Characterising and altering maladaptive behaviours and tendencies in obesity

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TABLE OF CONTENTS

LIST OF ABBREVIATIONS

AAT – approach-avoidance task

ACC – anterior cingulate cortex

AG – angular gyrus

AI – asymmetry index

Amy – amygdala

ANOVA – analysis of variance

AU – arbitrary units

BA – Brodmann Area

BDI – Beck's depression inventory

BIS/BAS – Behavioural Inhibition System/Behavioural Activation System

BMI – body mass index

BOLD – blood-oxygen level dependent

CBM – cognitive bias modification

CC – cognitive control

CI – confidence intervals

DC – degree centrality

DD – delay discounting

DI – disinhibition

dlPFC – dorsolateral prefrontal cortex

dStr – dorsal striatum

EC – eyes closed

EEG – electroencephalography

EO – eyes opened

EPI – echo-planar imaging

FA – flip angle

fALFF – fractional amplitude of low-frequency fluctuations

fMRI – functional magnetic resonance imaging

FWE – family-wise error

FWHM – full width at half maximum

GLM – general linear model

H – hunger

ICA-AROMA – independent component analysis automatic removal of motion artifacts

IFG – inferior frontal gyrus

IP – indifference point

ITI – intertrial interval

L – left

LDR – later delayed reward

MFG – middle frontal gyrus

MNI – Montreal Neurological Institute

mOFC – medial orbitofrontal cortex

MPRAGE – magnetisation-prepared rapid gradient echo

MRI – magnetic resonance imaging

NAcc – nucleus accumbens

NKI – Nathan Kline Institute

PCA – principal component analysis

PPI – psychophysiological interactions

R – right

RC – rotated component

ROI – region of interest

rsEEG – resting-state electroencephalography

rsfMRI – resting-state functional magnetic resonance imaging

SCA – seed-based connectivity analysis

SD – standard deviation

SFG – superior frontal gyrus

SIR – sooner immediate reward

SV – subjective value

TE – echo time

TFEQ – Three Factor Eating Questionnaire

TI – inversion time

TR – repetition time

VAS – visual analogue scale

vmPFC – ventromedial prefrontal cortex

VOI – volume of interest

VTA – ventral tegmental area

ZTPS – Zaubermann time perception scale

LIST OF FIGURES

LIST OF SUPPLEMENTARY FIGURES

LIST OF TABLES

1 The obesity problem

Weight change and maintenance is determined by energy intake and energy expenditure. If calories consumed and calories burned, e.g. through resting and physical activity, are balanced, weight remains relatively unchanged (Stubbs and Lee, 2004). However, an increased energy intake, combined with a decreased or stable energy expenditure might lead to fat accumulation and weight gain. From an evolutionary perspective, fat accumulation might be related to a previously adaptive process, since in the past fat deposits protected people from starvation in states of famine (Speakman, 2013; Genné-Bacon, 2014). Mechanisms that lead to such fat accumulation and were once adaptive, such as increased responsivity to food cues or high metabolic efficiency, might prove problematic in the current obesogenic environment, which is filled with food cues and palatable, unhealthy foods (Swinburn et al., 1999; Ravussin and Bogardus, 2000). In short, processes that were adaptive have now become the opposite – maladaptive. Together with changes in lifestyle, such as a decrease in physical activity, these processes associated with increased food intake are problematic and can lead to overweight and obesity.

It has become evident in the past that obesity is a global problem and that it carries personal and economic burden (James, 2008; Finucane et al., 2011; Stevens et al., 2012). Obesity is defined by the World Health Organisation as abnormal or excessive fat accumulation presenting a health risk (WHO, 2000). One measure for classification of the degree of obesity is the body mass index (BMI), which is the ratio of a person's weight in kilograms to their squared height in meters (kg/m^2). BMI of 25-30 is classified as overweight, and that above 30 as obesity. Overweight and obesity have a number of comorbidities, such as diabetes or hypertension (Khaodhiar et al., 1999; Gärtner, 2018), which decrease life quality and expectancy. It is therefore a problem that must be solved sooner, rather than later. Tackling a problem involves its precise characterising and finding strategies that would use this knowledge in a beneficial manner. Research in this thesis focuses on the definition of certain behavioural characteristics that are associated with obesity and which could potentially lead to excessive weight gain. Secondly, it tackles the problem of altering those maladaptive processes towards more beneficial routines. The focal point of this thesis is on automatic

behaviours that lead to overconsumption of food, and on other processes that might prove helpful in dealing with maladaptive decision-making processes in obesity. In this theoretical introduction, I will characterise behavioural and neural correlates of obesity, and present possible targets for modern obesity interventions.

1.1 Maladaptive behaviours in obesity

A large factor contributing to the obesity epidemic is the environment (Swinburn et al., 1999). The abundance of food-related cues potentially works to our disadvantage by increasing food consumption. Indeed, obese individuals differ in their susceptibility to environmental food-related and food-unrelated cues (e.g. Carnell and Wardle, 2008; Kemps et al., 2014a; Simmank et al., 2015). Moreover, obesity is characterised by deficits in a number of different behavioural domains, not only food-related. In their systematic review, Vainik and colleagues conclude that people with higher BMI consistently show lower executive functioning and altered responses on food motivational tasks (tasks testing responses to food stimuli; (Vainik et al., 2013). Executive functions (also termed executive or cognitive control) generally adapt people's behaviour to current goals. They include response inhibition, working memory and cognitive flexibility (Diamond, 2013). Executive functions are also related to control of food intake and their impairment is consistently related to increased food intake and weight gain (Guerrieri et al., 2007; Hofmann et al., 2009; Jansen et al., 2009; Nederkoorn et al., 2010; Horstmann et al., 2011; Hall, 2012; Dietrich et al., 2016a). In obesity, executive functions have been shown to be altered in the context of inhibition of prepotent responses or decision-making (Levitan et al., 2015; Price et al., 2016a). This alteration is especially pronounced in the intertemporal domain (Weller et al., 2008; Rasmussen et al., 2010; Bickel et al., 2014; Jarmolowicz et al., 2014; Lawyer et al., 2015; Simmank et al., 2015; Amlung et al., 2016; Price et al., 2016b), where individuals are faced with a choice between two monetary options: a smaller one, available immediately (e.g. 20 Euro), or a larger one, available after a variable delay (e.g. 40 Euro after 2 months). Subjective value of the latter amount is discounted due to its temporal distance; hence, this behaviour is called delay discounting, and is reflective of an individual's temporal impulsivity. Temporal impulsivity is considered a proxy of executive functions (Bickel and Yi, 2008).

Food motivation tasks, in contrast to executive functioning, test participants' tendencies towards food-related stimuli. Behaviour in those tasks was previously shown to be associated with obesity (Roefs and Jansen, 2002; Castellanos et al., 2009; Epstein et al., 2010; Giesen et al., 2010; Epstein et al., 2011; Roefs et al., 2011; Werthmann et al., 2011; Kemps et al., 2014b, but see: Mathar et al., 2016). One such task is the approach-avoidance task (AAT), which measures approach bias. This bias reflects higher approach, rather than avoidance towards problematic stimuli, such as unhealthy foods. It is believed that increased responses to food stimuli are a reflection of their increased incentive salience (Berridge et al., 2010). Because those stimuli are highly rewarding, and constitute well-conditioned cues, they are perceived more easily in the environment by obese participants and might render automatic responses. Such automatic approach responses are considered maladaptive, as they might lead to unhealthy weight-gain and obesity. This, in combination with a decrease in executive functioning, especially response inhibition, constitutes a serious risk for some people and might be an underlying factor of unhealthy weight gain and obesity.

On a more general level, obesity is associated with changes in a number of self-reported measures, such as eating- or general motivational behaviours. Eating behaviour can be measured using the Three-Factor Eating Questionnaire (TFEQ; Stunkard and Messick, 1985), which encompasses cognitive control of food intake, disinhibition, and influence of hunger on behaviour. General motivational behaviour, can be assessed using the Behavioural Inhibition System/Behavioural Activation System questionnaire (BIS/BAS; Carver and White, 1994), which describes sensitivity to reward/approach behaviour and sensitivity to punishment/withdrawal, respectively. Eating behaviour, especially in the cognitive control and disinhibition aspects, accounts for a large portion of variance in BMI (Dietrich et al., 2014). Furthermore, approach/avoidance measures are also related to obesity, showing positive correlations with BMI in women, and an opposite relationship in men. This shows that the associations between behavioural measures and BMI are not straightforward, and that gender should be taken into account in similar investigations. This gender aspect could potentially point to different mechanisms that are engaged in increased BMI, such as compensatory eating in females (increased approach behaviour), or disregard for long-term

consequences of overeating in males (decreased avoidance behaviour/sensitivity to punishment).

In sum, studies show that obesity is related to a number of maladaptive behaviours, such as increased temporal impulsivity, or increased approach towards unhealthy foods. These behaviours can be related to general executive functioning, predominantly response inhibition, but also to reactions to food stimuli in food motivation tasks. Obesity is also associated with alterations in general approach and avoidance tendencies, and self-reported measures of eating behaviour. Thus, characterising these maladaptive tendencies is an important step in the development of modern, improved interventions.

1.2 Measuring neural correlates of maladaptive behaviours in obesity

The behavioural characteristics of obesity described above are merely a reflection of altered neural functioning, since behavioural processes are inherently driven by the brain. It is therefore of utmost importance to investigate neural mechanisms underlying these maladaptive behaviours in obesity. A valuable tool for assessing brain function is functional magnetic resonance imaging (fMRI). Using the phenomenon of magnetic resonance, this method non-invasively assesses the ratio of oxygenated to deoxygenated blood within the brain's vascular system. This creates a blood-oxygen-level-dependent (BOLD) contrast, which indirectly reflects activations of brain regions, as brain areas with higher activation require more oxygenated blood (Ogawa et al., 1990). Higher neural activity results in an increased BOLD signal, which can then be analysed to find out which brain regions were significantly more active either during certain cognitive tasks (task-based fMRI), or during rest (resting-state fMRI). fMRI has a relatively good spatial resolution which depending on the magnetic field strength can reach around 1mm. However, since imaging the entire brain using fMRI is quite a slow process, its temporal resolution is relatively low – usually around 1 image /2 seconds. This means that it can only measure slow processes, missing out on the very fast-paced ones.

A different measure to investigate brain activity is electroencephalography (EEG). It is a non-invasive method to measure electrical activity of the brain by placing electrodes on the scalp. Since neurons communicate through ionic currents, their activity can be indirectly measured

by measuring electrical fields in the brain. In contrast to fMRI, EEG does not possess a high spatial resolution and the sources of measured currents can only be approximately matched to specific locations in the brain. However, the temporal resolution of EEG is much higher than that of fMRI, making it possible to measure fast-paced processes in the brain. EEG can be used to measure neural oscillations within different frequency ranges at rest (resting-state EEG) and electrical potentials evoked by specific tasks (event-related potentials).

These two neuroimaging methods can be used to better understand maladaptive behaviours in obesity, but also to understand mechanisms through which existing obesity interventions work. This, in turn, might lead to creating new targets for obesity interventions, and fine-tuning the already existing ones.

1.3 Neural correlates of maladaptive behaviours in obesity

Generally, there are three brain systems that control eating behaviour – the homeostatic system, the reward/motivational system, and the executive system (Figure **1.3.1**, Berthoud and Morrison, 2008; Carnell et al., 2012). The homeostatic system, regulates eating behaviour based on peripheral hormonal and metabolic input signalling energy requirements. Its main hub in the brain is the hypothalamus. This system will not be discussed as a part of this thesis (for further details see a review by Berthoud and Morrison, 2008). Second, the reward/motivational system, regulates food intake according to previous reward experiences. Here, the dopaminergic reward system plays an important role, and especially two of its pathways – the mesolimbic pathway, connecting dopaminergic midbrain regions (the ventral tegmental area, VTA) with the ventral striatum (most prominently the nucleus accumbens, NAcc), and the mesocortical pathway, connecting the VTA with the ventromedial prefrontal cortex (vmPFC) and orbitofrontal cortex. This system also encompasses the insula, hippocampus and amygdala. Third, the executive system, regulates behaviour based on more abstract goals, such as health, or body image. This system exerts self-control on food-related behaviours and is tightly paired with frontal cortical areas, especially the dorsolateral prefrontal cortex (dlPFC), and the anterior cingulate cortex (ACC). It might seem that these systems function independently, however, in his review from 2012,

Dagher describes one network consisting of all three systems (Dagher, 2012). This 'appetitive network' is a crucial one driving and controlling food intake.

Obesity, being related to a number of behavioural alterations. is also related to alterations on the neural level. In the context of executive functioning, the dlPFC has often been shown to have changed activity in participants with higher BMI. The dlPFC generally guides certain aspects of cognitive control in the food context. Specifically, focusing attention on health aspects of food (Hare et al., 2011), or downregulating appetitive responses to palatable foods (Hollmann et al., 2012; Dietrich et al., 2016b). Participants with higher BMI have been shown to have decreased dlPFC activity related to an attentional bias towards food (Janssen et al., 2017). Moreover, lower activity in the dlPFC on a delay discounting task was associated with higher long-term weight gain in women (Kishinevsky et al., 2012). Together, this evidence suggests that obesity might be related to decreased executive control, especially inhibition and impulse control, over prepotent responses to food cues, which is driven mostly by the dlPFC. This, in turn, might lead to an inability to adhere to long-term dietary goals, resulting in weight gain. This hypothesis is further corroborated by the fact that disinhibited eaters (people who find exerting control over their food intake difficult) show lower pre-meal activity to food cues in the ACC, which is a part of the executive system (Carnell et al., 2012; Vainik et al., 2013).

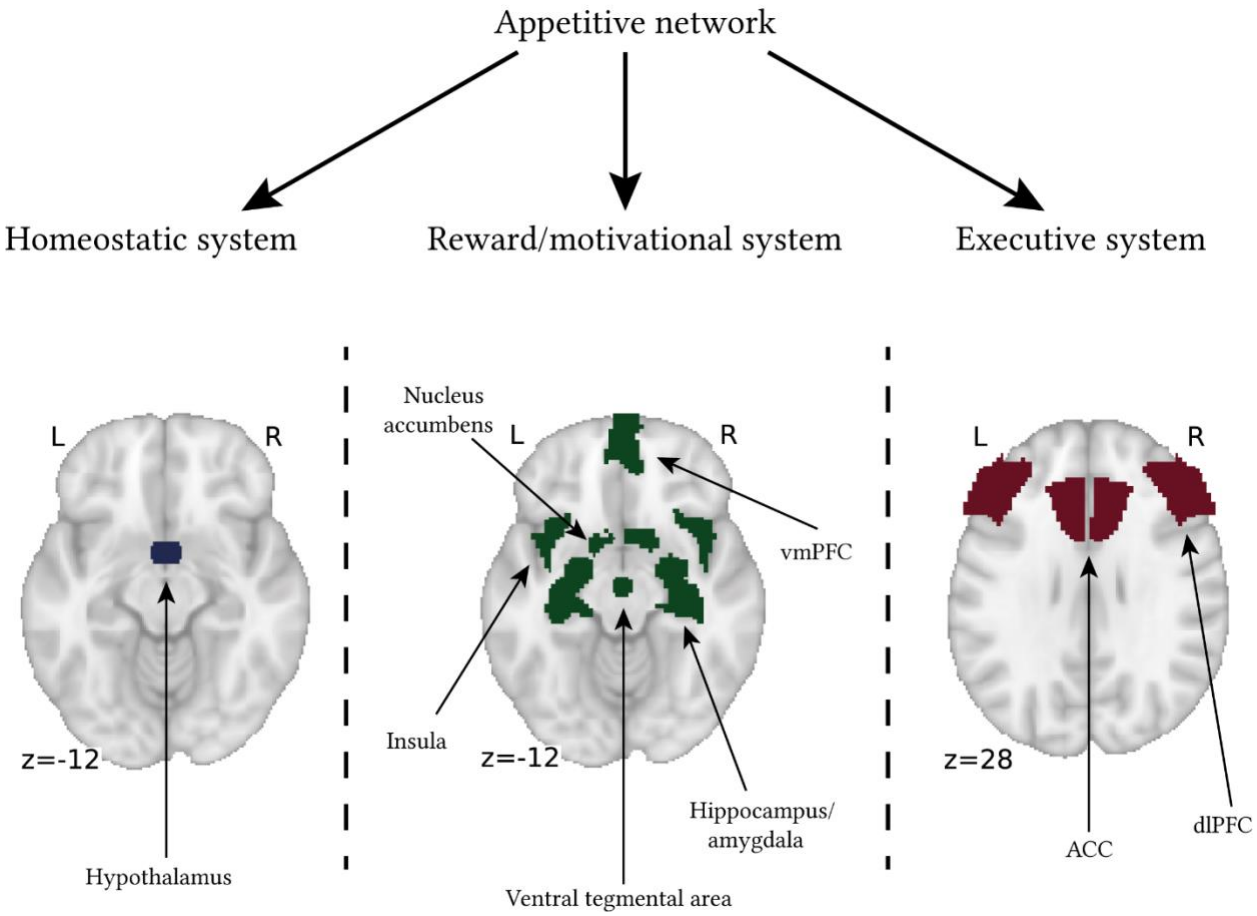

Figure 1.3.1 Representation of the three main systems driving and controlling food intake (appetitive network). The homeostatic system consists of the hypothalamus, the reward/motivational system consists of the dopaminergic reward system, the ventromedial prefrontal cortex (vmPFC) and the hippocampus, amygdala and insula, whereas the executive system includes the anterior cingulate cortex (ACC) and the dorsolateral prefrontal cortex (dlPFC). z – MNI coordinate of the slice on the z-axis.

Information about obesity-related alterations in the dopaminergic reward/motivational system can be derived from animal and human literature (Volkow et al., 2008; Geiger et al., 2009; Stice et al., 2011; Vucetic et al., 2012; Cone et al., 2013; Narayanaswami et al., 2013; Horstmann et al., 2015; Friend et al., 2016). This system predominantly governs responses on food motivation tasks. Changes reported regarding behavioural findings in those tasks are corroborated by imaging findings in corresponding domains. For example, higher incentive salience of food-related stimuli in obesity is reflected in larger BOLD responses of

the reward system to those stimuli (van der Laan et al., 2011; García-García et al., 2013; García-García et al., 2014). Regarding neural correlates of approach bias, insight comes from studies investigating alcohol- and marijuana-dependent individuals. These studies often show that substance-dependent patients have an increased approach bias towards their respective problematic stimuli (Wiers and Rinck, 2009; Cousijn et al., 2011; Cousijn et al., 2012; Wiers et al., 2013; Wiers et al., 2014). This increased bias has been related to higher activations in the vmPFC, amygdala and NAcc (Cousijn et al., 2012; Wiers et al., 2014). The amygdala is important for Pavlovian learning and formation of emotional memories (Volkow et al., 2004; Koob and Volkow, 2010), suggesting that stimuli for which approach is high are highly salient conditioned stimuli. The NAcc receives and sends dopaminergic projections in response to rewarding stimuli (Volkow et al., 2004; Hyman et al., 2006; Heinz et al., 2009; Koob and Volkow, 2010). The medial prefrontal cortex is commonly referred to as the brain's reward valuation centre – its responses to rewarding stimuli positively correlate with their subjective (Kable and Glimcher, 2007; Hare et al., 2009). Together, activation of these brain regions to approaching problematic stimuli, as opposed to neutral stimuli (non-alcoholic beverages) suggests that they have a higher rewarding value for alcohol-dependent individuals. However, these studies do not involve participants with obesity and food stimuli, and there is a need to fill this research gap to better understand how approach bias comes about in obesity.

The right brain theory of obesity is a general theory regarding neural underpinnings of obesity that possibly integrates changes in the executive and the reward/motivational systems (Alonso-Alonso and Pascual-Leone, 2007). Here, obesity is seen as a disease of increased approach behaviour/decreased inhibitory behaviour. It therefore concerns both the motivational system (since approach and avoidance behaviours are basic motivational dimensions; Gray, 1981; Gray and McNaughton, 1992), and the executive system (since it controls performance of actions and plans, and interacts with the motivational system; Spielberg et al., 2011). A background to this theory is the fact that the right hemisphere shows more robust engagement in behavioural inhibition, withdrawal and negative affect (Davidson, 2004), whereas the left hemisphere shows predominance over goal-directed, approach behaviours (Davidson, 1994; Sutton and Davidson, 1997; Davidson, 2004). The

theory itself posits that obesity is driven by a decreased activation of the right frontal brain areas relative to the left. This in turn is related to higher approach behaviours, since they are mostly driven by the left hemisphere. This theory finds its support in a number of studies relating the hemispheric asymmetry described above to self-reported eating behaviour. Higher left compared to right brain activity was shown to be associated with a bias to respond to reward (vs. punishment) related cues (Pizzagalli et al., 2005), disinhibition, hunger (as measured by the TFEQ), and appetitive responsivity (within an overweight/obese sample (Ochner et al., 2009), and cognitive restraint (Silva et al., 2002). None of these studies, however, investigated whether hemispheric asymmetries are directly related to obesity measures. Additionally, as previous studies used only EEG, which suffers from a poor spatial resolution, it is difficult to state exactly which parts of the brain are related to specific outcome measures. Since sources of EEG signal are limited and come predominantly from the cerebral cortex (the executive system), it is difficult to measure activity in deep brain structures, such as the NAcc or ventral tegmental area (the reward/motivational system). This limits the generalizability and interpretation of such asymmetry findings. Research regarding the asymmetries could benefit from an in-depth investigation into the whole brain. Hence, new studies should focus on direct links of hemispheric asymmetries in obesity, while trying to increase spatial resolution, e.g. by using fMRI.

In sum, obesity is associated with alterations in the appetitive network, especially in the executive and the reward/motivational systems. Of course, those systems interact with each other and are not fully separate, which must be taken into account while designing potential obesity interventions.

1.4 Obesity treatment interventions

Described maladaptive behaviours related to obesity can be seen as somewhat automatic processes. However, most of current interventions do not target these processes, instead aiming to change explicit knowledge of participants – from food education to increasing physical activity (Figure **1.4.1**). Unfortunately, traditional lifestyle and educational interventions present short-term effects and relatively small reductions in BMI (Jeffery et al.,

2000; Curioni and Lourenço, 2005; Franz et al., 2007; Barte et al., 2010; Kirk et al., 2012). Even though individuals with obesity realise that their behaviour could have negative consequences, such as weight gain, it is difficult for them to change it. Marteau and colleagues suggest that the presence of automatic maladaptive behaviours make traditional therapies fairly ineffective (Marteau et al., 2012). Accordingly, it is imperative that novel obesity interventions target the automatic processes. The idea is to alter behaviours that actually underlie obesity, which may provide long-term beneficial effects (Figure **1.4.1**).

