during unbiased viewing **(Chapters 2 and 3)**, which differ from previous studies. These previous studies found opposite results (i.e., more reward activation in overweight versus healthy-weight participants), but these participants were tested in a hungry state (e.g., Murdaugh, Cox, Cook, & Weller, 2012; Stice, Spoor, Bohon, Veldhuizen, & Small, 2008; Stoeckel et al., 2008).

Limitations of "unbiased viewing"

One of the conditions in the first experiment **(Chapters 2 and 3)** was unbiased viewing, that is, viewing of the food stimuli without prior instructions. It was assumed that this is the most natural way of presentation of food pictures to participants. However, one may argue that the environment in which the brain responses to these stimuli are recorded is not natural at all: the participant is lying supine in the scanner and is not allowed to move, while noise levels are very high and communication with the researcher is not possible other than by a microphone and an alarm button. Therefore, brain activation in response to real food in a supermarket or a restaurant may differ from brain activation that is recorded during an fMRI session. This drawback is common to all fMRI experiments. An advantage of our first experiment compared to other fMRI studies is that our experiment contained a task (in both the unbiased viewing and the taste imagination condition). In many other studies involving passive viewing, no task is given. Therefore, in those studies it remains largely unknown what participants have been thinking about during the presentation of stimuli, even if this had to be indicated in an exit questionnaire.

Participant characteristics

In both experiments **(Chapters 2 to 5)**, only female participants were selected to take part, because men and women seem to differ regarding food reward processing both behaviourally (Havermans, Giesen, Houben, & Jansen, 2011) and neurally (Frank et al., 2010; Haase et al., 2011; Uher et al., 2006; Wang et al., 2009). It remains to be investigated

what the neural reaction of male participants would be. Furthermore, in the first experiment **(Chapters 2 and 3)**, only four of the participants in the overweight group could be considered obese. Results may have differed if the whole group had been obese instead of overweight, because there is evidence that the relationship between sensitivity to reward and body mass index (BMI) is of an inverse U-shape (Davis & Fox, 2008), which suggests that brain responses to food stimuli in regions associated with reward might differ in overweight versus obese participants.

Comparison of results with previous fMRI-studies

For the interpretation of the results of the studies in this dissertation regarding brain activation it was necessary to compare them with previous neuroimaging studies. This comparison turned out to be laborious, as there was a large variation in the naming of brain regions, even if the studies meant the same brain region. For example, a region in the lateral prefrontal cortex can be called "pars triangularis", "Brodmann Area 45", "inferior frontal gyrus" or "ventrolateral prefrontal cortex", depending on the level of precision which is employed by the authors. These varying denominations made it very time-consuming to systematically search previous papers for results in brain regions similar to the ones found in our experiments. Additionally, the indications of the peak voxel coordinates of the brain region can be given in different coordinate systems, the comparison of which requires an extra conversion step, such as Talairach coordinates (used in this thesis) and Montreal Neurological Institute (MNI) coordinates. Comparison of Talairach and MNI coordinates can only be done after one of the coordinates has been converted into the other system. Apart from this requiring an extra conversion step, a coordinate disparity of around 1 to 2 mm will remain due to the different scaling, orientation and origin of reference brains of the two coordinate systems (Lancaster et al., 2007). A standardisation of the naming of brain regions, together with a uniform coordinate system which is used for the localisation of voxels, would have been very helpful. Finally, the results of the tool which we used to automatically localize brain regions (Talairach Client (www.talairach.org) (Lancaster et al., 1997, 2000)) regularly needed to be corrected manually because several brain regions determined by the Talairach Client clearly differed from the activated brain regions in our analyses.