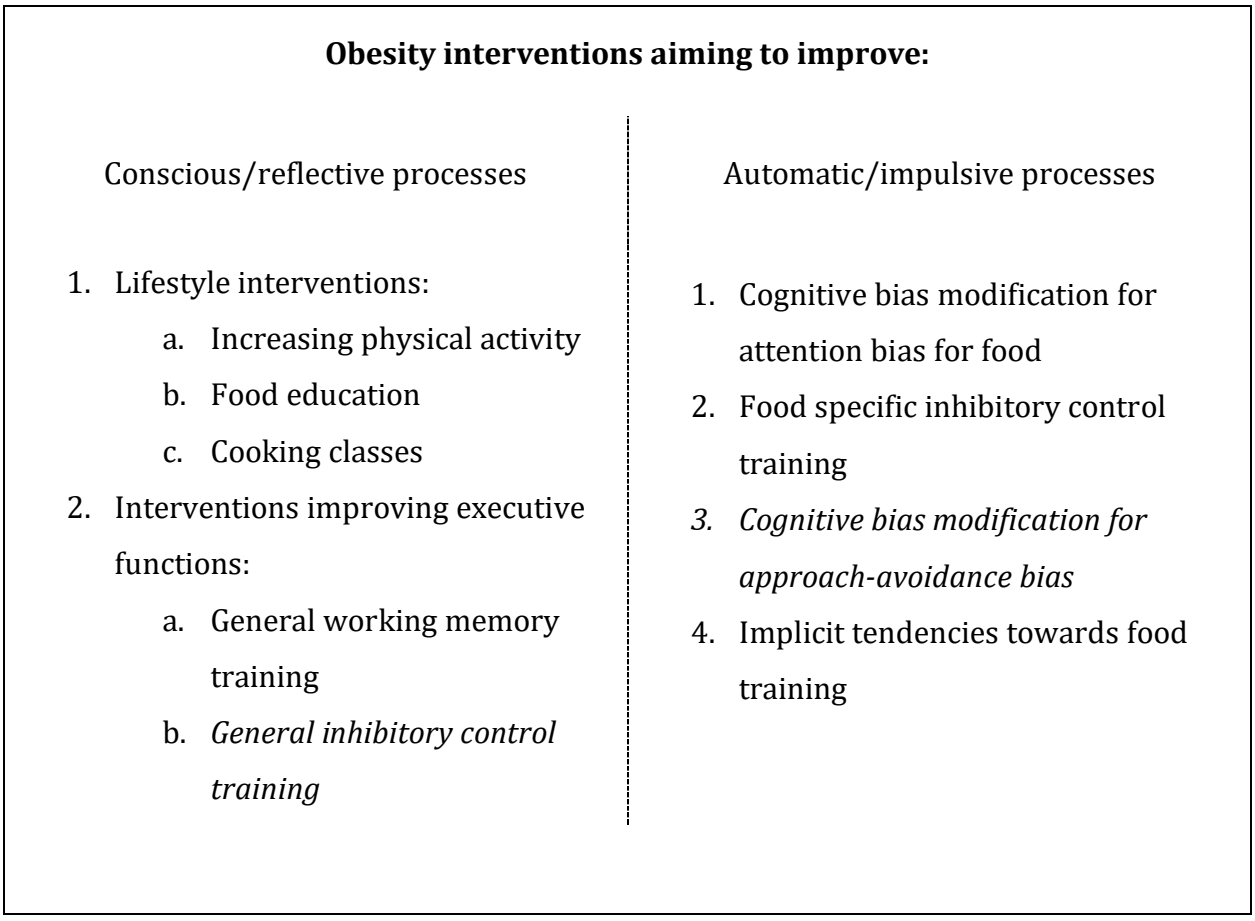

Figure 1.4.1 Figure representing some of the possible intervention targets for the treatment of obesity (based on Jones et al., 2018). Italic font represents ones that are targeted as part of this thesis.

Many studies have focused on this problem and aimed to apply this sort of interventions in the context of eating behaviours with varying degrees of success (Jones et al., 2018). One idea

was to apply cognitive bias modification (CBM) to decrease approach bias in individuals with obesity. CBM is a promising tool that aims to change automatic tendencies towards problematic stimuli, subsequently improving the regulation of unhealthy or maladaptive behaviour. An example of CBM is the approach-avoidance task, where automatic approach/avoidance responses to problematic stimuli are measured using a joystick in a reaction time task. Those responses are then trained in a desired direction, e.g. increasing approach for positive/healthy and avoidance for negative/unhealthy stimuli. CBM was previously successfully used to decrease alcohol consumption (Wiers et al., 2010), and chocolate consumption (Schumacher et al., 2016). Notably, CBM was also successfully applied to reduce bias towards unhealthy food cues in obese vs. lean participants (Mehl et al., 2018). CBM can take many different forms and is a popular therapy for decreasing attentional, approach or interpretation biases. However, it remains unclear what the behavioural and neural mechanisms of CBM in the food context are.

A different approach to tackling problems of disadvantageous decision making involves using increased reactivity to environmental cues to the benefit of obese individuals. This approach focuses on general executive functioning, not only limited to the food context. However, since general executive functions influence food motivational behaviour and food-related decision making, this approach is equally important. Admittedly, executive functioning can be a largely conscious, reflective process. However, using incidental cues to alter and possibly improve executive functioning would be an automatic influence over this reflective process, which renders this intervention suitable for approaching the problem of obesity in light of Marteau's arguments. It was shown that higher temporal impulsivity – a preference for immediate rewards over later but larger ones – can be altered by means of incidental cues (Simmank et al., 2015) unrelated to the decision-making process at hand, e.g. pictures of happy couples or sexually arousing images. It is still largely unstudied how these processes come about in the brain and which mechanisms they involve.

In sum, evidence suggests that obesity interventions should rather tackle automatic processes, than explicit knowledge and actions. This can be done in many ways and can possibly involve food specific tasks targeting specific reactions to food stimuli (approach-avoidance task), but also targeting general executive functioning (temporal impulsivity).

2 Characterising maladaptive behaviours in obesity

Studies performed as parts of this thesis focus on 1) the behavioural and neural characterisation of certain aspects of maladaptive decision making and automatic processes in obesity – such as food approach bias, temporal impulsivity, general motivational and eating behaviour, and 2) the utilization of different strategies for altering these processes towards more beneficial ones. Neuroimaging measures are applied to investigate these phenomena. The remainder of this introduction will provide methodological details concerning testing of specific behavioural aspects of obesity. Additionally, it will describe methodological and conceptual considerations that should be taken into account while interpreting findings. Lastly, it will focus on behavioural strategies that we applied in order to alter disadvantageous behaviours towards more beneficial routines.

2.1 The approach bias and approach-avoidance task

Approach bias is a tendency to approach rather than avoid certain problematic stimuli. A tool to assess the approach bias is the approach-avoidance task, which was proposed by Rinck and Becker in 2007 (Rinck and Becker, 2007). The idea of the task is the following: participants are presented with a set of pictures of different categories – usually including a problematic and a more neutral category, e.g. healthy and unhealthy foods or alcoholic and non-alcoholic beverages. Using a joystick placed in their hands, they are asked to respond as quickly as possible to the pictures by either pushing or pulling the joystick. The pushing or pulling reaction is based on an irrelevant stimulus feature, such as format of the pictures (horizontal vs. vertical). This, in turn, creates congruent conditions, where participants are required to pull (approach) the joystick as a reaction to a stimulus that they happen to want to approach, and incongruent conditions, where participants are required to push (avoid) the joystick as a reaction to stimuli that they want to approach. This allows assessing automatic reactions to the implicitly perceived content of the pictures. By measuring reaction times investigators may assess whether participants show higher approach (shorter reaction times for pulling), or avoidance (shorter reaction times for pushing) for stimuli of a certain category. Here, longer reaction times might indicate a conflict between intended reaction (e.g. approaching unhealthy foods) and a required reaction (e.g. avoiding

unhealthy foods). Hence, responses on this task require two systems of the appetitive network – the executive and the reward/motivational system.

The AAT can take many forms and was previously successfully used in a number of contexts. These involved showing increased approach for alcohol, marijuana or nicotine in dependent individuals (Wiers and Rinck, 2009; Cousijn et al., 2011; Wiers et al., 2013; Wiers et al., 2014). It was also used in a food context, demonstrating increased approach for a number of different food stimuli (Kemps et al., 2013; Kemps and Tiggemann, 2015; Schumacher et al., 2016). AAT was further applied to assess approach bias towards food cues in obese individuals (Kemps and Tiggemann, 2015; Mehl et al., 2018). Here, participants were faster in their approach, as opposed to avoidance, for unhealthy foods. Moreover, the study by Mehl et al. (2018) indicated that participants with obesity show increased automatic approach tendencies towards unhealthy food stimuli as compared to healthy food stimuli, but also as compared to lean participants.

Furthermore, the AAT can be used as a tool to investigate neural mechanisms of approach bias. These are still largely unknown in obese participants in the food context. However, the literature on approach bias towards alcoholic beverages in alcohol-dependent patients and towards cannabis in cannabis users offers interesting insights (Cousijn et al., 2012; Wiers et al., 2014). Those fMRI studies suggest that regions engaged in the approach bias are the amygdala, NAcc and medial prefrontal cortex – structures belonging to the reward/motivational system within the appetitive network. Remarkably, these structures were consistently shown to have altered functioning in obesity (Volkow and Baler; Wang et al., 2001; Carnell et al., 2012; García-García et al., 2014). This could suggest that the approach bias for food in obesity shares similar neural correlates with approach bias in alcohol-dependence. It follows that altering the behavioural phenomenon of approach bias might involve changes in these specific brain areas.

2.2 Cognitive bias modification

A novel tool to alter approach bias for problematic cues is cognitive bias modification. In the food context it takes a form of an altered AAT, where participants are trained to avoid problematic stimuli, such as chocolate or unhealthy foods in general, and approach more

beneficial stimuli, such as salad and other healthy foods. This is done by presenting stimuli in such a way that 90% of negative stimuli are required be avoided, and 90% of positive stimuli are required be approached (Mehl et al., 2018). Repeating these reactions was shown to effectively decrease approach to alcohol cues (Wiers and Rinck, 2009; Wiers et al., 2010; Wiers et al., 2011; Wiers et al., 2015), but also to chocolate (Schumacher et al., 2016) and unhealthy foods (Mehl et al., 2018).

To investigate neural correlates of CBM, it was applied in the alcohol context using fMRI (Wiers et al., 2015). Here, alcohol-dependent individuals decreased their approach bias towards alcoholic beverages, which was related to decreases in activity of the mPFC – brain's valuation centre – suggesting a lower incentive value of problematic stimuli after the experiment. The question, however, remains, whether neural correlates of approach bias and CBM in the food context are similar to those in the alcohol context, or follow a different pattern.

2.3 Temporal impulsivity and delay discounting

A behavioural tendency that is most consistently related to obesity is temporal impulsivity (Weller et al., 2008; Amlung et al., 2016; McClelland et al., 2016). It describes a preference for lower reward available sooner, rather than larger rewards available later. A paradigm that tests these differences is delay discounting (DD). Here, participants are faced with two hypothetical (most often) monetary rewards – a smaller reward received sooner (e.g. 20 Euro now), or a larger reward received later (e.g. 45 Euro in a month). By asking participants to repeat similar choices many times, researchers are able to calculate a general measure of temporal impulsivity that describes behaviour in this context. Delay discounting is most often used with monetary rewards, also in the obesity context, however studies show that delay discounting behaviour is not different for rewards of different modalities (such as food, drinks or even weight loss; McClure et al., 2007; Lim and Bruce, 2015). As mentioned, obese participants often tend to choose smaller and sooner rewards over larger and later rewards. This is because the value of later rewards is discounted due to their temporal distance – in other words, later rewards, even though larger in value, are not seen as equally rewarding as sooner ones.

Temporal impulsivity and its neural correlates are a well-studied phenomenon. A large number of previous studies showed brain structures related to this phenomenon. In 2004, McClure and colleagues proposed an elegant concept of two systems – hot and cold – governing decision towards immediate and delayed choices, respectively (McClure et al., 2004). The hot, more impulsive system was represented by reward related brain areas, such as the NAcc or the vmPFC. On the other hand, the cold, less impulsive system was represented by the posterior parietal cortex, parietal cortex, and the dlPFC. There is, however, some debate about whether those two systems indeed take part in delay discounting. Kable and Glimcher argue that there is only one valuation system composed mainly of the mPFC and the ventral striatum that takes part in the valuation of potential rewards (Kable and Glimcher, 2007; Kable and Glimcher, 2010). Higher subjective value of available rewards results in increased activity in the valuation regions, where sooner and later rewards are compared and a choice is made. In fact, a number of predominantly prefrontal brain structures has been shown to be engaged in delay discounting (Monterosso et al., 2007; Shamosh et al., 2008; Figner et al., 2010; Hare et al., 2014). Independent of whether the hot and cold systems indeed govern decisions related to temporal impulsivity, it is again clear that brain structures engaged in these choices are similar to the ones that were shown to have altered functioning in obesity. In fact, a longitudinal investigation of weight change and delay discounting showed that activity in the dlPFC correlated negatively with weight gain (Kishinevsky et al., 2012). dlPFC being an inhibitory structure also responsible for exerting cognitive control over behaviour (Figner et al., 2010) might actually protect from weight gain in the long-term.

2.4 Incidental priming and temporal impulsivity

Priming is a phenomenon in which exposure to a stimulus affects subsequent behaviour in a domain related, or unrelated to said stimulus. For example, reading a passage about elderly people slows down the gait in young healthy subjects (Bargh et al., 1996); likewise environmental stimuli can influence our consumer choices (Dijksterhuis et al., 2005); e.g. priming with thirst-related words might increase beverage consumption in thirsty participants (Strahan et al., 2002). Priming was also shown to be effective in the context of temporal impulsivity, where delay discounting rates were altered using different stimuli,

such as pictures of natural and urban landscapes (van der Wal et al., 2013), pictures of attractive women (Wilson and Daly, 2004), faces with positive and negative expressions (Luo et al., 2014), or famous brand logos (Murawski et al., 2012). In the latter study, priming towards more immediate choices involved modulation of brain structures such as the vmPFC and medial orbitofrontal cortex (mOFC). As mentioned earlier, the vmPFC values potential rewards (Kable and Glimcher, 2007; Hare et al., 2009), while the mOFC integrates emotional and cognitive information (De Martino et al., 2006), but also reward values (Hare et al., 2008; Kahnt et al., 2011). Priming towards more delayed choices was observed while priming participants with faces showing negative expression (Luo et al., 2014). Here, participants showed higher preferences towards larger delayed rewards as opposed to neutral conditions. Perception of the negatively valenced faces was related to activations in the dlPFC, while priming towards delayed choices *per se* was related to activity in the anterior cingulate cortex and parietal cortex. While the dlPFC is related to exerting cognitive control and generally choosing delayed rewards, the anterior cingulate cortex directs attention towards relevant stimuli and together with the parietal cortex is a part of the fronto-parietal control network. This suggests that priming might increase amounts of cognitive control exerted during the task performance.

Since individuals with obesity seem to be generally more susceptible to environmental priming, perhaps altering their maladaptive decision-making processes with priming could prove beneficial. This idea was exploited by a study by Simmank and colleagues (2015). Using positive visual stimuli unrelated to food, the authors effectively primed obese men towards more immediate decisions, and obese women towards more delayed choices. Since this was a behavioural study, it unfortunately remains unclear what the neural mechanisms of those changes are.

3 General rationale of the experimental work

The overall aim of this thesis is to gain a deeper understanding of maladaptive behaviours and their neural correlates in obesity. Further, the goal is to alter certain maladaptive behaviours using newly developed behavioural and cognitive strategies. We chose to tackle performance on a food motivation task and executive functions, since previously those two

aspects have been most consistently related to obesity (Vainik et al., 2013). This new knowledge might help to better design future obesity interventions and focus them more on maladaptive automatic processes which might contribute to obesity therapy.

Study 1 describes neural correlates of self-reported approach/avoidance and eating behaviours in obesity with a focus on hemispheric asymmetries and was designed in part to facilitate interpretation of study 2.

Study 2 focuses on the approach-avoidance task, which engages both the executive and the motivational/reward systems. Within this study we aimed to assess and alter food approach bias by means of the cognitive bias modification in obese participants.

Study 3, on the other hand, is a behavioural experiment to set up a methodological framework for study 4, and replicate previous findings concerning temporal impulsivity in lean, overweight and obese participants.

Lastly, study 4 involves delay discounting, which represents executive functioning. Here, we assessed baseline delay discounting rates and aimed to alter them using incidental cues unrelated to the decision-making process in obese individuals.

4 Experimental work

4.1 Study 1 – relationship between obesity measures, self-reported eating behaviour, approach/avoidance tendencies and hemispheric asymmetries

4.1.1 Rationale of the study

We performed study 1 to investigate how self-reported eating and approach/avoidance behaviour and obesity in general are related to hemispheric asymmetries. According to the right brain theory of obesity, hypoactivation of the right relative to the left hemisphere, might be related to increased approach behaviour (e.g. approach bias). This, in turn, is related to increased BMI and decreased behavioural inhibition, also in the food context. This study was designed to replicate previous EEG findings in a lean sample (Sutton and Davidson, 1997), showing that increased activation of the left hemisphere, relative to the right, is related to higher approach behaviour as measured by questionnaires. Additionally, within the same sample of participants, we aimed to replicate the EEG findings within fMRI modality to 1) increase spatial resolution of previous findings, and 2) directly investigate relationships between EEG and fMRI measures. Further, we recruited an independent sample of lean, overweight and obese participants and, using resting-state fMRI, investigated whether asymmetry measures obtained in the Sutton and Davidson (1997) are related to BMI and self-reported eating behaviour. As a final validation step, another, larger sample of lean, overweight and obese participants was used to further replicate the findings.

We hypothesised that, within the EEG study, higher relative right hemispheric activity will be related to increased avoidance behaviour, whereas higher relative left hemispheric activity will be related to increased approach behaviours. Similar relationships were hypothesised for the fMRI experiments in all three samples. Regarding eating behaviour, we hypothesised that disinhibition will be related to increased relative left hemispheric asymmetry, with an opposite relationship for cognitive control.

4.1.2 Materials and methods

Analysed data were parts of different projects, all of which were conducted according to the Declaration of Helsinki and approved by local Ethics Committees (University of Leipzig, Germany – Sample 1 and 2; Montclair State University and Nathan Kline Institute – Sample 3). All participants gave their written informed consent prior to participation.

4.1.2.1 Participants

4.1.2.1.1 Sample 1

Sample 1 consisted of 117 healthy, right-handed, predominantly lean participants aged 20-35 years (mean age: 25 years, SD: 3 years, mean BMI: 23.01 kg/m^2, SD: 2.57 kg/m^2; 42 females) with following inclusion criteria: no medications taken, no substance abuse and no history of neurological diseases. The data were collected at the Max-Planck Institute for Human Cognitive and Brain Sciences in Leipzig. Data available for this sample were self-reported eating (TFEQ) and approach/avoidance behaviour (BIS/BAS) data, anthropometric data (BMI), resting-state EEG and resting-state fMRI (Table **4.1.1**). For analysis of EEG data, 1 participant of the 117 participants was excluded during the preprocessing (electrode of interest had to be excluded from the analysis). For analysis of fMRI data, 3 participants were excluded due to data preprocessing problems (failed registration), and 3 additional participants were excluded due to excessive head motion during data acquisition (maximum framewise displacement parameter exceeding 2.3). All participants were compensated with 9 Euro/hour for their participation.

4.1.2.1.2 Sample 2

Sample 2 consisted of 89 healthy, right-handed, lean, overweight and obese participants aged 20-37 years (mean age: 27 years, SD: 4 years, mean BMI: 29.54 kg/m^2, SD: 8.25 kg/m^2; 73 females). The data were collected at the Max-Planck Institute for Human Cognitive and Brain Sciences in Leipzig. This sample was created by merging data of two different studies from the O'BRAIN Lab investigating decision-making in obesity. Sub-sample 1 consisted of 53 lean, overweight and obese females, whereas sub-sample two consisted of 36 obese participants, males and females. Data available for this sample were self-reported eating

(TFEQ) and approach/avoidance behaviour (BIS/BAS) data, anthropometric data (BMI) and resting-state fMRI data (Table **4.1.1**). Exclusion criteria were as follows: history of psychiatric or neurological disease, hypertension, MRI-related contraindications. No participants had to be excluded during data analysis. All participants were compensated with 10 Euro/hour for their participation.

4.1.2.1.3 Sample 3

Sample 3 consisted of participants from an open source database of the enhanced Nathan Kline Institute-Rockland Sample (NKI, http://fcon_1000.projects.nitrc.org/indi/enhanced/; releases up to 6th). From this database we extracted resting-state fMRI data of 152 healthy, right-handed lean, overweight and obese participants aged 18-35 years (mean age: 24 years, SD: 4.5 years, mean BMI: 26.40 kg/m^2, SD: 5.62 kg/m^2; 84 females). Additional data available for this sample were self-reported eating behaviour (TFEQ) data and anthropometric data (BMI; Table **4.1.1**).

Table 4.1.1 Table representing available data for each of the investigated samples. x marks available datasets

Data	Sample 1 (n=117)	Sample 2 (n=89)	Sample 3 (n=152)
TFEQ	x	x	x
BIS/BAS	x	x	
Anthropometric data (BMI, xxx)	x	x	x
rsEEG	x		
rsfMRI	x	x	x

TFEQ – Three Factor Eating Questionnaire; BIS/BAS – behavioural activation/inhibition system questionnaire; rsEEG – resting-state EEG; rsfMRI – resting-state fMRI

4.1.2.2 Questionnaire data

To investigate how hemispheric asymmetries reflect approach and avoidance behaviours, we used the BIS/BAS (behavioural inhibition system / behavioural activation system)

questionnaire (Carver and White, 1994). This questionnaire was administered in Samples 1 and 2. It consists of 4 different scales – three subscales reflecting BAS – drive, reward responsivity and fun seeking – and a subscale reflecting BIS. According to Carver and White, the drive scale reflects persistent pursuit of desired goals; the fun seeking scale reflects a desire for new rewards and the inclination to approach a rewarding event; the reward responsivity scale focuses on positive responses to rewarding events. The BIS scale, on the other hand, describes individual sensitivity to punishment. With regard to the self-reported eating behaviour, we used the Three Factor Eating Questionnaire (TFEQ; Stunkard and Messick, 1985). It describes eating behaviour on three dimensions – cognitive control for food (CC), disinhibition (DI), and susceptibility to hunger (H). In this study we were predominantly interested in the first two factors, as they might reflect avoidance and approach behaviour towards food, respectively.

4.1.2.3 Neuroimaging data

4.1.2.3.1 EEG data collection – Sample 1

EEG data was collected in Sample 1. Within the study participants completed three assessment sessions in three days. The first assessment day included a cognitive test battery, and on the second assessment day resting-state electroencephalographic (EEG) data were acquired. In the present study resting state EEG (rsEEG) data were analysed together with BIS/BAS and TFEQ, as described below. Resting state EEG data acquisition consisted of 16 blocks, each lasting 1 min of intermittent eyes closed (EC) and eyes open (EO) conditions, summing up to a total duration of 8 min per condition. Resting state EEG was recorded (Brain Vision ActiCAP; Brain Products GmbH, Munich, Germany) in an electrically shielded room with 62 active electrodes placed according to the international standard 10–20 extended localization system, also known as 10-10 system (Oostenveld and Praamstra, 2001), referenced to FCz. Electrooculographic (EOG) activity was recorded with one electrode placed below the right eye, the ground electrode was placed on the sternum. During data acquisition EEG signals were band-pass filtered between 0.015 Hz and 1 kHz at 2500 Hz sampling rate, and the amplifier was set to 0.1 μV amplitude resolution. Electrode impedance was kept below 5kΩ.

4.1.2.3.2 fMRI data collection – Sample 1

Within Sample 1, a third assessment day included acquisition of the resting-state fMRI (rsfMRI) data. We have analysed T2* resting-state, MP2RAGE and fieldmap data collected with a 3T Siemens Trio scanner. Resting-state data parameters: 657 volumes, TE=30ms, FA=69^{o}, TR=1400ms, 64 slices, voxel size: 2.3x2.3x2.3mm^{3}, FoV: 202mm, multiband acceleration factor: 4. The images were acquired in an interleaved order. High-resolution anatomical MP2RAGE image was acquired for each participant using the following parameters: TE=2.92ms, FA1=4^{o}, FA2=5^{o}, TR=2500ms, TI1=700ms, TI2=2500ms, voxel size: 1x1x1mm^{3}, FoV: 256mm.

4.1.2.3.3 fMRI data collection – Sample 2

fMRI data for both of the subsamples within this sample were collected using a 3T Siemens Skyra scanner. We have analysed T2* resting-state, MPRAGE and fieldmap data. 320 T2*-weighted resting-state images were collected using the following parameters: TE=22ms, FA=90^{o}, TR=2000ms, 40 slices, voxel size: 3.0x3.0x2.5mm^{3}, FoV: 192mm. The images were acquired in an ascending order. High-resolution anatomical MPRAGE image was acquired for each participant using the following parameters: TE=2.01ms, FA=9^{o}, TR=2300ms, TI=900ms, voxel size: 1x1x1mm^{3}, FoV: 256mm.

4.1.2.3.4 fMRI data acquisition – Sample 3

For this sample, we analysed resting-state and anatomical data collected with a 3T Siemens Trio scanner. 900 T2*-weighted resting-state images were acquired using the following parameters (http://fcon_1000.projects.nitrc.org/indi/enhanced/mri_protocol.html): TE: 30ms, FA=60^{o}, TR=645ms, 40 slices, voxel size: 3.0x3.0x2.5mm^{3}, FoV: 222mm. The images were acquired in an interleaved order. High-resolution MPRAGE image was acquired for each participants using the following parameters: TE=2.52ms, FA=9^{o}, TR=2600ms, TI=900ms, voxel size: 1x1x1mm^{3}, FoV: 256mm.

4.1.2.4 Data preprocessing

4.1.2.4.1 EEG data - Sample 1

EEG data were pre-processed using EEGLAB toolbox (version 14.1.1b; Delorme and Makeig, 2004) and custom Matlab (MathWorks, Inc, Natick, Massachusetts, USA) scripts. EEG data were band-pass filtered between 1-45 Hz (4th order, Butterworth filter) and downsampled to 250 Hz. EC and EO conditions were extracted and concatenated which resulted in an 8-min block per condition. Artifactual channels and data segments were removed after visual inspection. After principal component analysis (PCA), components (N=30) explaining 95% of the total variance were selected. Independent component analysis (Infomax; Bell and Sejnowski, 1995) was performed in order to reject artifacts relating to eye movements, muscle activity, and heartbeats from EEG data. For further analysis of alpha power, data was transformed to a common average reference.

4.1.2.4.2 fMRI data – Sample 1 and 2

fMRI data preprocessing for the Samples 1 and 2 was identical. The general pipeline is described in details in (Mendes et al., 2017) and was done within the Nipype framework. However, note that not all of the steps described in that paper were used for our pipeline. In short, the preprocessing steps included discarding first five functional volumes, motion correction (FSL MCFLIRT; Jenkinson et al., 2002), distortion correction (FSL FUGUE; Jenkinson et al., 2012), coregistration of temporal mean image to individual's anatomical image (bbregister; Greve and Fischl, 2009), denoising (rapidart and aCompCor; Behzadi et al., 2007), spatial normalisation to MNI 152 2mm (Sample 1), and 3mm (Sample 2) standard space (ANTs; Avants et al., 2011).

4.1.2.4.3 fMRI data – Sample 3

fMRI data preprocessing for the NKI data was done within the Nipype framework and follows the one described in the supplementary methods of (Liem et al., 2017). Note that the bandpass filtering described in Liem et al. was not performed for our data, since further statistical analysis of the fMRI data (fALFF) require them to be unfiltered. In short, the preprocessing steps included discarding first five functional volumes, motion correction

(FSL MCFLIRT; Jenkinson et al., 2002), denoising (rapidart, aCompCor; Behzadi et al., 2007), removal of linear and quadratic signal trends), spatial normalisation to a 3mm standard MNI 152 space (FSL FNIRT; Jenkinson et al., 2012).

4.1.2.5 Neuroimaging measures

4.1.2.5.1 Aim 1: EEG replication analysis

In this step we attempted to directly replicate previous findings of Sutton and Davidson (1997) showing a positive correlation of left hemispheric bias with BAS – BIS differential scores. Firstly, we calculated EEG asymmetry index (AI) in frontal areas by subtracting absolute alpha power (mean value for eyes open and eyes closed, 8-12Hz) in the F3 electrode from absolute alpha power in the F4 electrode for averaged EO and EC conditions.

Next, we wanted to expand on previous findings concerning EEG hemispheric bias, approach and avoidance behaviour, and eating behaviour. Due to the fact that resting-state fMRI data was collected only in the eyes open condition, we decided to only use eyes open condition for the EEG analysis. This step made future comparisons of EEG and fMRI asymmetries data more reliable. We selected alpha power in the broad spectrum (8-12Hz) and in the low spectrum (8-10Hz) for our analysis. Alpha and low alpha power were calculated as means of the squared amplitude obtained after filtering the signal (4th order Butterworth filter) in 8-12Hz and 8-10Hz frequency range, respectively. In humans, the most prominent resting state oscillatory activity is measured at alpha frequency band (8–12 Hz, (Romei et al., 2008; Bazanova, 2012; Bazanova and Vernon, 2014), which has been previously linked to cortical inhibition by top-down control and suppression of task-irrelevant brain regions (Klimesch et al., 2007; Bazanova, 2012) in this way facilitating information gating (Jensen and Mazaheri, 2010). Low alpha power was previously shown to reflect general attentional demands, basic alertness, vigilance and arousal (Petsche et al., 1997). Including both of the measures allowed us to replicate previous results (broadband alpha) and narrow down possible mechanistic interpretations to e.g. general attentional demands (low alpha). For this analysis we used relative alpha and relative low alpha power that we calculated as the ratio of alpha or low alpha power to the power within the frequency range of 4-40Hz. We chose to study relative alpha power to control for individual differences in contaminating factors such

as skull thickness and properties of scalp and meninges that might affect tissue conductivity, consequently influencing electrical signal captured at the sensor level (Babiloni et al., 2011).

An additional improvement in our study compared to previous research was the fact that we calculated asymmetry indices with a different equation: (L-R)/(L+R). These indices better reflect actual asymmetries than the simple L-R difference, and are more straightforward to interpret (Pivik et al., 1993; Hiroshige and Dorokhov, 1997). This is because they are normalised within each subject regarding individual differences in alpha power magnitude. In line with Sutton and Davidson (Sutton and Davidson, 1997), the pair of frontal electrodes included in this analysis was F4 and F3. We also included a parietal pair, P4 and P3, as a control to investigate whether the observed relationship with frontal asymmetries is specific. After calculation of asymmetry indices, we have excluded outliers from all variables of interest using the *a priori* defined criterion (see section 4.1.2.6).

4.1.2.5.2 Aim 2+3: Hemispheric asymmetries in fMRI

After preprocessing (sections 4.1.2.4.2 and 4.1.2.4.3), analysis of fMRI data in all 3 samples was identical. To be able to conceptually compare EEG results with fMRI results, we decided to use the fractional amplitude of low frequency fluctuations (fALFF) as a measure of resting-state brain activity (Zou et al., 2008). fALFF quantifies low frequency oscillations in the resting brain, which in turn reflect baseline brain activity. This measure is usually defined as a ratio of power within frequency range of 0.01-0.1Hz and the power within the entire detectable frequency range. However, in order to further compare results between the samples, we adjusted this analysis. Since each of the samples had a different sampling frequency during fMRI data collection (repetition time, TR), the detectable frequency range would be different for each of them. We therefore changed the definition of the fALFF and divided the power within frequency range of 0.01-0.1Hz by detectable power of 0.00Hz – 0.50Hz (reflecting largest detectable frequency for the sample with lowest TR). This analysis was performed within the Nipype framework and using CPAC (Configurable Pipeline for the Analysis of Connectomes, version 1.0.3) f/ALFF function. In order to be able to compare EEG and fMRI results from our original analysis, we defined a number of regions of interest (ROI) for the fMRI analysis. Since for the EEG analysis we have investigated frontal and parietal

electrodes, we found brain areas closely corresponding to the ones measured by F4/F3 and P4/P3 electrodes. Based on previous literature (Towle et al., 1993; Herwig et al., 2003; Giacometti et al., 2014), we came up with 7 ROIs: Brodmann areas 8, 9, 10, 46 reflecting frontal contributions, Brodmann area 7, postcentral gyrus and paracentral gyrus reflecting parietal contributions. These ROIs were defined using pickatlas (Maldjian et al., 2003). Additionally, since fMRI allows to investigate subcortical brain areas, we investigated hemispheric bias in the ventral tegmental area (sphere with a 6mm radius, coordinates based on Adcock et al., 2006), and the nucleus accumbens (sphere with a 6mm radius, coordinates based on Neto et al., 2008). This is in line with previous studies showing hemispheric asymmetries in these subcortical areas (Tomer et al., 2008; Aberg et al., 2015). Each of the ROIs was defined separately for the left and for the right hemisphere. For each of those ROIs we extracted mean fALFF using SPM 12 (Wellcome Department of Cognitive Neurology, London, United Kingdom) and calculated an asymmetry index as follows: (R-L)/(R+L). Note that this is an inverse index compared to the one we used for EEG data, since we hypothesised that measures used in EEG and fMRI analysis are inversely correlated to each other. This let us directly compare relationships of EEG and fMRI data with behavioural measures. Finally, for each of the variables of interest we excluded outliers based on the *a priori* criterion.

4.1.2.6 Statistical analysis

For all following analyses, we specified *a priori* criterion for outlier detection: 2.2*interquartile range below or above the first or third quartile, respectively (Tukey, 1977; Hoaglin et al., 1986; Hoaglin and Iglewicz, 1987). Further, all regression p-values were corrected for multiple comparisons using Bonferroni correction, by dividing the alpha value 0.05 through the number of regressions performed on the same dataset. All Statistical analyses were performed using R within JupyterNotebook.

4.1.2.6.1 Aim 1: EEG replication analysis

To directly replicate Sutton's and Davidson's research, for each participant we calculated the differential BAS – BIS score. We then removed outliers from both measures of interest (EEG and questionnaire data) using *a priori* specified criteria (section 4.1.2.6). To analyse the data

we performed Pearson's correlation of the obtained asymmetry indices (section 4.1.2.5.1) and the BAS – BIS scores. Final sample size for this analysis after outlier exclusion was 109 participants.

To investigate the relationship between approach and avoidance behaviours and hemispheric bias, we performed four separate multiple regression analyses with asymmetry indices from relative frontal alpha power, relative parietal alpha power, relative frontal low alpha power and relative parietal low alpha power as outcome variables. Predictors included BAS fun, BAS drive and BAS reward responsivity and BIS - BAS scores. To investigate whether gender influences the relationship between questionnaire measures and hemispheric bias, we added an interaction term with gender for each of the questionnaire variables. To control for age and BMI differences we also added this information to the model as predictors. In general, BMI is a variable of interest in this study, however, Sample 1 included participants with a low range of BMI. We therefore did not look at findings concerning BMI in this sample, since the interpretation would prove problematic. This and all following regression analyses were calculated using permutation tests in the 'lmPerm' R package. Alpha threshold for this analysis were corrected for multiple comparisons using Bonferroni correction (divided by the number of regression analyses; α=0.125).

To analyse self-reported eating behaviour, similar regression analysis was performed as described in previous paragraph with different questionnaire variables: cognitive control and disinhibition (TFEQ) and their interactions with gender (Bonferroni corrected α=0.125).

4.1.2.6.2 Aim 2: EEG-fMRI correspondence

Firstly, we wanted to directly investigate the relationship of EEG asymmetries (frontal and parietal) and whole brain fALFF asymmetries in Sample 1. Whole brain fALFF asymmetries were calculated by means of 1) flipping left and right hemispheres in fALFF images, 2) subtracting the flipped image from the original image, 3) adding flipped image to the original image, and 4) dividing image obtained in step 2 by image obtained in step 3. This way we obtained an image of voxel-wise values corresponding to the asymmetry index (L-R)/(L+R) (on the left side of the image). A significant correlation between the EEG asymmetry index as calculated in 4.1.2.5.1 and whole brain fALFF asymmetries would indicate that those two

measures, even though methodologically very distinct, measure similar brain processes. This analysis was performed in SPM12 using GLM with voxel-wise fALFF asymmetries as an outcome variable and the EEG asymmetry index as an explanatory variable. Results were thresholded on a voxel-level with a 0.001 threshold, and corrected for multiple comparisons using the whole-brain 0.05 FWE corrected threshold.

To investigate relationships of fMRI hemispheric bias, approach/avoidance behaviours and eating behaviours, we first used rotated principal component analysis (PCA) on the imaging data. This was done to reduce the number of comparisons in further analyses, and PCA is often used to this end (Jolliffe and Cadima, 2016). We have used the varimax rotation to make the resulting components easier to interpret. This strategy drives component loadings (correlations of components and original variables) either towards zero or towards a maximum possible value, decreasing a number of components with medium loadings, which are difficult to interpret (Richman, 1986; Richman, 1987; Jolliffe, 2002). As a criterion for retaining components we chose the minimum cumulative variance explained to be over 70% (Jolliffe, 2002). This resulted in 5 components for each of the samples.

To investigate relationships of fMRI hemispheric bias and approach/avoidance behaviour, we performed a similar analysis to the one using EEG data. 5 rotated principal components were defined as outcome measures, and predictors included BAS fun, BAS drive, BAS reward responsivity and BIS - BAS scores and their interaction with gender. Additionally, we included BMI and age as control variables (Bonferroni corrected α=0.100).

Similar analysis was performed to investigate relationships between fMRI hemispheric bias and eating behaviour. It included similar predictors as the EEG investigation of eating behaviour – cognitive control and disinhibition and their interaction with gender. Outcome variables were 5 rotated principal components. We added BMI and age as control variables (Bonferroni corrected α=0.100).

4.1.2.6.3 Aim 3: fMRI investigations in samples including obese participants

Investigations of approach/avoidance behaviours in Sample 2 were performed similarly to the ones in Sample 1. 5 rotated components were defined as outcome variables, and

predictors included BIS/BAS questionnaire measures, their interaction with gender, and BMI. Age was added as a regressor of no interest (Bonferroni corrected α=0.100).

Similar analysis was performed to investigate associations of self-reported eating behaviour and hemispheric asymmetries for Samples 2 and 3. Predictor variables included eating questionnaire measures and their interaction with gender, BMI, age (regressor of no interest), while outcome variables were 5 rotated components (Bonferroni corrected α=0.100).

4.1.2.7 Final sample sizes

For measurement of approach/avoidance behaviours within Sample 1, to be able to compare EEG results with fMRI findings, we reduced the sample size to 100 participants due to outlier exclusion in EEG and in fMRI data matrices simultaneously. Further, after outlier exclusion, sample size of Sample 2 was reduced to 87. Concerning the analysis of eating behaviour, final Sample 1 size was 95. Final Sample 2 size was 87 (however, with different participants excluded) and the NKI sample size was 138 participants. We decided to exclude outliers separately for analysis of BIS/BAS data and TFEQ data in order to maximise sample sizes between analyses which were anyway performed as separate multiple regressions. Hence, a potential participant who would be excluded as an outlier in the BIS/BAS data analysis could be retained for the TFEQ data analysis.

4.1.3 Results

4.1.3.1 Samples comparison

To compare the three samples regarding their demographic characteristics we ran separate one-way ANOVAs for BMI and age, and a χ^2 test for equality of gender distribution between the samples. We followed up the ANOVAs with *post hoc* Tukey's tests to determine which groups differed from each other. The results of these analyses can be found in Table 4.1.2. We found that regarding BMI all samples differed from each other, while regarding age, Sample 2 differed from both other samples, which did not significantly differ from each other. Concerning gender distribution, all samples differed from each other.

4.1.3.2 Questionnaire data – samples comparison

Table 4.1.2 represents questionnaire data of all 3 samples included in the study. Performed ANOVAs indicated group differences in both cognitive control and disinhibition scales. Tukey's tests showed that concerning cognitive control there were no significant pairwise differences between groups. Regarding disinhibition, Sample 2 differed significantly from both Samples 1 and 3. We further performed four ANOVAs to compare BIS/BAS data in Samples 1 and 2. This analysis revealed no significant differences for this questionnaire.

Table 4.1.2 Means, standard deviations and statistical tests concerning questionnaire differences in all experimental samples. BIS/BAS questionnaire data were available for Samples 1 and 2, whereas TFEQ data were available for all samples.

	Sample 1 (n=117)			Sample 2 (n=89)			Sample 3 (n=152)			ANOVA		Sample 1 vs. Sample 2	Sample 1 vs. Sample 3	Sample 2 vs. Sample 3
	Mean	SD	Range	Mean	SD	Range	Mean	SD	Range	F(2,355)-value	p-value	p-value	p-value	p-value
BMI (kg/m^2)	23.01	2.57	17.95-31.80	29.54	8.25	17.67-59.78	26.40	5.62	16.26-49.96	33.70	<0.0001	<0.0001	<0.0001	<0.0001
Age (years)	25	3	20-35	27	4	20-37	24	4.5	18-35	18.08	<0.0001	0.0002	0.1544	<0.0001
CC	5.56	4.53	0-18	6.92	4.60	0-20	6.78	4.57	0-20	3.073	0.0480	0.0885	0.0777	0.9719
DI	5.23	2.48	1-12	6.79	3.52	1-15	4.63	2.90	1-15	15.36	<0.0001	0.0006	0.2158	<0.0001
										F(1,204)	p-value			
BAS fun	3.13	0.41	2.25-4.00	3.03	0.50	1.75-4.00	-	-		2.213	0.138	-	-	-
BAS drive	2.94	0.51	2.00-4.00	2.92	0.51	1.50-4.00	-	-		0.103	0.749	-	-	-
BAS reward responsivity	3.41	0.38	2.40-4.00	3.33	0.34	2.60-4.00	-	-		2.561	0.111	-	-	-
BAS – BIS	0.27	0.61	-1.37-2.13	0.18	0.59	-1.25-1.58	-	-		1.077	0.3	-	-	-
Gender										χ^2 test value	p-value			
	42 females			73 females			84 females			53.636	<0.0001	<0.0001	0.0001	<0.0001

4.1.3.3 Aim 1: EEG replication analysis – Sample 1

In this analysis, we aimed to directly replicate findings of Sutton and Davidson (1997) of increased hemispheric asymmetry (F4 – F3 electrodes, absolute alpha power, mean values for EO and EC conditions) being related to increased BAS – BIS differential scores. We therefore performed Pearson's correlation between the AI and BAS – BIS scores for all participants. This analysis, however, did not reveal a significant relationship between those variables (r=0.051, p=0.60). Partial correlation after controlling for BMI, age and gender also did not reveal a significant relationship (r=0.002, p=0.98).

Next, we attempted to expand previous findings linking EEG and approach/avoidance behaviours to 1) additional frequencies spectra, 2) additional questionnaire measures. We therefore investigated relationships between EEG parietal and frontal asymmetry indices as measured by the relative alpha power and relative low alpha power. For questionnaire data we included BAS fun seeking, drive, reward responsivity and BAS – BIS differential scores. Results of performed multiple regression analyses can be found in Table **4.1.3**. They indicated a significant relationship of BAS drive and frontal hemispheric bias in low alpha frequency for females (as shown by a main effect of BAS drive and an interaction of BAS drive with gender – females in the analyses coded as 0). This relationship was not significant for overall alpha power. For scatter plots of these relationships see Figure **4.1.1**. We also observed a significant interaction of BAS – BIS scores and gender on alpha parietal AI, suggesting gender influence on the relationship between BAS – BIS and EEG asymmetries. We do not interpret significant findings for BMI, age and gender, since those variables were added into the model as covariates of no interest.

Further, we investigated the relationship between self-reported eating behaviour (as measured by the TFEQ) and the EEG hemispheric activity. Predictor variables in this case included cognitive control, disinhibition and their interactions with gender (BMI and age entered as regressors of no interest). Here, we did not find any significant associations. Detailed results of these analyses can be found in Table **4.1.4**.

Table 4.1.3 Table with results of multiple regression analyses investigating the relationship between EEG asymmetry indices and approach/avoidance questionnaire measures. Statistically significant coefficients have been marked in bold. Please note that the p-value threshold after Bonferroni correction for four separate regression analyses is 0.0125.

	Alpha frontal		Low alpha frontal		Alpha parietal		Low alpha parietal	
	Beta	p-value	Beta	p-value	Beta	p-value	Beta	p-value
BAS fun	-0.14	0.5275	0.14	0.2508	0.16	0.4318	0.27	1.0000
BAS fun * gender	-0.02	1.0000	-0.13	0.6545	-0.29	0.3721	-0.27	1.0000
BAS drive	0.32	0.3420	**0.66**	**0.0108**	0.31	0.5217	0.08	0.8630
BAS drive * gender	-0.51	0.1000	**-0.88**	**0.0018**	-0.34	0.4815	0.06	0.7450
BAS RR	0.54	0.0477	0.34	0.1083	0.08	0.6545	-0.22	0.3270
BAS RR * gender	-0.54	0.0660	-0.35	0.1747	-0.22	0.4184	0.03	0.6860
BAS - BIS	-0.38	0.2312	-0.35	0.6863	-0.77	0.0304	-0.53	0.1350
BAS – BIS * gender	0.57	0.1294	0.59	0.1241	**0.97**	**0.0078**	0.56	0.4130
Age	0.02	0.8039	0.04	0.7255	0.12	0.3122	0.00	1.0000
BMI	**0.31**	**0.0024**	**0.25**	**0.0076**	-0.13	0.1793	-0.11	0.2530
Gender	0.45	0.0330	0.44	0.0373	0.42	0.4214	0.27	0.2350
R^2	0.22		0.25		0.12		0.07	

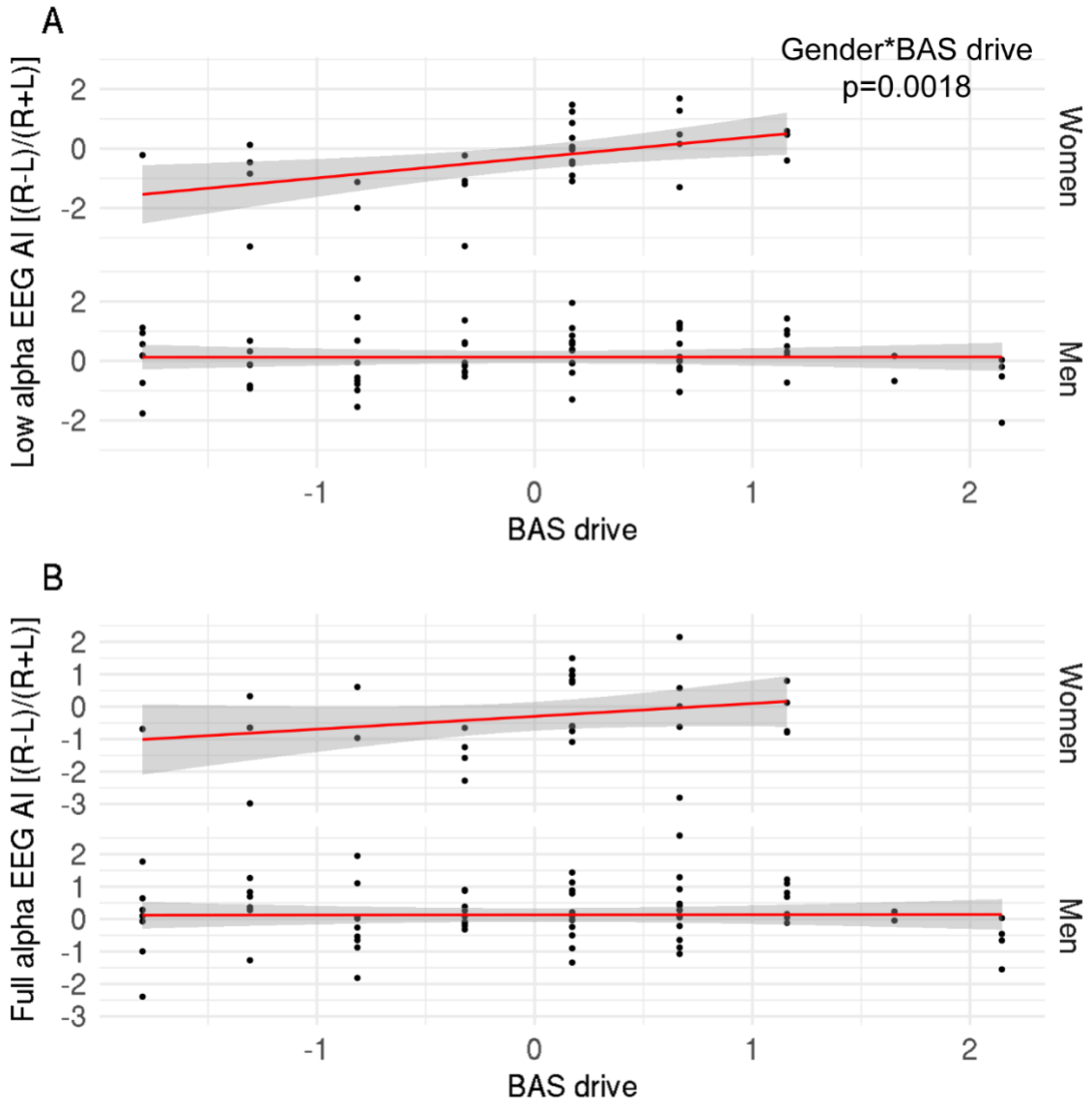

Figure 4.1.1 Figure representing relationship between low/full alpha EEG asymmetry index (AI) and BAS drive scores; this relationship was statistically significant for females. Black dots represent data points, red line represents the best fit, and grey shaded areas are 95% confidence intervals. AI – asymmetry index, R – right, L – left.

Table 4.1.4 Table with results of multiple regression analyses investigating the relationship between EEG asymmetry indices and eating questionnaire measures. Please note that the p-value threshold after Bonferroni correction for four separate regression analyses is 0.0125. CC – cognitive control; DI - disinhibition

	Alpha frontal		Low alpha frontal		Alpha parietal		Low alpha parietal	
	Beta	p-value	Beta	p-value	Beta	p-value	Beta	p-value
CC	-0.11	0.5476	-0.02	0.8627	0.28	0.2444	0.26	0.5810
CC * gender	0.11	0.5476	-0.11	0.6863	-0.36	0.1537	-0.16	0.7840
DI	0.26	0.5000	0.23	0.4110	0.28	0.0966	0.12	0.6230
DI * gender	-0.27	0.4951	-0.23	0.4583	-0.29	0.2210	-0.16	0.6670
Age	0.01	0.9804	0.03	1.0000	0.11	0.8039	-0.02	0.9220
BMI	0.21	0.0292	0.14	0.5217	-0.14	0.6029	-0.05	0.6600
Gender	0.35	0.1625	0.45	0.0502	0.33	0.1419	0.16	0.7650
R^2	0.11		0.09		0.08		0.03	

4.1.3.4 Aim 2: fMRI correspondence analysis – Sample 1

Firstly, we investigated direct relationships between EEG asymmetries and whole-brain fALFF asymmetry measures in the same sample. This analysis did not produce significant results.

Next, we investigated relationships between fMRI asymmetry indices and approach/avoidance behaviours in Sample 1. The analysis included 5 retained components describing asymmetry data and questionnaire variables – BAS fun, BAS drive, BAS reward responsivity, BAS – BIS and their interactions with gender. Additionally, we included BMI and age as covariates of no interest.

Results of this analysis can be found in Table **4.1.5**. We found significant relationships of BAS Drive interaction with gender and rotated component 1 (RC1), and of BAS drive and RC1. For a visualisation of the data see Figure **4.1.2**. Loading of each of the rotated components in the PCA analysis can be found in Table **4.1.6**. It indicates that the RC1 was mostly influenced by

the BA9, BA8 and VTA. For visualisation purposes we present raw ROI (BA9, BA8, VTA) data relationships with BAS Drive scores for males and females in Figure **4.1.3**. The ROIs are visualised in Figure **4.1.4**.

Further, we investigated whether hemispheric asymmetries measured with fMRI are related to self-reported eating behaviour. This analysis included cognitive control, disinhibition and their interactions with gender as predictor variables, while the outcome variables were 5 rotated components from the PCA analysis. Variables of no interest included BMI and age. Here, we did not find any significant relationships. Results of this analysis can be found in Table **4.1.7** and Table **4.1.8**.

Table 4.1.5 Table with results of multiple regression analyses investigating the relationship between fMRI asymmetry indices (Sample 1) and approach/avoidance questionnaire measures. Please note that the p-value threshold after Bonferroni correction for four separate regression analyses is 0.0100. The components have been ordered according to decreasing variance explained.

	RC1		RC2		RC3		RC5		RC4	
	Beta	p-value	Beta	p-value	Beta	p-value	Beta	p-value	Beta	p-value
BAS fun	-0.23	0.2560	0.43	0.0727	0.03	1.0000	-0.07	0.5940	0.40	0.0684
BAS fun * gender	0.32	0.1424	-0.41	0.7647	0.06	1.0000	0.13	0.4900	-0.56	0.0401
BAS drive	**-0.62**	**0.0032**	0.36	0.1673	-0.25	0.3706	-0.09	0.9610	-0.17	0.2996
BAS drive * gender	**0.73**	**0.0002**	-0.52	0.4054	0.30	0.2714	0.19	0.6060	0.23	0.2910
BAS RR	0.17	0.3827	-0.13	0.3043	0.36	0.5733	-0.05	0.8040	-0.38	0.1781
BAS RR * gender	-0.43	0.1002	0.16	0.3636	-0.39	0.5476	0.24	0.5410	0.45	0.1729

BAS - BIS	0.39	0.3030	-0.05	0.7843	-0.05	0.8431	-0.07	0.8430	-0.07	1.0000
BAS – BIS * gender	-0.51	0.2704	0.24	0.6429	-0.12	0.8627	-0.06	0.9410	0.07	0.9216
Age	0.08	0.3300	0.09	1.0000	-0.15	0.0689	-0.09	0.3800	0.10	0.2652
BMI	-0.12	0.2333	-0.11	0.2525	-0.10	0.7647	0.07	0.5410	-0.20	0.0438
Gender	0.02	0.9020	-0.21	0.4234	0.52	0.0277	0.07	0.7250	-0.16	0.7059
R^2	0.14		0.10		0.12		0.06		0.11	

Table 4.1.6 Table representing component loadings for each of the PCA's rotated components (Sample 1) in the BIS/BAS analysis. ROIs represent 9 regions of interest selected for the fMRI analyses

ROI	RC1	RC2	RC3	RC5	RC4
BA10	0.08	0.68	0.16	0.41	-0.22
BA9	0.73	0.38	-0.11	-0.04	-0.13
BA8	0.71	0.27	0.10	0.14	-0.17
BA46	0.24	0.75	-0.02	-0.12	0.10
NAcc	-0.01	-0.02	0.93	-0.05	0.01
VTA	0.79	-0.24	0.00	0.18	0.18
BA7	0.17	0.04	-0.09	0.92	0.04
ParacG	-0.06	0.67	-0.49	0.06	-0.01
PostcG	-0.06	0.00	0.01	0.02	0.96
Cumulative variance explained	0.20	0.39	0.52	0.64	0.76

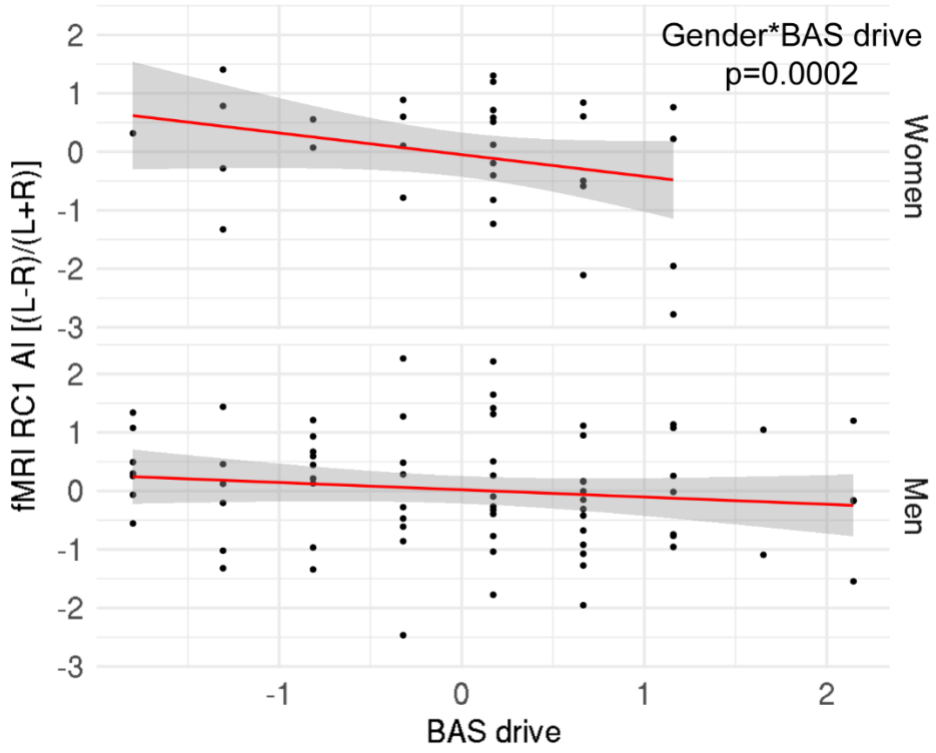

Figure 4.1.2 Figure representing relationship between RC1 and BAS drive scores; there was a significant interaction effect of BAS drive scores and gender on RC1, and a significant effect of BAS drive scores on RC1 in females. Black dots represent data points, red line represents the best fit, and grey shaded areas are 95% confidence intervals. RC – rotated component, AI – asymmetry index, R – right, L – left.

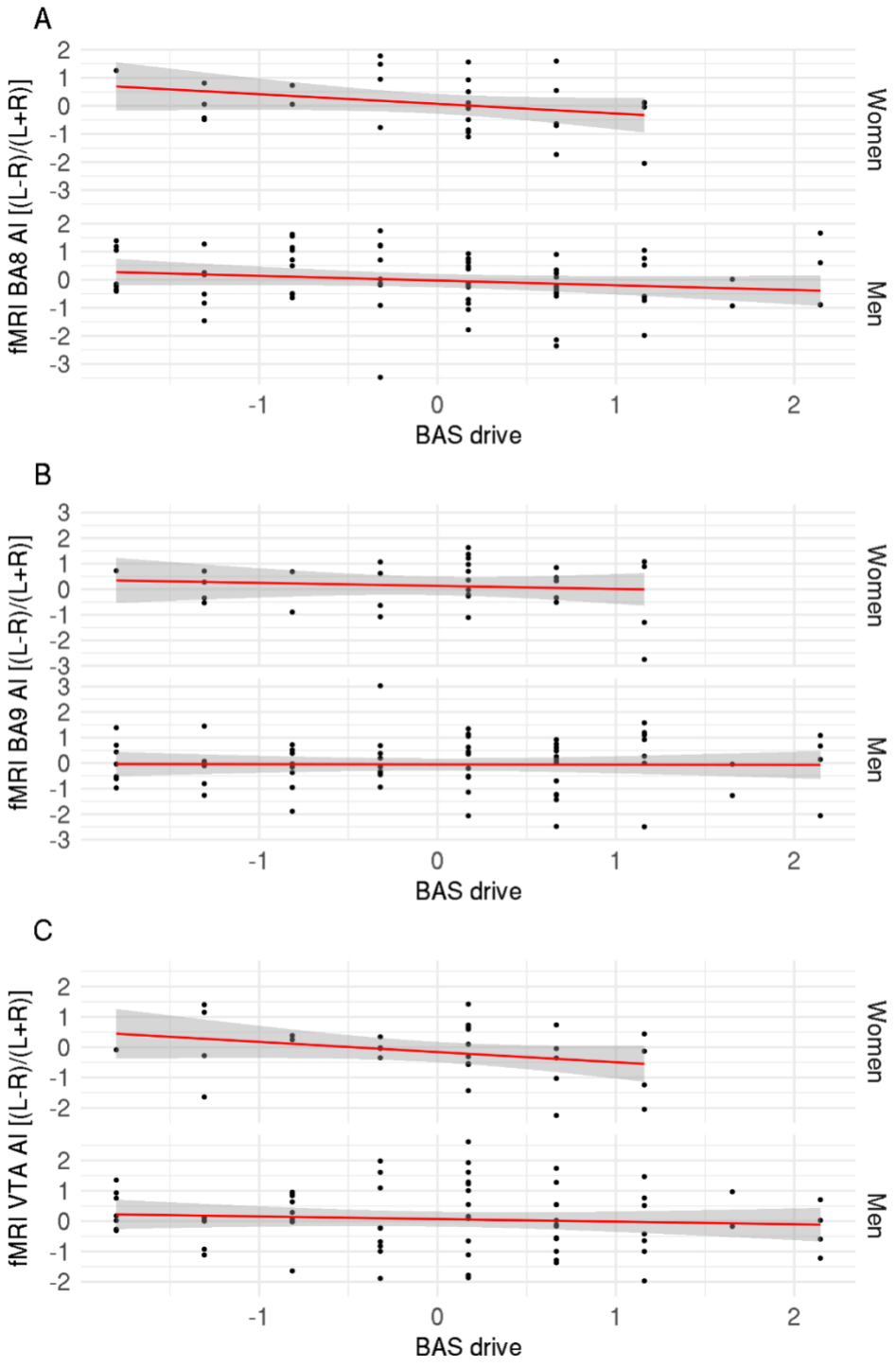

Figure 4.1.3 Figure representing relationship between A BA8 and BAS drive scores; B BA9 and BAS drive scores; C VTA and BAS drive scores; black dots represent data points, red line represents the best fit, and grey shaded areas are 95% confidence intervals. BA – Brodman Area, AI – asymmetry index, R – right, L – left.

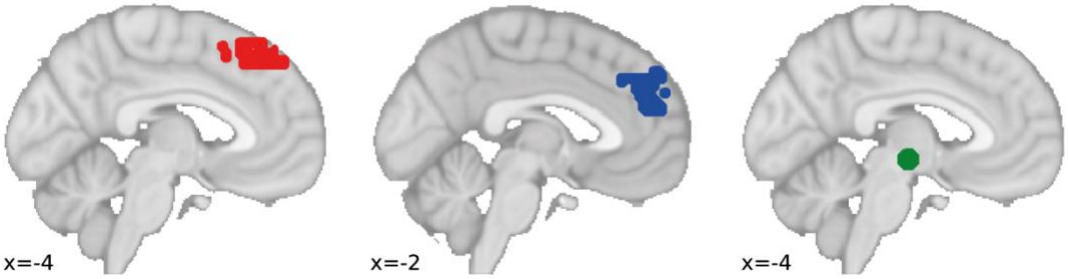

Figure 4.1.4 Figure depicting regions of interest in the BA8 (red), BA9 (blue), and VTA (green)

Table 4.1.7 Table with results of multiple regression analyses investigating the relationship between fMRI asymmetry indices (Sample 1) and eating behaviour. Please note that the p-value threshold after Bonferroni correction for four separate regression analyses is 0.0100. The components have been ordered according to decreasing variance explained. CC – cognitive control; DI - disinhibition

	RC2		RC1		RC4		RC5		RC3	
	Beta	p-value	Beta	p-value	Beta	p-value	Beta	p-value	Beta	p-value
CC	-0.15	0.9410	-0.31	0.0802	-0.09	0.5833	0.32	0.0604	-0.24	0.1940
CC * gender	0.29	0.1960	-0.02	1.0000	-0.05	1.0000	-0.53	0.0201	0.30	0.1170
DI	-0.03	0.8430	-0.02	0.7647	0.12	0.4265	-0.13	0.1670	-0.05	0.9410
DI * gender	0.12	0.4050	-0.02	1.0000	-0.16	0.3961	0.17	0.4265	-0.14	0.6550
Age	0.11	0.2010	0.06	0.3657	-0.15	0.1601	-0.09	1.0000	0.06	0.5940
BMI	-0.16	0.4230	-0.02	0.9804	-0.17	0.8824	0.11	0.1537	-0.02	0.7060
Gender	-0.09	0.7840	-0.21	0.4296	0.50	0.0386	0.07	0.4815	-0.44	0.1440
R^2	0.05		0.12		0.11		0.07		0.08	

Table 4.1.8 Table representing component loadings for each of the PCA's rotated components (Sample 1) in the TFEQ analysis. ROIs represent 9 regions of interest selected for the fMRI analyses

ROI	RC2	RC1	RC4	RC5	RC3
BA10	0.60	0.09	0.17	0.52	-0.20
BA9	0.42	0.68	-0.08	0.02	-0.15
BA8	0.25	0.72	0.12	0.15	-0.12
BA46	0.77	0.16	-0.02	-0.04	0.06
NAcc	-0.05	0.00	0.92	-0.06	0.01
VTA	-0.24	0.80	-0.03	0.13	0.12
BA7	-0.01	0.19	-0.12	0.91	0.05
ParacG	0.67	-0.04	-0.49	0.05	0.00
PostcG	0.00	-0.06	0.01	0.01	0.97
Cumulative variance explained	0.19	0.38	0.50	0.63	0.75

4.1.3.5 Aim 3: fMRI investigations in samples including obese participants

Here, we investigated relationships between fMRI asymmetry indices and approach/avoidance behaviours in Sample 2. The analysis included 5 retained components describing asymmetry data as outcome variables and questionnaire variables – BAS fun, BAS drive, BAS reward responsivity, BAS – BIS their interactions with gender, and BMI as predictors. Additionally, we included age as a regressor of no interest.

Results of this analysis can be found in Table **4.1.9**. We did not find any significant relationships between approach/avoidance behaviours and fMRI hemispheric asymmetries in this sample. Loadings of each of the rotated components in the PCA analysis can be found in Table **4.1.10**.

Further, we investigated whether hemispheric asymmetries measured with fMRI are related to self-reported eating behaviour in Samples 2 and 3. These analyses included cognitive control, disinhibition, their interactions with gender and BMI as predictor variables, while the outcome variables were 5 rotated components from the PCA analysis. Age was entered as a regressor of no interest. Our analyses revealed no relationships between hemispheric asymmetries and eating behaviour in both samples. Details of these analyses can be found in Tables 4.1.11-4.1.14.

Table 4.1.9 Table with results of multiple regression analyses investigating the relationship between fMRI asymmetry indices (Sample 2) and approach/avoidance questionnaire measures. Please note that the p-value threshold after Bonferroni correction for four separate regression analyses is 0.0100. The components have been ordered according to decreasing variance explained.

	RC5		RC3		RC2		RC1		RC4	
	Beta	p-value	Beta	p-value	Beta	p-value	Beta	p-value	Beta	p-value
BAS fun	-0.10	0.3111	0.09	0.4860	-0.11	0.5050	-0.04	0.7843	-0.02	0.7059
BAS fun * gender	0.08	1.0000	-0.51	0.0715	-0.45	0.1600	-0.30	0.7059	0.58	0.0332
BAS drive	-0.03	0.7843	-0.29	0.0416	-0.06	0.8820	0.17	0.1433	-0.11	0.6230
BAS drive * gender	0.29	0.3728	0.57	0.0348	-0.03	0.9220	-0.44	0.0926	0.01	1.0000
BAS RR	0.26	0.0412	-0.05	0.5942	0.20	0.1260	-0.05	0.6863	-0.06	0.6667
BAS RR * gender	-0.49	0.0317	0.34	0.1245	-0.32	0.2380	0.26	0.2927	-0.13	0.6029
BAS - BIS	0.03	0.9608	0.11	0.6190	0.02	0.5620	-0.17	0.2797	-0.14	0.6863

BAS – BIS * gender	0.08	0.9020	-0.35	0.2915	-0.23	0.2820	0.16	0.7843	-0.20	0.3678
Age	0.26	0.0217	0.04	0.6333	0.02	0.8820	0.11	0.5275	0.16	0.0977
BMI	0.11	0.8431	-0.07	0.5275	-0.10	0.6550	-0.14	0.2551	0.08	0.8431
Gender	-0.19	0.4815	0.50	0.0692	0.55	0.1400	-0.03	0.7451	0.27	0.3165
R^2	0.17		0.14		0.13		0.09		0.15	

Table 4.1.10 Table representing component loadings for each of the PCA's rotated components (Sample 2) in the BIS/BAS analysis. ROIs represent 9 regions selected for the fMRI analyses

ROI	RC5	RC3	RC2	RC1	RC4
BA10	0.02	0.15	-0.01	0.86	-0.16
BA9	0.22	0.75	-0.06	0.11	-0.29
BA8	0.53	0.39	0.00	0.31	0.02
BA46	0.11	-0.27	-0.61	0.55	-0.05
NAcc	-0.01	-0.01	-0.08	-0.17	0.88
VTA	0.30	-0.68	0.00	0.01	-0.26
BA7	0.78	-0.11	-0.12	-0.18	-0.22
ParacG	0.06	-0.14	0.90	0.03	-0.08
PostcG	0.64	-0.05	0.27	0.22	0.34
Cumulative variance explained	0.16	0.31	0.45	0.59	0.71

Table 4.1.11 Table with results of multiple regression analyses investigating the relationship between fMRI asymmetry indices (Sample 2) and eating behaviour. Please note that the p-value threshold after Bonferroni correction for four separate regression analyses is 0.0100.

The components have been ordered according to decreasing variance explained. CC – cognitive control; DI - disinhibition

	RC5		RC3		RC2		RC1		RC4	
	Beta	p-value	Beta	p-value	Beta	p-value	Beta	p-value	Beta	p-value
CC	0.02	0.9412	0.08	0.3700	-0.10	0.4350	0.16	0.4810	-0.08	0.2983
CC * gender	0.29	0.5811	-0.07	1.0000	0.31	0.9020	-0.20	0.3070	-0.34	0.2444
DI	0.03	0.8431	0.01	1.0000	0.07	0.8040	0.09	0.2890	0.00	1.0000
DI * gender	0.46	0.1789	-0.01	1.0000	0.03	0.6550	-0.02	1.0000	0.72	0.0146
Age	0.30	0.0048	0.09	0.2020	-0.01	1.0000	0.08	0.5710	0.22	0.0499
BMI	0.09	0.2824	-0.13	1.0000	-0.08	0.6060	-0.17	0.1330	0.06	1.0000
Gender	-0.12	0.9020	0.26	1.0000	0.36	0.2330	-0.08	0.7840	-0.12	0.4775
R^2	0.12		0.03		0.03		0.04		0.16	

Table 4.1.12 Table representing component loadings for each of the PCA's rotated components (Sample 2) in the TFEQ analysis. ROIs represent 9 regions selected for the fMRI analyses

ROI	RC5	RC3	RC2	RC1	RC4
BA10	0.02	0.15	-0.01	0.86	-0.16
BA9	0.22	0.75	-0.06	0.11	-0.29
BA8	0.53	0.39	0.00	0.31	0.02
BA46	0.11	-0.27	-0.61	0.55	-0.05
NAcc	-0.01	-0.01	-0.08	-0.17	0.88
VTA	0.30	-0.68	0.00	0.01	-0.26
BA7	0.78	-0.11	-0.12	-0.18	-0.22
ParacG	0.06	-0.14	0.90	0.03	-0.08
PostcG	0.64	-0.05	0.27	0.22	0.34

Cumulative variance explained	0.16	0.31	0.45	0.59	0.71

Table 4.1.13 Table with results of multiple regression analyses investigating the relationship between fMRI asymmetry indices (Sample 3) and eating behaviour. Please note that the p-value threshold after Bonferroni correction for four separate regression analyses is 0.0100. The components have been ordered according to decreasing variance explained. CC – cognitive control; DI - disinhibition

	RC1		RC5		RC2		RC3		RC4	
	Beta	p-value	Beta	p-value	Beta	p-value	Beta	p-value	Beta	p-value
CC	-0.08	0.7450	0.09	0.1947	-0.17	0.7451	0.18	0.1020	-0.05	0.5733
CC * gender	0.25	0.8630	0.14	0.3125	0.20	0.2062	-0.01	1.0000	0.01	0.9608
DI	-0.04	1.0000	0.10	0.5714	0.12	0.2500	0.00	0.9410	0.02	0.7647
DI * gender	-0.12	0.4300	-0.25	0.1154	0.02	0.9804	-0.09	0.8820	-0.27	0.1009
Age	0.08	0.3110	0.01	0.9608	0.20	0.0176	-0.05	0.5400	0.07	0.2880
BMI	0.02	1.0000	0.14	0.0479	0.03	0.7451	-0.11	0.6330	-0.11	0.0857
Gender	-0.12	1.0000	0.18	0.4737	-0.40	0.0142	0.16	0.8820	0.01	0.9608
R^2	0.03		0.08		0.11		0.04		0.03	

Table 4.1.14 Table representing component loadings for each of the PCA's rotated components (Sample 3) in the TFEQ analysis. ROIs represent 9 regions of interest selected for the fMRI analyses

ROI	RC1	RC5	RC3	RC2	RC4
BA10	0.28	0.63	-0.09	0.01	-0.09
BA9	0.78	0.07	0.02	0.06	-0.04
BA8	0.81	0.10	0.07	0.02	0.00
BA46	-0.05	0.86	0.00	-0.06	0.05

NAcc	0.05	-0.08	-0.04	0.91	-0.05
VTA	-0.04	-0.03	-0.02	-0.03	0.96
BA7	0.35	0.20	-0.67	-0.11	0.21
ParacG	0.29	-0.08	0.70	-0.27	0.04
PostcG	0.17	0.29	0.54	0.39	0.22
Cumulative variance explained	0.18	0.32	0.46	0.58	0.70

4.1.4 Discussion

In this study we aimed at replicating previous EEG findings concerning relationships of resting-state hemispheric asymmetries and approach/avoidance behaviours in healthy participants. Second, we aimed to investigate whether EEG asymmetry findings and fMRI asymmetry findings correspond to each other in the approach/avoidance context, similarly to language or attention context (Powell et al., 2006; Chakrabarty et al., 2017; Mazza and Pagano, 2017). Further, we attempted to expand the findings to self-reported eating behaviour and BMI (which indirectly reflects approach behaviour) using resting-state fMRI. Here, we tested 3 independent samples. In Sample 1 we were not able to directly replicate previous EEG finding showing positive association between BAS – BIS scores (describing individual differences between approach and avoidance behaviours) and higher left resting-state hemispheric bias. We, however, show a conceptual replication of this bias with BAS drive in females only. Secondly, we show that BAS drive scores are related to asymmetries measured by the resting-state fMRI – with an opposite relationship to the one found in EEG. Further, in Sample 2 – including a number of overweight and obese participants and rsfMRI data – we did not find any relationship of hemispheric bias and approach/avoidance behaviour or BMI using the same measures as in Sample 1. Finally, in none of the samples did we find relationships of hemispheric bias and self-reported eating behaviour.

Past work by Gray and colleagues has suggested that human behaviour is driven by behavioural inhibition system and behavioural activation system (Gray, 1981; Gray and McNaughton, 1992). Davidson and other authors in a number of previous clinical and laboratory research proposed that those fundamental behavioural dimensions are driven by

asymmetric engagements of anterior brain regions (Davidson and Hugdahl, 1995). In detail, they showed that neural substrate for inhibition system/withdrawal behaviour is the right prefrontal cortex, while the left prefrontal cortex was related predominantly to approach behaviour. Those conclusions are based predominantly on resting-state EEG studies, but also on studies in patients with anterior frontal brain lesions. In this work we aimed to replicate a seminal study by Sutton and Davidson (1997), which showed a positive association of BAS – BIS differential scores with left hemispheric bias, as measured by rsEEG. We did not find this effect in our study, even though we analysed our dataset in a similar way. There were, however, small methodological differences. Firstly, our defined alpha power spectrum was 8-12Hz, as compared to Sutton's 8-13Hz. Secondly, the reference electrode for our study was different. Thirdly, in our study, the rsEEG duration was 16 minutes (eyes closed + eyes open) as opposed to 8 minutes in Sutton's study (eyes closed + eyes open), and longer duration might provide a better estimation of resting-state processes. Yet it is unlikely that those small methodological differences can explain lack of direct replication. However, our sample size was much larger and included participants in a wider age range. Additionally, gender distribution was not equal, whereas in Sutton's work 50% of the sample were women (however, we controlled for age, BMI and gender). Those factors might influence results beyond what is possible to be corrected by means of statistical analysis.

Importantly, however, in a different type of analysis, one not aimed at methodologically replicating previous work, we found effects that are very similar from a conceptual point of view. Namely, we found a positive relationship between left hemispheric bias (low alpha power) and BAS drive. This effect indicates that higher approach behaviour (or drive towards positive reinforcement) is related to higher left brain activity. This effect points in a similar direction to that of Sutton and colleagues. While they found a similar association to be true for both genders, in our sample it was only true for females. However, we used a different measure of approach behaviour (BAS drive, versus BAS – BIS scores). BAS drive describes an absolute strength of the approach system (drive towards positive stimuli), while BAS – BIS difference scores represent the balance between the two systems. It is possible that those different measures are related to hemispheric asymmetries in a distinct, gender-dependent way. Future studies should replicate this result and investigate

asymmetries with regard to gender differences. It is worth noting that we found significant associations of questionnaire measures and hemispheric asymmetries measured with low relative alpha power, but not with broadband relative alpha power, as it was shown previously. Since low alpha power represents attentional processes, vigilance etc. (Petsche et al., 1997), our results show that hemispheric asymmetries are related to those processes, rather than to general inhibitory processing within the brain.

In our EEG analysis in Sample 1 we also found a significant effect of BMI, where increased BMI was related to higher left, vs. right, hemispheric activity. This sample included predominantly lean participants and we cannot interpret this findings in relation to overweight or obesity. It indicates that this relationship is true within the healthy BMI range. In light of the fact, that obesity is related to increased approach behaviour (Mehl et al., 2018), this association of asymmetries and BMI is in line with previous literature. However, it needs to be replicated in a sample of overweight and obese participants to draw definitive conclusions.

The second aim of our study was to investigate, whether approach/avoidance-related asymmetries can be measured with both EEG and fMRI. We show that the relationship between hemispheric asymmetries, as measured by fMRI and fALFF, and BAS drive, is opposite to the one found in the EEG data (asymmetry index for fMRI data was calculated in the opposite manner to the one for EEG data to account for opposite physiological meaning of alpha power and fALFF measurements). This is interesting for two reasons. Firstly, it shows an indirect relationship between two fundamentally different measures of brain activity. Secondly, it provides evidence that fMRI measures of hemispheric asymmetry can be meaningfully related to approach and avoidance behaviours. This is an important contribution to the field as it provides additional methodological possibilities to investigate relationships between hemispheric asymmetries and behavioural measures of approach/avoidance. Interesting here is the fact that the direction of the relationships measured by EEG and fMRI were opposite. It indicates that alpha power and fALFF might measure very different processes, which is also reflected in lack of direct relationship between EEG and whole brain fALFF asymmetries. Alpha power indeed is conceptualised to

be inversely related to brain activity, but also to measure active inhibition (Klimesch et al., 2007). fALFF on the other hand is said to be a direct measure of brain activity (Zou et al., 2008). We hypothesised that those measures could simply be inversely related to each other, however, as our results indicate, this relationship seems to be more complicated. This might be due to the fact that EEG and fMRI measure electrical activity and hemodynamic response, respectively, but also the fact that the oscillations measured by those two methods differ greatly in frequency ranges (8-12Hz vs. 0.01-0.1Hz). It comes therefore as no surprise that we did not find relationships between relative alpha power and fALFF asymmetries in our direct comparison of the two measures. It is nevertheless encouraging that the asymmetries measured with fMRI and EEG show relationships to the same behavioural measures. This provides a first step for further investigations of relationships between relative alpha power and fALFF measurements.

Being able to find relationships between fMRI asymmetry measures and behaviour, we focused on the third aim of the study – investigations of this relationships in samples including overweight and obese participants, where only fMRI data were available. Concerning approach and avoidance behaviours, we used data of a sample which included lean, overweight and obese people. We investigated relationships between hemispheric bias and BIS/BAS questionnaires. Additionally, we investigated a direct relationship between hemispheric bias and BMI, since BMI is oftentimes related to increased approach behaviour, and obesity has been described as deficiency of right-brain activation (Alonso-Alonso and Pascual-Leone, 2007). These analyses showed a significant relationship neither between hemispheric bias and BMI, nor between hemispheric bias and approach/avoidance behaviour. It means that we did not find support for the right-brain theory of obesity. There are several possible explanations of this lack of support. Firstly, we used rsfMRI measures, which were not included in any studies on which the theory was based. Secondly, our sample was heterogenous, including males and females of a wider age range and BMI values. This heterogeneity might introduce noise which in turn makes it impossible to exactly measure associations of BMI and hemispheric asymmetries. Further, the right brain theory of obesity is based on a number of findings relating eating behaviours and physical activity to hemispheric asymmetries (Regard and Landis, 1997; Short et al., 2005; Uher and Treasure,

2005; Colcombe et al., 2006). None of those studies, however, relates hemispheric asymmetries to obesity measures, and the evidence is very sparse in general. To our knowledge, ours is a first study investigating relationships between BMI and hemispheric asymmetries in large samples and using resting-state neuroimaging measures. Additionally, to our knowledge, none of the previous studies on which the right-brain theory of obesity is based used functional resting-state brain measures. Instead, the studies predominantly investigated patients with unilateral brain lesions or structural asymmetries. Hence, lack of significant findings in the resting-state functional domain is not contradicting previous findings. Future studies need to focus on relationships between obesity measures and hemispheric asymmetries in both resting-state and task contexts to confirm or revise the right brain theory of obesity.

We further investigated associations between hemispheric asymmetries and self-reported eating behaviours in all 3 samples. Here, we were unable to find any relationships using rsEEG and rsfMRI data. This means we were not able to replicate previous rsEEG findings showing hemispheric bias relationships with disinhibition, hunger (Ochner et al., 2009), or restrained eating (Silva et al., 2002). The study by Ochner and colleagues included overweight and obese participants (so did 2 of our 3 samples), and the study by Silva and colleagues included only lean females (one of our samples included mostly lean participants and we investigated interactions with gender). However, certain differences between those studies and our research exist, which might explain different results. Firstly, Ochner and colleagues investigated a group of much older participants (mean age: 49 years). Not knowing the causal relationship between obesity, self-reported eating behaviours and hemispheric asymmetry measures prevents us from directly comparing our and Ochner's results. It is conceivable that the duration of obesity influences prefrontal asymmetries, hence age might explain differences between results. Furthermore, in our study we were very conservative with regard to multiple comparisons correction, while Ochner and colleagues were more liberal in this respect.

Some limitations of this study include the fact that EEG data were only available for one sample. It would provide additional evidence to investigate differences between EEG and

fMRI asymmetry associations with behavioural measures in other samples, especially concerning BMI and eating behaviour – aspects not investigated as thoroughly as approach/avoidance behaviours. Further, our study investigates relationships between self-reported approach/avoidance behaviours and resting-state neuroimaging measures. Future studies should focus on investigating task-based approach/avoidance behaviour and, ideally, task-based neuroimaging measures, especially in the context of obesity. This might turn out to be a more precise proxy for everyday motivational behaviours and therefore have higher ecological validity.

In sum, we were able to conceptually replicate findings showing relationships between hemispheric bias and approach/avoidance behaviours, but not self-reported eating behaviour. Moreover, this study is the first one to investigate relationships between rsEEG alpha power measures and rsfMRI fALFF. We show that associations of hemispheric asymmetries measured with rsEEG and rsfMRI are opposite. Future studies should answer the question of how those measures relate to each other in a more systematic way, which was impossible for us, since in our study samples including obese individuals were samples with no EEG data available. We suggest that future studies should be performed using well controlled samples of lean, obese and overweight participants using both EEG and fMRI measures.

4.2 Study 2 - unhealthy yet avoidable – how cognitive bias modification alters behavioural and brain responses to food cues in obesity

4.2.1 Rationale of the study

Study 2 was implemented in order to investigate neural correlates of the approach bias found in obesity, and mechanisms underlying successful modification of this bias. This study tackled automatic tendencies towards food in obesity. Since similar studies were performed only in the alcohol context, it was important to investigate, whether approach bias towards food cues and CBM in obesity share similar neural correlates and mechanisms. In our study we presented participants with healthy and unhealthy food pictures, to which participants were asked to respond by either pulling (approach) or pushing (avoidance) a joystick placed in their hands. This reaction was per test instructions based on the format of the picture, not its content, to investigate automatic responses to food stimuli. We hypothesised that, in line with previous literature, obese participants will show larger approach bias towards unhealthy food cues, as compared with healthy food cues. We further expected that this would be related to higher activity in the reward-related dopaminergic brain regions, such as the ventral striatum, the amygdala or the mPFC. To investigate mechanisms of CBM, we trained participants to avoid unhealthy food pictures and approach healthy food pictures. We then investigated how this training related to changes in the neural activity measured with XXX in responding to food pictures. There were two possible candidate mechanisms: 1) changes in brain regions related to reward valuation and perception; 2) changes in the brain's inhibitory system. We hypothesised that CBM will decrease approach tendencies towards unhealthy foods and increase approach tendencies towards healthy foods in the training group only. We further hypothesised that, should our intervention be successful, it will be reflected in changes in activity in the ventral striatum, amygdala and medial prefrontal cortex, or within brain inhibitory regions, such as the frontoparietal network, including the dlPFC and parietal cortex.

4.2.2 Materials and methods

4.2.2.1 Participants

34 obese participants aged 18-35 years took part in the experiment (mean BMI=36.49kg/m^2, σ=6.29, mean age=29.5 years, σ=4.5; for a more detailed sample characteristics see Table 4.2.1). The sample size was selected according to a similar previous study investigating CBM effects in alcohol-dependent patients (Wiers et al., 2014). Participants met the following inclusion criteria: no history of neurological/psychological diseases, no thyroid disease, normal or regulated to normal blood pressure, no drug or alcohol addiction, no smoking, and no MRI-related contraindications. Volunteers were compensated with an amount of 10 Euro/hour. The study was conducted according to the Declaration of Helsinki and approved by the Ethics Committee at the location which will be identified if the article is published. All participants gave their written informed consent prior to their participation in the study.

4.2.2.2 Behavioral assessment

In our study we included the Three Factor Eating Questionnaire (TFEQ; Stunkard and Messick, 1985), assessing eating behavior on three dimensions: cognitive restraint, disinhibition and hunger. The behavioral inhibition/activation system (BIS/BAS; Carver and White, 1994) was used to evaluate how a person's behavior is driven by reward and punishment. Questionnaires were used as baseline comparison of groups included in the study.

Participants' BMI was assessed on the day of experiment. Before and after the MRI part, participants rated their mood, hunger and tiredness on a visual analogue scale (VAS, scale 0-10). Moreover, subjects were asked to sort a set of forty food pictures concerning their perceived healthiness and liking (see section 4.2.2.4 for details). This picture set was independent of the one used in the fMRI task (see section 4.2.2.3 for details). It included healthy and unhealthy food pictures of comparable healthiness and liking to the fMRI picture set. Each of these credit card-sized pictures was placed by a participant on a large cardboard with a printed scale (0-10).

4.2.2.3 fMRI task

The overview of the experimental paradigm can be found in Figure 4.2.1. We randomly assigned participants to either a training or a no-training group. Participants were not informed and not aware that training will take place, and the experiment introduction was performed by a blinded experimenter. The fMRI part consisted of a training version of the Approach-Avoidance task (AAT; Wiers et al., 2010), which measures and modifies automatic action tendencies. The AAT consisted of three main phases: a pre phase, a training or a no-training phase, and a post phase. Transitions between the phases happened unbeknownst to participants. During the task, participants were presented with healthy and unhealthy food pictures in two different formats – horizontal and vertical. They were instructed to react to them by pushing (avoidance) or pulling (approach) a joystick placed in their right hand. Subjects reacted to the format of the picture, not its content, e.g. by pushing the joystick away every time a picture in a horizontal format appeared. In this study, participants were randomly assigned to either a push-vertical or a push-horizontal condition to make sure that picture format did not systematically influence results. Moreover, a zooming feature was implemented to highlight avoid and approach reactions. Impressions of approaching and avoiding stimuli were created by a consecutive presentation of three pictures increasing or decreasing in size, when pulling or pushing the joystick, respectively (Figure 4.2.2).

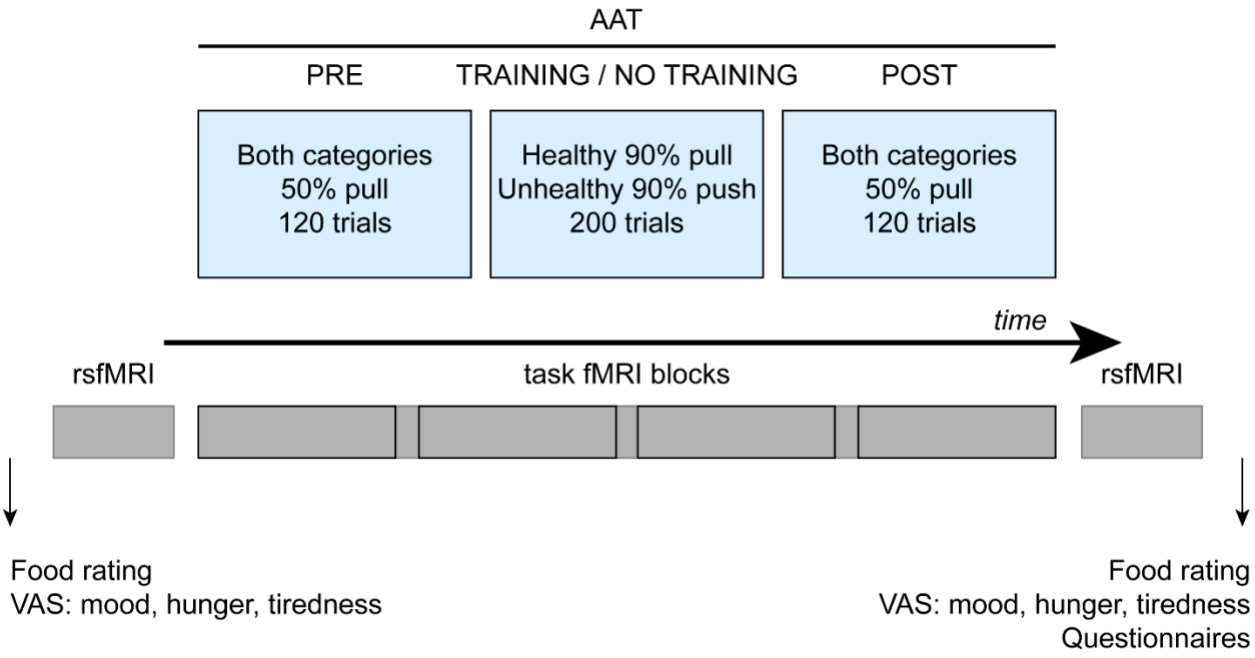

Figure 4.2.1 Overview of the experimental paradigm

During the pre and post phase all pictures appeared equally often in push and pull format in both groups. Within the training phase, in the training group, 90% of unhealthy pictures appeared in a push format, and 90% of healthy pictures appeared in a pull format. This way we attempted to train an avoidance of unhealthy food images and an approach towards healthy food images. In the no-training group, the training phase did not differ from the pre and post phase.

Pre and post phases consisted of 120 trials each, whereas the training phase consisted of 200 trials. Each trial consisted of a picture presentation period, for which participants had to react as fast as possible by pushing or pulling the joystick (max. 2000ms), a zooming period, where pictures increased or decreased in size depending on participants' reactions (3*250ms), and an intertrial interval (ITI). Duration of the ITI was jittered (1000-3000-5000ms, exponential distribution of respective durations). In order to keep the duration of each trial independent of reaction time, time left from the picture presentation period (2000ms – reaction time) was added to the ITI (Figure 4.2.2).

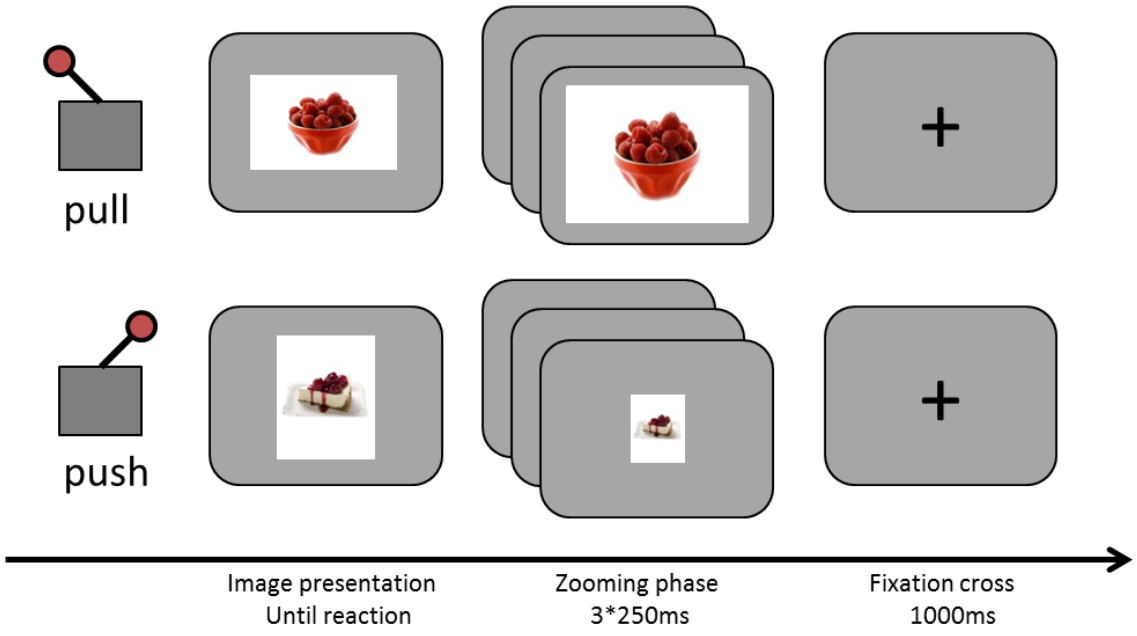

Figure 4.2.2 Modified Approach-Avoidance-Task

Further, we aimed to test whether potential changes in automatic action tendencies are specific to pictures included in the training phase or can be generalized to the entire category (healthy vs. unhealthy). Therefore, only a subset of pictures used in pre and post phases was used for training (randomly chosen set of 20 out of 30 pictures for each participant).

The entire AAT lasted around 40 minutes and was symmetrically divided into four runs, each including 110 trials (independent of pre, training, or post phases). Participants were offered breaks between runs to relax and close their eyes.

During the 90-minute-long fMRI part following scans were collected: fieldmap, pre resting state scan, 4 blocks of functional MRI with the AAT, post resting state scan and an anatomical scan (for details see section 4.2.2.5).

4.2.2.4 Selection of stimuli

Food images for the AAT and the picture sorting task were selected from the food-pics database (Blechert et al., 2014). According to a previous study (Mehl et al., 2018) images were categorized in healthy and unhealthy images in line with current nutritional guidelines, such as the Healthy Eating Index (Guenther et al., 2013) or the Dietary Guidelines for American Adherence Index (Fogli-Cawley et al., 2006). Additionally, an online pre-rating had been conducted, where participants (n=100) rated images regarding perceived healthiness and liking. Only images that were clearly identified as healthy or unhealthy were included in the picture set (Mehl et al., 2018).

4.2.2.5 Neuroimaging

Neuroimaging data were acquired using a 3T Siemens SKYRA scanner with a 20-channel head coil. For the AAT, 1104 T2*-weighted images were collected using the following parameters: TE=22ms, FA=90^{o}, TR=2000ms, 40 slices, voxel size: 3.0x3.0x2.5mm^{3}, distance factor: 20%, FoV: 192x192mm^{2}. 2*320 open-eyes resting state T2*-weighted images were acquired using the same parameters. The images were acquired in an ascending order. High-resolution anatomical MPRAGE image was acquired for each participant using the following parameters: TE=2.01ms, FA=9^{o}, TR=2300ms, TI=900ms, voxel size: 1x1x1mm^{3}, distance factor: 50%, FoV: 256x256mm^{2}.

4.2.2.6 Data analyses

4.2.2.6.1 Behavioral analysis

In line with previous studies, mean reaction times were calculated for the picture categories (healthy vs. unhealthy food) and across both conditions (avoid vs. approach) during all three phases of the experiment. Bias scores were generated by calculating difference scores per category and condition: healthy_push – healthy_pull and unhealthy_push – unhealthy_pull. Thus, a positive score reflects faster approach reactions for the respective category, while a negative score indicates faster avoidance reactions.

No subject had to be excluded due to outliers or error rate. Outliers were defined as mean reaction times within a condition lying below or above 2 standard deviations from the group

mean. The task was performed with a high level of accuracy (mean accuracy = 97%, SD=3.23%).

Baseline behavioral tendencies were assessed by testing whether bias scores significantly differed from zero during the pre-training phase. Further, we compared the training and the no-training group, to ensure that no baseline differences were present. The analyses were carried out using one-sample and independent samples t-tests, respectively.

Changes from pre to post were analyzed using a repeated-measures 2x2x2 analysis of variance. Group (training vs. no-training) was used as a between-subject factor, and image category (healthy vs. unhealthy food) and time (pre vs. post) as within-subject factors.

We further followed up by testing if bias scores significantly differed from zero in the post phase and whether bias scores for the two food categories significantly differed from each other. Both analyses were performed with t-tests.

Questionnaire data were analyzed in order to investigate potential group differences using an independent-samples t-test. Distribution of all questionnaire measures was normal or close to normal, and equal variance between groups was assumed for all the tests.

Distributions and confidence intervals / observed power for all statistical tests can be found in the statistical table (Table 4.2.10).

4.2.2.6.2 fMRI data analysis

- **Data preprocessing**

AAT-fMRI and rsfMRI data were preprocessed in a similar fashion. Data were preprocessed and statistically analyzed using FMRIB Software Library 5.0.8 (FSL, The University of Oxford, Oxford, United Kingdom (Jenkinson et al., 2012), SPM 12 revision 6225 (Wellcome Department of Cognitive Neurology, London, United Kingdom), Analysis of Functional NeuroImages version 17.0.04n (AFNI; Cox, 1996), Advanced Normalization Tools (ANTs; Avants et al., 2011) and MATLAB R2012b (The MathWorks, Inc., Natick, Massachusetts, United States). Firstly, to enable further preprocessing steps, high resolution anatomical images were skull-stripped using FSL's brain extraction tool (Smith, 2002) and SPM 12

segmentation tool. Functional data were motion corrected using McFLIRT (Jenkinson et al., 2002), fieldmap corrected and registered to high resolution anatomical images (FLIRT, boundary based registration; Jenkinson and Smith, 2001; Jenkinson et al., 2002; Greve and Fischl, 2009), slice-timing corrected, and smoothed with a 6mm FWHM Gaussian kernel (not rsfMRI data used for connectivity analysis (Alakörkkö et al., 2017) using FSL's FEAT. To ensure that motion- and physiological noise-related artefacts were removed from the functional time-series, we used independent component analysis automatic removal of motion artefacts (ICA AROMA; Pruim et al., 2015) toolbox on the time-series. Further, we regressed out the signal in white matter and cerebrospinal fluid from the functional data. Then, anatomical images were normalized to a 3mm MNI template using ANTs. Using transformation information from the previous registration steps, functional images were registered to the 3mm MNI template using ANTs. Prior to statistical analysis on an individual level, AAT-fMRI data were high-pass filtered with a filter of 128s (SPM). Prior to connectivity analyses, resting state data were high pass filtered (FSL; σ=22).

- **AAT fMRI data analysis**

A random-effects analysis was performed using SPM12. Individual regressors on a subject level were entered into a general linear model and convolved with a double-gamma hemodynamic function. Individual contrast files were then entered into second-level analysis, where we compared subjects as groups. In this step, BMI and age were entered into the analysis as covariates of no interest. Entering BMI as a covariate enabled us to only investigate general obesity effects and discard between-subjects differences that could potentially be caused by different BMI values. As obesity is defined as having a BMI value above 30 kg/m^2, the variance in this respect can be large, hence the necessity to adjust our analyses for BMI values. Age was entered as a covariate since our groups differed in this respect. Results were always thresholded at a whole-brain voxel-wise level with a threshold of 0.005, and on a cluster level with a family wise error corrected threshold of 0.05. The voxel-wise threshold was chosen *a priori* and is more conservative than recently suggested fMRI practice (Bansal and Peterson, 2018).

- **GLM1: Pre and post data analysis**

In this analysis we investigated neural correlates of food approach bias, as well as training effects on the brain. On a single-subject level we entered only the pre and post trials into a general linear model. This resulted in 16 different regressors over 2 sessions. 4 regressors for the picture presentation period pre-training (healthy_pull, healthy_push, unhealthy_pull, unhealthy_push), 4 regressors for the zooming period pre-training (corresponding to four different types of trials) and a similar set of 8 regressors for the post phase. For the picture presentation period, onsets of the regressors were time-locked to the picture presentation, and event duration was equal to the reaction time. This variable epoch model was described as the most appropriate for reaction time tasks (Grinband et al., 2008). The onsets of the zooming period regressors were time-locked to the end of the picture presentation period, and the durations were set to 750ms. For the pre phase, first level contrasts included general food approach and avoidance, and similar contrasts specific to each food category. Moreover, we investigated pre to post changes only in trained conditions. We also investigated training effects on food avoidance tendencies separately for healthy and unhealthy food pictures. On a second-level, individual contrasts regarding the pre phase were entered into a one sample t-test, in order to investigate neural correlates of food approach bias independent of group membership. To make sure that no pre-training differences in task-related brain activity between groups were present, we entered individual contrasts into a two-sample t-test. Further, contrasts involving comparisons of pre and post phases were entered into two sample t-tests to investigate effects of training.

- **GLM2: PPI analysis**

In order to investigate whether our intervention was related to changes in functional connectivity, we conducted a psychophysiological interactions analysis. This analysis compares brain connectivity changes from a specified seed in the brain between two different experimental conditions. Firstly, we defined a 6mm sphere (radius) around the peak voxel in a cluster reflecting training effects (right angular gyrus). Secondly, we extracted raw time-series from this volume of interest (VOI). Thirdly, we defined a new GLM consisting of six different regressors: the time course of the VOI pre-training (physiological

factor), the main effect of unhealthy_push condition (psychological factor), the interaction term between the two factors for the pre-training phase, and 3 corresponding regressors for the post-training phase.

- **Resting-state fMRI data analysis**

We acquired and analyzed resting state data in order to investigate whether the effects of CBM are transferrable to functional changes in the brain not directly related to AAT. These data can be used to analyze resting state functional connectivity – answering the question of how different brain regions interact with each other. Resting state connectivity analysis helps to understand how all brain regions generally interact with each other (degree centrality, DC), but also how specific *a priori* defined brain regions correlate with other brain areas (seed-based connectivity analysis, SCA). To our knowledge, this is the first study investigating this particular aspect. Hence, we decided to use a hypotheses-based approach of seed-based connectivity analysis with different inhibitory and reward-related seed regions, but also a hypotheses-free approach of degree centrality.

- **Seed-based connectivity analysis**

In our study we investigated seed-based connectivity using predefined ROIs (see section 'definition of seeds') as seeds. Unsmoothed (Alakörkkö et al., 2017), slice-timed, motion-corrected and registered to the MNI template images were entered into the analysis. The analysis was performed using Nipype and Nilearn algorithms. It resulted in eight connectivity maps, one for each ROI, and one for each of the phases of the experiment (pre- and post-AAT). Connectivity maps were then smoothed with a 6mm FWHM Gaussian kernel, andpre-AAT maps were subtracted from the post-AAT maps. Resulting volumes were then entered into a two-sample t-test to investigate group differences. Here, FWE-corrected statistical thresholds were also Bonferroni corrected for number of seeds.

  - **Definition of seeds**

To investigate task-unrelated connectivity differences caused by CBM, we defined a number of seeds directly related to reward processing, visual food stimuli processing and inhibitory control. This was done in order to test our hypotheses of reward vs. inhibitory mechanisms

involved in the CBM. The following seeds were included in our study: the medial and the left and right dorsolateral prefrontal cortex (mPFC, dlPFC, cooridnates from: Shirer et al., 2012), the left and right amygdala and nucleus accumbens (Amy, NAcc, coordinates from: pickatlas Maldjian et al., 2003) and the left middle frontal gyrus (MFG, coordinates from: van der Laan et al., 2011). The mPFC, amygdala and the nucleus accumbens were previously shown to be engaged in approach-avoidance tendencies and are widely accepted reward-related brain regions (Wiers et al., 2014). The mPFC is widely accepted as the brain's valuation center (Kable and Glimcher, 2007), the amygdala is important for Pavlovian learning and formation of emotional memories (Volkow et al., 2004; Koob and Volkow, 2010), whereas the nucleus accumbens receives and sends dopaminergic projections as response to rewarding stimuli (Volkow et al., 2004; Hyman et al., 2006; Heinz et al., 2009; Koob and Volkow, 2010). The dlPFC was previously related to approach-avoidance tendencies and is an inhibitory brain region (Hare et al., 2011; Dietrich et al., 2016b). Lastly, the left MFG is a region preferentially activated for viewing high versus low caloric food stimuli (van der Laan et al., 2011).

- **Degree centrality**

Degree centrality is defined as a number of direct connections of a node to all other nodes in the network (Zuo et al., 2012). This measure was calculated using AFNI within the Nipype framework, with correlation thresholds set to 0.5 (only correlations with r>0.5 included in results). Firstly, we calculated DC maps separately for each participant and phase of the experiment. Secondly, similarly to previous resting-state analyses, we subtracted the pre-AAT maps from the post-AAT maps. These volumes were then entered into a two-sample t-test.

4.2.3 Results

4.2.3.1 Behavioral results

To check for possible baseline group differences, we compared VAS ratings, questionnaire variables, and AAT picture ratings between groups. Participants in the training and no-training group did not statistically differ at baseline regarding hunger, tiredness, and mood (smallest p = .534[d-f],Table 4.2.1). The groups also did not differ regarding all questionnaire

variables (smallest p = .082[g-m]) and subjective ratings of the AAT stimulus material in terms of healthiness and liking (smallest p = .498[n-q], Table 4.2.2).

Table 4.2.1 Sample characteristics of the training and no-training groups; p-values reflect significance of group differences

	Training Group	No-Training Group	p-value/t(31) value (unless stated otherwise)	Effect size |d| (unless stated otherwise)
	Mean/SD (unless stated otherwise)			
n	17	16		
Sex[a]	11 ♀. 6 ♂	7 ♀. 9 ♂	0.227/χ^2=1.460	φ=0.043
Age [years][b]	28/5	31/4	**0.027/2.314**	0.663
BMI [kg/m^2][c]	35.57/4.63	36.95/7.63	0.530/0.635	0.219
Hunger [VAS cm; not hungry – hungry][d]	2.31/1.81	2.73/1.91	0.534/0.629	0.226
Tiredness [VAS cm; not tired – tired][e]	4.31/2.60	4.00/2.30	0.726/-0.354	0.126
Mood [VAS cm; in a bad mood – in a good mood][f]	7.69/1.58	8.20/1.26	0.711/=0.374	0.357
TFEQ cognitive control[g]	8.11/6.12	6.63/4.01	0.417/-0.822	0.286
TFEQ disinhibition[h]	9.29/3.16	7.19/3.56	0.082/-1.800	0.624
TFEQ hunger[i]	6.94/4.35	5.75/3.44	0.391/-0.869	0.303
BIS[j]	20.53/4.61	19.94/5.23	0.732/-0.345	0.120

BAS drive[k]	12.00/2.06	11.62/2.63	0.651/-0.457	0.161
BAS fun seeking[l]	13.18/2.16	12.38/1.89	0.267/-1.131	0.394
BAS reward responsivity[m]	16.76/1.92	16.75/1.39	0.980/-0.025	0.006

Table 4.2.2 Ratings of healthy and unhealthy images used in the AAT paradigm for healthiness and liking on a scale from 0 to 10

Image category	Scale	Training Group	No-training Group	p-value/t(31)-value	Effect size |d|
		Mean/SD			
Unhealthy	Liking[n]	6.11/0.90	5.95/1.34	0.692/-0.399	0.140
	Healthiness[o]	1.81/0.78	1.76/1.21	0.885/-0.146	0.049
Healthy	Liking[p]	7.64/0.71	7.44/1.17	0.555/-0.596	0.207
	Healthiness[q]	8.67/0.67	8.73/0.62	0.775/0.288	0.093

Next, we investigated whether participants rated the AAT pictures differently depending on their respective category. Healthy images were rated as significantly healthier ($t(32)=36.723$; $p < .001$[r], $d=6.40$) and were more liked ($t(32)=5.507$; $p < .001$[s]. $d=0.96$) than unhealthy images.

Further, we hypothesized that ratings of the independent picture set that participants sorted before and after the fMRI AAT (Table 4.2.3) would be affected by training (interaction with factor group). To this end we performed separate 2x2x2 ANOVAs for healthiness and liking ratings with image category, time and group as factors. They revealed no interactions with group (healthiness: $F(1,31)=0.001$, $p=0.975$, $\eta^2_p = .000$; liking: $F(1,31)=0.453$, $p=0.503$[u], $\eta^2_p = .014$)

Table 4.2.3 Picture sorting task – ratings of healthy and unhealthy images on healthiness and liking on a scale from 0 to 10. We observed no significant group differences

Image Category	Scale	Training Group		No-training Group		Image category * time * group interaction	Effect size η2p
		Pre	Post	Pre	Post		
		Mean/SD				p-value/F(1,31)-value	
Liking	Unhealthy	5.76/ 1.17	5.37/ 1.57	5.97/ 1.82	5.39/ 1.94	0.975t/0.001	0.014
	Healthy	7.24 /0.99	7.39/ 1.07	7.23/ 1.63	7.35/ 1.63		
Healthiness	Unhealthy	1.38/ 0.82	1.53/ 0.88	1.25/ 1.01	1.50/ 1.16	0.503u/0.453	0
	Healthy	8.42/ 0.76	8.43 /0.83	8.27/ 0.97	8.38/ 0.90		

4.2.3.1.1 Approach-avoidance task

To analyze the AAT data, we first computed bias scores and tested for baseline approach bias towards food. As expected, at baseline, both groups showed a significant approach bias

towards food, as bias scores for both healthy and unhealthy images were significantly greater than zero (training group: $t(16)=2.994$, $p = .009$[v] and $t(16)=2.334$, $p = .033$[w], no-training group: $t(15)=3.728$, $p = .002$[x] and $t(15)=2.218$ $p = .042$[y], respectively). Further, we investigated whether bias scores differed from *pre* to *post* (independent of group) and whether there were differences between picture categories. We found significant main effects for image category ($F(1,32) = 4.471$, $p = .042$[z], $\eta^2_p = .123$) and time ($F(1,32) = 9.655$, $p = .004$[aa], $\eta^2_p = .232$). The first main effect reflects generally higher bias scores for healthy food images independent of experimental phase. The second main effect reflects lower bias scores in the post compared to pre phase of the experiment.

The main question of our study was whether CBM can affect approach behavior towards food stimuli, and whether this effect depends on picture category. To answer this question, we used a 2x2x2 ANOVA with group, image category and time as factors. Indeed, we found a significant three-way interaction of group (training or no-training), image category (healthy vs. unhealthy) and time (pre-vs. post-training) ($F(1,31) = 8.902$, $p = .006$[ab], $\eta^2_p = .223$). We then performed follow-up paired t-tests to investigate in which conditions there was a significant change from pre to post phase. They indicated that in our study individuals in the training group, as opposed to the no training group, decreased approach tendencies towards unhealthy images only (Table 4.2.4[ac-af], Figure **4.3.2**).

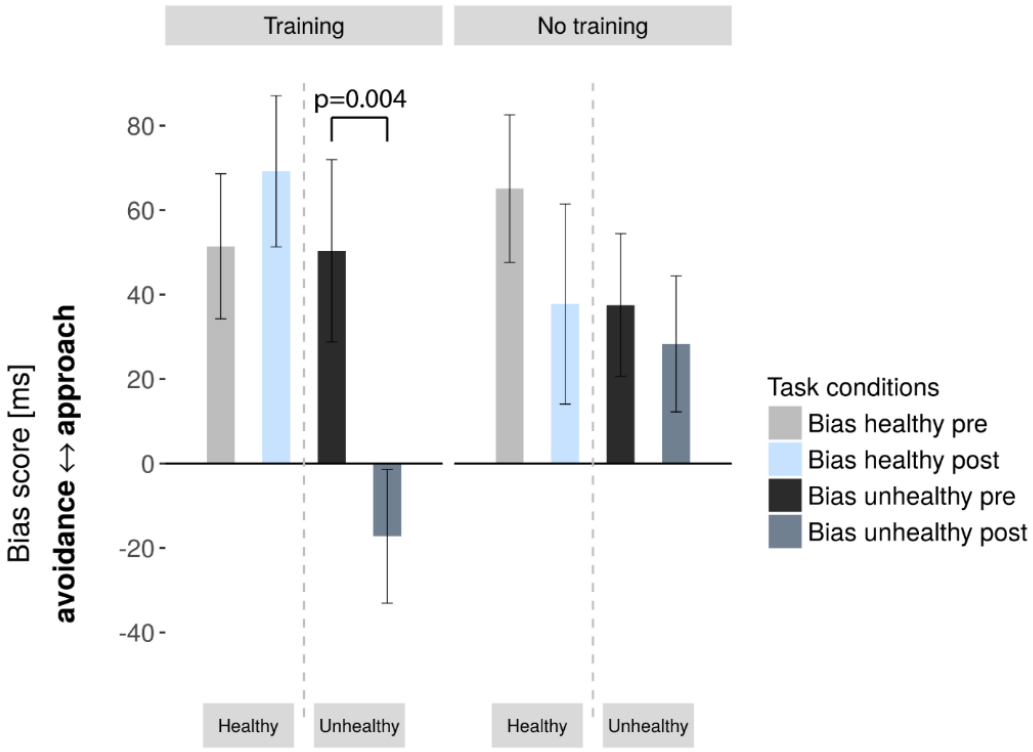

Figure 4.2.3 Bias scores in the training and no-training groups pre and post training (errorbars: standard error of the mean). We observed a significant interaction of group by time by image category.

Table 4.2.4 Bias scores for healthy and unhealthy images in the training and no-training group for the pre and post phases. P-values reflect significance of changes from pre to post in bias scores.

Image category	Training Group				No-training Group			
	Pre	Post	p-value/ t(16)-value	effect size d	Pre	Post	p-value/ t(15)-value	effect size d
	Mean/SD				Mean/SD			
Unhealthy	50.35/ 88.97	- 17.24/	**0.004/ -3.336**[ac]	0.810	37.50/ 67.63	28.31/ 64.34	0.585/ 0.559[ad]	0.140

		65.18						
Healthy	51.41/ 70.80	69.18/ 73.78	0.429/ -0.812[ae]	0.197	65.06/ 69.81	37.75/ 94.76	0.126/ 1.610[af]	0.403

In the AAT training phase we used a subset of pictures from the pre and post phases. This enabled us to assess whether training effects can be generalized to images that were not included in training phase. To test for this effect, a 2x2x2 repeated measures ANOVA was carried out in the training group. Factors included picture set (trained vs. not-trained images), image category (healthy vs. unhealthy) and time (pre- vs. post-training). A significant three-way interaction would indicate lack of the generalization effect, as it would show that bias scores for trained and not-trained images of the same category were not similarly affected by the training phase. The three-way interaction was marginally not significant ($F(1,15) = 4.464$, $p = .051$[ag], $\eta^2_p = .218$), which suggests that generalization to untrained pictures might indeed have occurred. We followed up this analysis with Bayesian repeated-measures ANOVA with identical factors to be able to better interpret the results (analysis performed with JASP version 0.9; JASP Team 2018). The evidence (Bayes factor) for a model with the three-way interaction, as compared to a model without this interaction, was 0.493. This magnitude of the Bayes factor indicates anecdotal evidence in favor of lack of generalization effects. We therefore cannot conclude with certainty, whether or not the generalization effect occurred.

4.2.3.2 Neuroimaging results

4.2.3.2.1 General Linear Model 1

- **Baseline food approach and avoidance**

In this analysis we investigated neural correlates of pre-training approach and avoidance tendencies towards food pictures. To this end we entered condition specific regressors into a one-sample t-test, as in this stage groups did not differ in any way. Our main contrasts of

interest included food approach and food avoidance, together and separately for healthy and unhealthy food cues. A contrast corresponding to general food avoidance (push>pull independent of picture category) revealed significant clusters in the right angular gyrus (rAG) and the cuneus. For the opposite contrast (pull>push, general approach for food), we found a significant cluster in the left postcentral gyrus. Further investigation showed that food avoidance activations were driven by the unhealthy food category. In analysis for unhealthy food avoidance bias (unhealthy_push>unhealthy_pull) we found significant clusters in the rAG and the cuneus (Figure 4.2.4, Table 4.2.5). Corresponding contrast for healthy food and contrasts for unhealthy/healthy food approach produced no significant results.

Moreover, we tested for group differences within the pre phase to ensure that groups were homogenous at the beginning of the experiment. This analysis for above mentioned contrasts did not elicit any significant clusters.

- **Pre to post changes**

As the main analysis of interest, we tested whether the training effect – decreased approach bias towards unhealthy foods – was associated with neuronal changes. To this end, we contrasted unhealthy food avoidance (unhealthy_push>unhealthy_pull) with healthy food avoidance (healthy_push>healthy_pull) before vs. after training. Indeed, in the training group, the rAG showed decreased activity post training, whereas the left middle occipital gyrus showed increased activity (Figure 4.2.5, Table 4.2.6). To investigate this effect further, we compared unhealthy food conditions (unhealthy_push>unhealthy_pull) pre and post training and found a similar effect. In addition, for this contrast we found a decreased activity in the left lingual gyrus for the no-training group, and a group difference in the cuneus (training>no-training group). Additional analysis showed that the effect in the rAG was driven by higher brain activity in the training group for the pre phase for unhealthy food avoidance (unhealthy_push>unhealthy_pull; Table 4.2.7). It indicates that brain activity in the right rAG for pushing vs. pulling unhealthy foods in the training group decreased after the training. In one of previous analysis we found the rAG to be associated with general food

avoidance. Hence, we suggest that CBM might make processes relying on this structure more efficient.

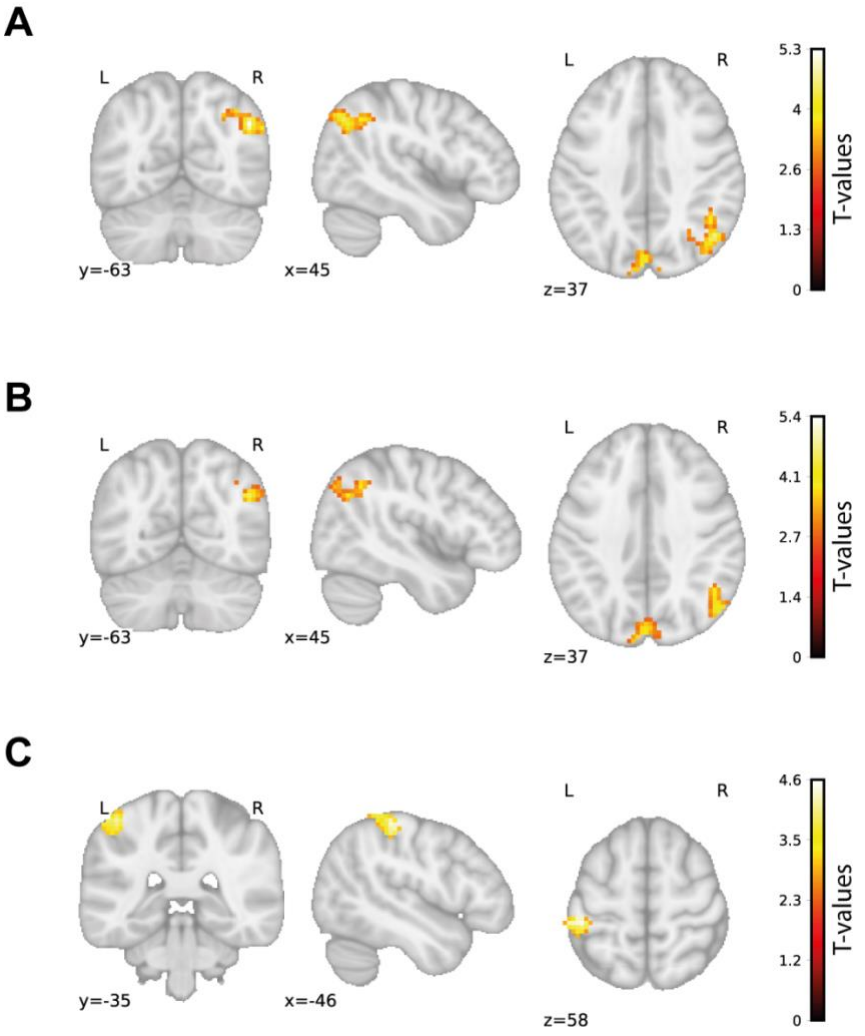

Figure 4.2.4 Figure showing main effects of food approach/avoidance *pre* training in both groups together. **A:** Main effect of food avoidance. **B:** Main effect of unhealthy food avoidance driving the effect presented in A. **C:** Main effect of food approach

- **PPI analysis**

We consistently found the rAG to be associated with unhealthy food avoidance and the effects of CBM. Therefore, we decided to perform a PPI analysis with the rAG as the seed. Here, we compared connectivity differences for the unhealthy food avoidance between pre and post phases. This analysis showed a significant cluster in the rSFG/rMFG and in the right caudate/putamen. This indicates that connectivity between the rAG and these structures was decreased post training, as compared to pre training, in the training group (Table 4.2.8, Figure 4.2.5).

4.2.3.2.2 Resting state data

- **Seed-based connectivity analysis**

To describe region specific functional connectivity within the brain we used seed-based connectivity analysis. This measure is also task-independent, as it uses resting-state fMRI data, and significant findings indicate that CBM elicits neuronal changes not only during AAT performance. Here, we investigated whether training was associated with resting state connectivity changes between the training and no-training groups. For the left MFG, we found a significant group by time interaction in the right MFG. Moreover, we observed a similar interaction effect for connectivity between the left nucleus accumbens and the left inferior frontal gyrus (IFG; Table 4.2.9, Figure 4.2.5).

- **Degree centrality**

Similar to SCA, DC describes task-independent connectivity changes within the brain. These changes, however, are general and not specific to chosen ROIs. In our study, this analysis did not produce any significant results.

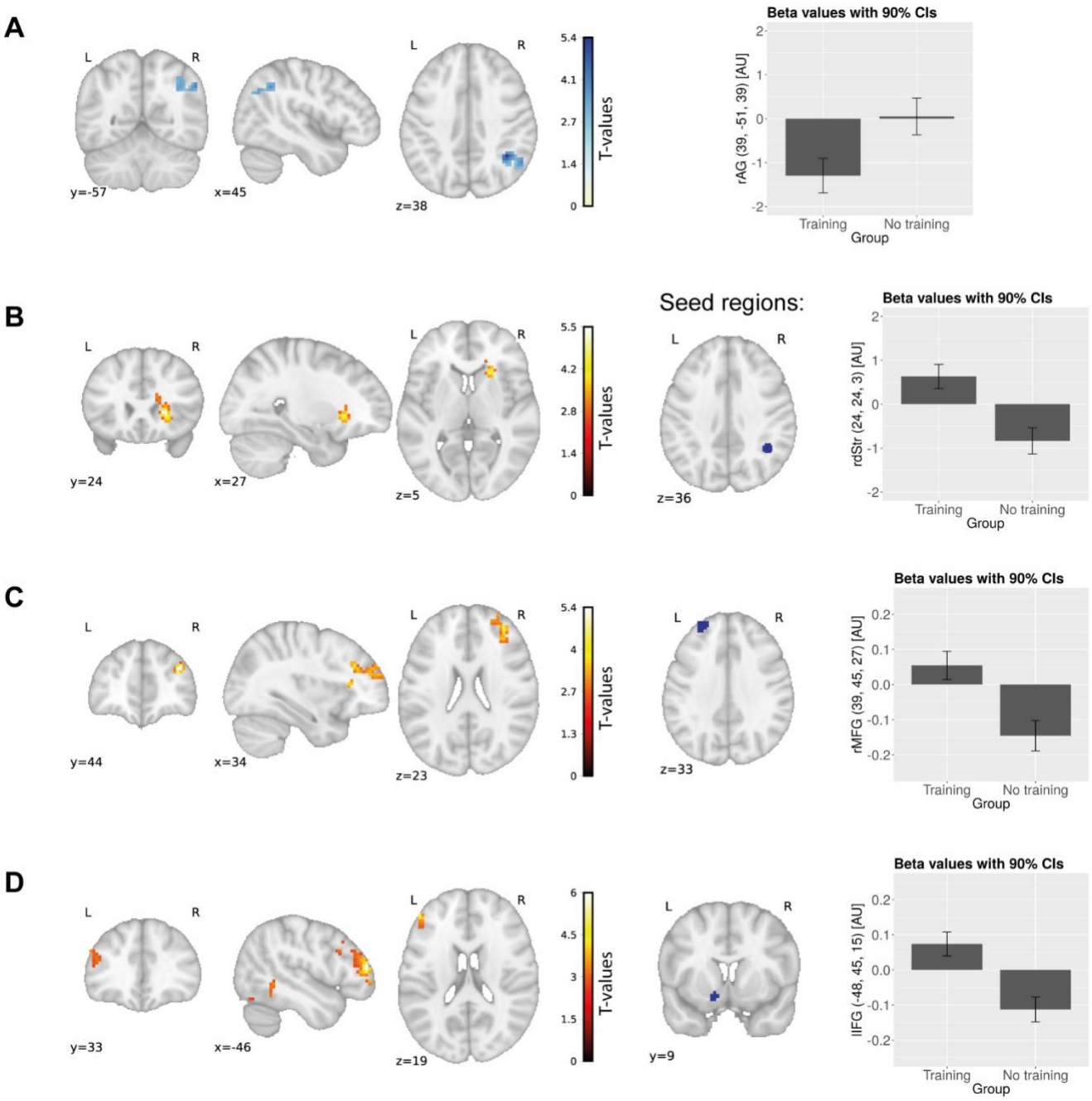

Figure 4.2.5 Figure showing effects of CBM training along with contrast estimates (arbitrary units - AU); please note a different scale in the parameter estimates for sub-figure A and B. A: Training effect was reflected in a decreased brain activity in the right angular gyrus for healthy food avoidance vs. unhealthy food avoidance. B: Cluster in the right dorsal striatum showing higher task-related connectivity with the right angular gyrus in the unhealthy push vs. unhealthy pull condition after training. C: resting-state seed-based connectivity analysis

showing increased connectivity post training in the training vs. no training group in the left and right middle frontal gyri. D: Resting-state seed-based connectivity analysis showing increased connectivity post training in the training vs. no training group in the left nucleus accumbens and inferior frontal gyrus. rAG – right angular gyrus, rdStr – right dorsal striatum, rMFG – right middle frontal gyrus, lIFG – left inferior frontal gyrus, AU – arbitrary units, CI – confidence intervals.

Table 4.2.5 Brain regions associated with baseline food approach/avoidance bias

Contrast	Region of the peak voxel	Cluster size [voxels]	Coordinates (MNI)			Peak z score	Peak t score
Food avoidance	Angular gyrus R	178	48	-63	36	4.40	5.28
	Cuneus	131	0	-87	24	4.21	4.96
Food approach	Postcentral gyrus L	98	-45	-39	63	3.98	4.62
Unhealthy food avoidance	Angular gyrus R	129	51	-66	33	4.51	5.45
	Cuneus	212	-3	-87	24	4.10	4.80

L – left, R – right

Table 4.2.6 Brain regions showing training-related changes (pre phase>post phase) between- and within-groups

Contrast		Region of the peak voxel	Cluster size [voxels]	Coordinates (MNI)			Peak z score	Peak t score
Unhealthy food avoidance > healthy food avoidance	Training group	Angular gyrus R	99	51	-69	33	4.06	4.77
		Middle occipital gyrus L	163	-21	-90	-15	-4.26	-5.07

Unhealthy food avoidance	Training group	Inferior parietal lobe R	124	39	-51	39	4.46	5.41
	No-training group	Lingual gyrus L	202	-3	-75	9	3.99	4.65
	Training>no-training	Cuneus L	163	-15	-75	9	-3.73	-4.27
	Pre phase; Training group	Angular gyrus R	97	51	-66	30	4.00	4.67

L – left, R – right

Table 4.2.7 Brain region showing altered activity for food avoidance *pre* training in the training group only for unhealthy food avoidance

Contrast	Region of the peak voxel	Cluster size [voxels]	Coordinates (MNI)			Peak z score	Peak t score
Unhealthy food avoidance	Angular gyrus R	97	51	-66	30	4.00	4.67

R – right

Table 4.2.8 Brain region showing increased connectivity with the right angular gyrus for the unhealthy food avoidance bias in the pre to post phase

Contrast	Region of the peak voxel	Cluster size [voxels]	Coordinates (MNI)			Peak z score	Peak t score
PPI connectivity in the training group; seed: right angular gyrus	Putamen R	170	24	24	3	4.51	5.53

R – right, PPI – psychophysiological interactions

Table 4.2.9 Regions showing a group by time interaction in the resting-state measures of brain activity and connectivity

Analysis	Region of the peak voxel	Cluster size [voxels]	Coordinates (MNI)			Peak z score	Peak t score
SCA, left middle frontal gyrus	Middle frontal gyrus R	182	39	45	27	4.443	5.38
SCA, left nucleus accumbens	Inferior frontal gyrus L	136	-48	45	15	4.80	6.01
	Inferior temporal gyrus L	118	-54	-48	-18	3.73	4.27

L – left, SCA – seed-based connectivity analysis

4.2.4 Discussion

Within this study we aimed to investigate underlying neural mechanisms of cognitive bias modification in obese individuals. To this end, a training form of the approach-avoidance task was applied in the fMRI scanner, where half of the participants received training, while the other half was part of a no-training condition. This between group design combined with fMRI measures design allowed us to clarify whether CBM works by a) changing rewarding values of food stimuli and brain activation in reward-related brain regions, or b) increasing inhibitory abilities and affecting brain regions engaged in inhibitory processing and cognitive control. Generally, we found that all participants showed faster approach than avoidance reactions towards both healthy and unhealthy food images, suggesting that approaching food is an automatic process. This is paralleled by our findings on the neural level, where the rAG shows increased activation for avoiding food. The rAG is usually shown to be engaged in suppressing stimulus response conflicts, attentional reorientation and response inhibition (Rushworth et al., 2001; Schiff et al., 2011; Seghier, 2013; Cieslik et al., 2015; Kolodny et al., 2017). Next, CBM specifically affected the training group, where we

were able to significantly decrease the approach tendencies towards unhealthy food. This was related to a decreased activation in the rAG. Additionally, we observed changes in task-related and resting-state connectivity patterns between inhibitory regions, such as the MFG or the IFG (Garavan et al., 1999; Simmonds et al., 2008; Boehler et al., 2010; Cai et al., 2014). We also observed task-related connectivity changes between the rAG and the right caudate/putamen, which constitute the dorsal striatum. Within our sample, avoiding food thus appears to be a potentially conflicting situation, hence requiring more cognitive resources. Cognitive bias modification, on the other hand, seems to decrease this demand by means of strengthening connectivity between inhibitory brain regions. Further, we did not find evidence for altered reward valuation of food stimuli after CBM.

Though we were able to significantly decrease approach behavior towards unhealthy food pictures, we did not increase approach behavior towards healthy food pictures. This is, however, in line with previous findings, where decreasing approach behavior towards unhealthy food was the main effect of the training (Ferentzi et al., 2018; Mehl et al., 2018). In the present study, decreasing approach tendencies towards unhealthy food was related to a decrease in brain activation in the rAG. This could indicate that training makes avoiding food a less conflicting and more automatic behavior, thus requiring less inhibitory resources. We further tested whether observed effects were specific to trained pictures only or would generalize to untrained pictures of the same category. Evidence for generalization effects, however, were inconclusive. While generalization effects were repeatedly observed when applying CBM in the alcohol context (e.g. Wiers et al., 2010) results in the context of food have, so far, been mixed. While Mehl and colleagues (2018) found no generalization effect, Ferentzi et al. (2018) observed training effects to generalize to new, untrained pictures.

Further, for unhealthy food avoidance, we found a higher task-related connectivity between the rAG and the right SFG/MFG post versus pre training. The right MFG is a part of the frontoparietal control network (Vincent et al., 2008) and is widely engaged in exerting cognitive control and inhibiting prepotent reactions (Garavan et al., 1999; Simmonds et al., 2008; Cai et al., 2014). The task-related connectivity post-training was also decreased between the rAG and the dorsal striatum. This brain area is related to executive attention

and exerting cognitive control, but also to stimulus-response learning (Balleine et al., 2007; Jankowski et al., 2009; Liljeholm and O'Doherty, 2012; Mestres-Missé et al., 2012; Robertson et al., 2015). Different connectivity patterns were also found in the resting-state data, where we showed changes in connectivity between the left and the right MFG, but also between the left nucleus accumbens and the left inferior frontal gyrus. We suggest that those findings could be interpreted as complementary effects of training. Firstly, we show a decrease in activity of the rAG, which might be related to a decreased cognitive conflict after training when having to push away unhealthy images. This is additionally related to a more efficient inhibition of automatic reactions, which is reflected in a higher functional connectivity between the rAG with the rMFG and the dorsal striatum. As an effect of this increased coupling of the rAG with these structures, it does not require similar activation strength as pre training. Secondly, we propose that the decrease in the rAG activity is related to a higher resting state connectivity between inhibitory regions in the brain – the bilateral middle frontal gyri, and left inferior frontal gyrus. The left MFG was shown to be activated for viewing high caloric food pictures (van der Laan et al., 2011). Changed connectivity between the left MFG and the right MFG structures engaged in response inhibition (Garavan et al., 1999; Simmonds et al., 2008; Boehler et al., 2010; Cai et al., 2014), might therefore be associated with training-induced stronger inhibitory tendencies towards unhealthy food pictures. Similarly, higher connectivity of a reward related region - the nucleus accumbens - and the left inferior frontal gyrus, also engaged in response inhibition (Swick et al., 2008), could be associated with increased inhibition of approach response to rewarding stimuli. This strengthened inhibitory network in the brain could facilitate avoiding unhealthy food pictures, therefore decreasing the demand for suppressing stimulus-response conflicts by the rAG.

To further confirm this, we decided to perform a degree centrality analysis. This was done to check whether inhibitory structures, such as the dlPFC or the IFG increased their centrality within the whole brain. We did not find any significant between-group changes in degree centrality after the training. Potentially, our intervention was not strong enough to elicit these changes. Alternatively, changes in DC were too small and could not be detected in our analysis.

In comparison to CBM in the alcohol context, underlying neural mechanisms seem to differ in the food context. A successful reduction of approaching alcohol appears to elicit changes in reward valuation areas. A successful reduction of approaching food appears to involve conflict, cognitive control and inhibitory areas. One apparent difference between the studies is duration of the training, which might potentially explain discrepancies in results. Our short training is able to target and change impulsive reactions, increasing inhibitory tendencies and decreasing cognitive conflict. Evaluation of stimuli, on the other hand, is more of a reflective process and might hence require longer training over multiple sessions. This may change rewarding value of problematic stimuli, therefore eliciting different activations in reward-related areas. A previous intervention study in obese individuals, applying food response training over a four week period, found decreased brain activations in attention and reward processing areas, such as the insula, inferior parietal lobe and putamen (Stice et al., 2017). Here, authors used a stop signal reaction time task, go/no-go training in a food context and a response signal training in a food context, generally training inhibitory reactions to high calorie food items. It therefore seems that a longer training elicits changes in brain's valuation system, which is further transferred to changes in motor responses. Potentially, short trainings train a motor response and do not have the strength to alter reward valuation processes.

A study by Ritschel and colleagues investigated decision making and cognitive control in recovered and acute anorexia nervosa patients. Brain regions including the rAG have been shown to be activated to a higher degree in the former group, as compared to the latter group, while performing a probabilistic selection task (Ritschel et al., 2017). The authors argue that these activations are related to a higher demand for cognitive control in the recovered AN patients, since their cognitive control is generally lower than that of acute AN patients. This could point to a potential involvement of the rAG in these processes. Further, Schonberg and colleagues trained participants to make healthier food choices and found a decreased activation in the frontoparietal network after training (Schonberg et al., 2013), which might indicate a lower need for cognitive control as a consequence of training. In summary, our findings are in line with the aforementioned studies, showing that decreased approach bias relates to more efficient connectivity between brain inhibitory regions, which

is linked to decreased activity in brain regions related to cognitive control, inhibition and suppressing stimulus response conflict. In addition to these studies, ours is the first one using a sample of only obese participants. We utilize CBM in the food context and provide additional measures that CBM could potentially transfer to, such as rating of an independent picture set, but also resting-state fMRI. Moreover, we show that it is possible to change people's tendencies and functional brain layout with just a 20-minute-long training. Altogether, our results provide further evidence for the effectiveness of cognitive bias modification, as we were able to find significant effects on the neural and behavioral level within one session

It is important to consider some limitations when discussing this study. First of all, sample size was moderate (34 participants). Secondly, CBM effects did not translate to the picture sorting task. This measure was important in the context of our task as it was meant to assess explicit evaluations of healthy and unhealthy food stimuli. We hypothesized that decreased approach tendencies towards unhealthy food pictures would relate to explicit evaluations of these stimuli. Possibly, additional features of food, such as sweet or savory taste, influence this process. Our training only focused on healthy and unhealthy categories without further divisions. This may decrease the sensitivity of our analyses and may be related to lack of significant effects on the picture sorting task, but also to the lack of generalization effects of this training to non-trained pictures. Additionally, in our study we only tested obese participants and we cannot infer whether similar training effects would occur in lean participants. However, a previous study by Mehl and colleagues hints towards the fact that lean participants are not that easily influenced by the CBM in an unhealthy food context, possibly because they do not show initial bias (Mehl et al., 2018). Lastly, we compared approach and avoidance tendencies between healthy and unhealthy food images, hence not including neutral images of non-food objects.

Importantly, we do not show effects of our training on food intake. This is a main goal of cognitive bias modification studies in the food context, which ultimately should lead to a decreased consumption of unhealthy foods. Future studies should hence aim to implement CBM interventions in real-life settings, assessing its impact on eating behavior and food

choice. We believe, however, that our study provides a basis on which further studies focusing on food approach bias might be conducted. Our findings shed light on underlying efficacy mechanisms of CBM in obesity, indicating that inhibitory control processes play an important role. Future studies should therefore aim to specifically strengthen inhibitory control, especially regarding unhealthy food. Additionally, showing that already one 20-minute-long session can modify people's approach tendencies in the laboratory context is very promising. It enables further research using more complicated designs with longer training period in a natural context.

In conclusion, we were able to show that obese individuals have automatic approach tendencies towards food. We further present a possibility to retrain and decrease approach tendencies, especially towards unhealthy foods, and give insight into underlying neural mechanisms. Potentially, this study could constitute a basis for intervention programs utilizing similar behavioral paradigms. We suggest that those kinds of studies implement a longer training period, similar to ones used with alcohol-dependent patients. Additionally, by showing neural correlates of CBM, our results contribute to possible brain stimulation research focusing on decreasing approach bias towards food.

Table 4.2.10 Statistical table showing distribution of variables, tests used for hypothesis testing and confidence intervals/observed power for each of the tests

	Distribution	Type of test	Confidence intervals / observed power
a	-	Chi square	0.065
b	Normal	T-test	0.40 – 6.34
c	Non-normal	T-test	-3.07 – 5.84
d	Normal	T-test	-0.94 – 1.79
e	Normal	T-test	-2.12 – 1.50
f	Normal	T-test	-1.53 – 1.06
g	Normal	T-test	-5.19 – 2.21
h	Normal	T-test	-4.49 – 0.28
i	Normal	T-test	-3.99 – 1.60

j	Normal	T-test	-4.09 – 2.31
k	Normal	T-test	-2.05 – 1.30
l	Normal	T-test	-2.25 – 0.64
m	Normal	T-test	-1.21 – 1.18
n	Normal	T-test	-0.96 – 0.65
o	Normal	T-test	-0.77 – 0.66
p	Normal	T-test	-0.89 – 0.48
q	Normal	T-test	-0.39 – 0.52
r	Normal	T-test	6.53 – 7.30
s	Normal	T-test	2.06 – 0.95
t	Normal	T-test	0.050
u	Normal	T-test	0.100
v	Normal	T-test	15.01 – 87.81
w	Normal	T-test	4.61 – 96.10
x	Normal	T-test	27.86 – 102.27
y	Normal	T-test	1.46 – 73.54
z	Normal	ANOVA	0.536
aa	Normal	ANOVA	0.854
ab	Normal	ANOVA	0.824
ac	Normal	T-test	24.64 – 110.54
ad	Normal	T-test	-25.85 – 44.23
ae	Normal	T-test	-64.15 – 28.62
af	Normal	T-test	-8.64 – 63.26
ag	Normal	ANOVA	0.510

4.3 Study 3 – temporal impulsivity in a sample of lean, overweight and obese participants

4.3.1 Rationale of the study

Study 3 was carried out in order to replicate previous results concerning increased delay discounting in participants with obesity (Amlung et al., 2016; McClelland et al., 2016). Secondly, in this study we established methodological framework for study 4. In a simple delay discounting paradigm, where participants are offered either smaller and immediate, or later but larger rewards, we tested a large group of lean, overweight and obese participants. We hypothesised that obese participants will show the highest delay discounting of all three subgroups. Additionally, we hypothesised that, based on previous reports (Weller et al., 2008), gender might play an important role in this relationship, where obese women choose more immediate options than lean women, with this difference being absent for men.

4.3.2 Materials and methods

4.3.2.1 Participants

162 healthy participants aged 18-35 years took part in this experiment (77 men in total; mean BMI = 27.47 kg/m^2, SD 6.03; mean age = 26 years, SD 4 years). BMI distribution in the sample can be seen in Figure **4.3.1**. Participants met the following *a priori* inclusion criteria: no history of neurological/psychological diseases, no drug, cigarette or alcohol addiction, no hypertension or diabetes. Volunteers were compensated for taking part in the experiment with 7 Euro/hour. Sample in this study consists of participants recruited as parts of two different studies investigating delay discounting. Those studies were conducted according to the Declaration of Helsinki and approved by the Ethics Committee at the University of Leipzig. All participants gave their written informed consent prior to their participation in the studies.

4.3.2.2 Behavioural task

The experimental session consisted of an introduction to the experiment and a computerised DD task. During the task, we offered participants two hypothetical monetary options, one smaller but immediately available reward (SIR) and one larger, delayed (available after a variable delay of 1, 2, 4, 6, 9 or 12 months) reward (LDR). The task was closely aligned to the procedures described in Simmank and colleagues' study (Simmank et al., 2015). The two-step procedure included a 'dynamic adjustment task' and a 'random choice task'. This session provided us with estimates of individual indifference points (IPs), which indicate the point of statistical indifference between immediate and delayed options. In other words, the IPs were defined as the ratio of SIR to LDR for a given delay where the subjective value (SV) of LDR was equal to the value of SIR. In the 'dynamic adjustment task', the IPs were calculated using a staircase procedure, where participants were offered different immediate and delayed rewards. This was done until two consistent IPs were obtained for each of the delays. Further, the 'random choice task', in which combinations of the previous task were administered again in a random order, was used to validate parameters obtained in the 'dynamic adjustment task'. This task allowed us to further calculate delay discounting parameters and compare them between participants.

To be able to control our analysis for socioeconomic status, we have included a short questionnaire with questions regarding individual's total income, money available to spend, satisfaction with the income, parents' income, school degree and professional degree.

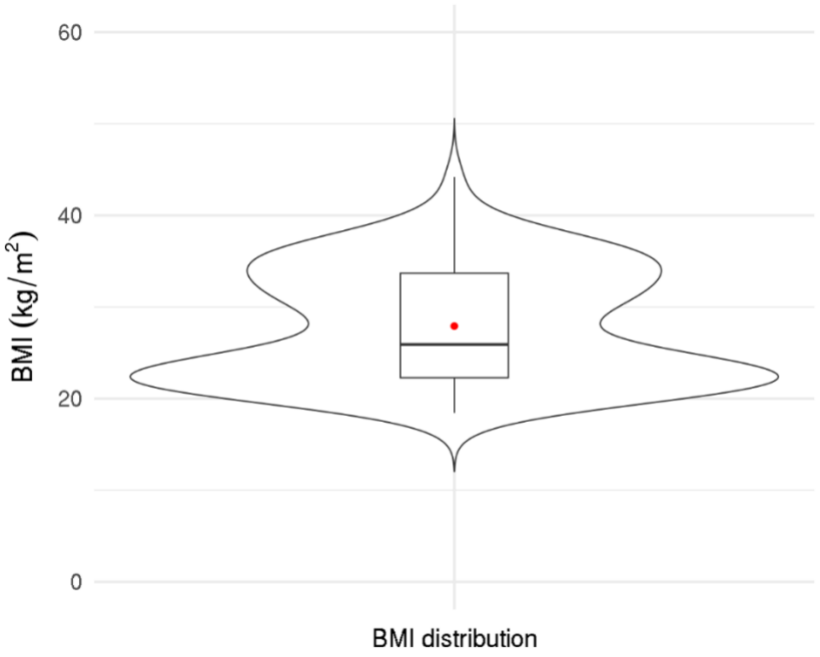

Figure 4.3.1 Figure showing the distribution of BMI in the study sample. Red dot depicts sample's mean, bold line represents sample's median, horizontal lines below and above represent 1st and 3rd quartiles, and the vertical lines represent sample's range. Violin plot depicts frequency of BMI.

4.3.2.3 Data analysis

Behavioural data were analysed using R language within Jupyter Notebook framework and MATLAB 2012b (The MathWorks, Inc., Natick, Massachusetts, United States, modelling of delay discounting data using quasi-hyperbolic model).

4.3.2.3.1 Delay discounting data modelling

Simmank and colleagues have used a similar sample of lean and obese participants and, to our knowledge, are the only ones to have compared the fit of hyperbolical and quasi-hyperbolical models to the delay discounting data. The hyperbolic model of delay discounting (Laibson, 1997) describes it as a function of a single discount factor *k*. The quasi-hyperbolic model assumes that delay discounting is dependent on two distinct parameters – beta and delta (Laibson, 1997). The first one describes a bias that is independent of delay – discounting the delayed reward just because it is delayed. The latter parameter describes

delay-dependent discounting – the larger the delay the more the reward is discounted. Findings of Simmank and colleagues showed that the quasi-hyperbolic model better fits the data. We therefore decided to follow their recommendations and use this model as well. The quasi-hyperbolic model is defined by:

$$\alpha=\beta\delta^{\tau},$$

where alpha is the subjective value of a delayed reward, beta is a delay-independent bias towards immediate rewards, delta is a delay-dependent discount factor, and tau is the delay (Laibson, 1997). Choices in each individual trial were entered into the model and beta and delta parameters were calculated (for details see 'Estimation of Discount Function' section in Simmank et al., 2015). We investigated the relationship between BMI and the DD parameters using permutation based multiple regression (lmperm package in R, 5000 permutations). Further, we investigated the interaction of gender and BMI, because an earlier study showed gender-dependent differences in DD between obese and lean participants (Weller et al., 2008). In this analysis we also included age and variables describing socioeconomic status of participants. Prior to the analysis all numerical variables were z-transformed.

4.3.2.3.2 Participants' exclusions

Before the analysis we excluded participants for whom the quasi-hyperbolic model estimation process was impossible (n=33). This happened if the estimation process returned values below 0 or above 1, since the parameters values must lie between 0 and 1. Other values indicate that the estimation process was unsuccessful. We then tested for outliers concerning BMI and beta and delta delay discounting parameters (no outliers detected). *A priori* outlier exclusion criterion was: values being 2.2*interquartile range below or above

the first or third quartile, respectively (Tukey, 1977; Hoaglin et al., 1986; Hoaglin and Iglewicz, 1987). This resulted in a final sample of 129 participants.

4.3.3 Results

The distribution of beta and delta parameters is depicted in Figure **4.3.2**. For detailed results of the regression analyses see Table **4.3.1**. The first regression analysis included beta parameter and its interaction with gender as variables of interest, and age and socioeconomic status as control variables. It showed a significant relationship between BMI and beta parameter dependent on gender (Figure **4.3.3**). Further, the second regression analysis focused on the delta parameter and its interaction with gender, as well as age and socioeconomic status as control variables. It indicated that the delta parameter was related to BMI (Figure **4.3.4**).

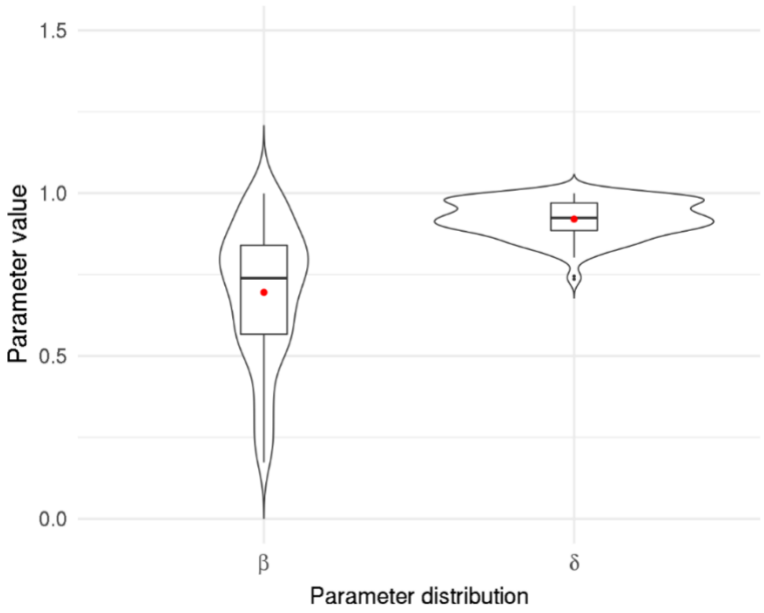

Figure 4.3.2 Figure presenting distribution of beta and delta delay discounting parameters in the study sample. Red dots depict sample's means, bold line represents sample's median, horizontal lines below and above 1st and 3rd quartiles, and the vertical lines sample's range.

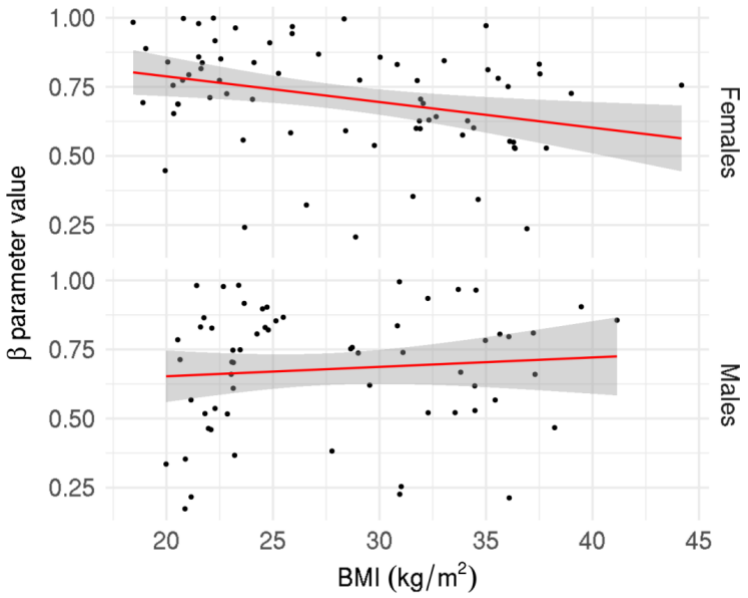

Figure 4.3.3 Figure presenting a significant interaction of BMI and gender on beta delay discounting parameter. Black dots represent data points, red line is the best fit, and the grey shaded areas are 95% confidence intervals.

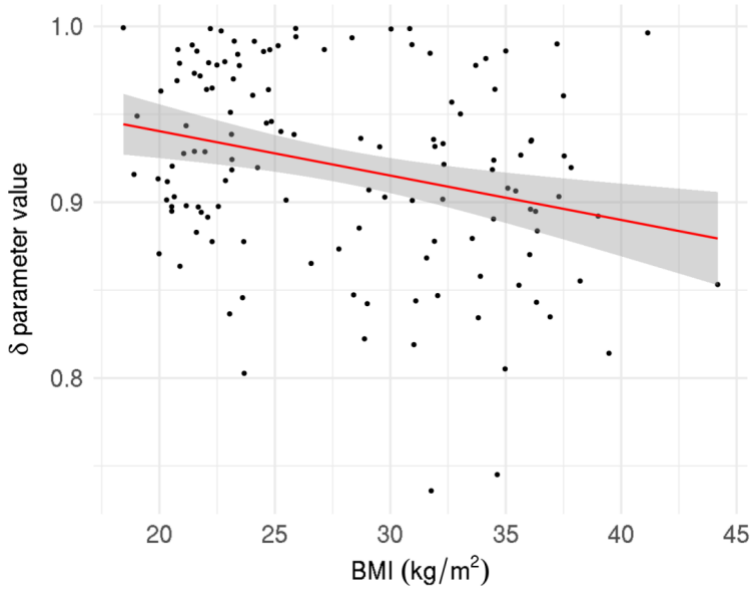

Figure 4.3.4 Figure representing relationship between delta delay discounting parameter and BMI in full sample. Black dots represent data points, red line is the best fit, and the grey shaded areas are 95% confidence intervals.

Table 4.3.1 Table with regression coefficients and p-values for both of regression analysis investigating influences of BMI on delay discounting. Significant p-values are marked in bold. After Bonferroni correction, p-value threshold indicating significance was 0.0250.

	Beta		Delta	
	Coefficient	p-value	Coefficient	p-value
BMI	-0.0013	0.5275	**-0.0022**	**0.0110**
BMI * Gender	**-0.0058**	**0.0224**	-0.0008	0.4622
Age	0.0011	0.6230	0.0011	0.8235
Total income	-0.0169	0.4110	-0.0088	0.1562
Money available to spend	0.0234	0.4655	0.0018	0.6333
Satisfaction with the income	0.0449	0.0532	0.0132	0.0515
Parents' income	-0.0153	1.0000	-0.0051	0.4615
Highest school degree	0.0754	0.4545	0.0002	0.9608
Professional degree	0.0035	0.6667	-0.0037	0.5102

Gender	0.0205	0.4234	0.0003	1.0000
Adjusted R^2	0.0340		0.0595	

4.3.4 Discussion

We performed this study in order to replicate previous findings relating temporal impulsivity to measures of obesity (Weller et al., 2008; Amlung et al., 2016; McClelland et al., 2016). Further, we wanted to develop a methodological framework for study 4, which would enable us to try altering maladaptive impulsive tendencies in obesity. We have successfully shown that temporal impulsivity is related to BMI, even after controlling for potential confounders, such as age or socioeconomic status. Interestingly, this was true for the delta parameter, describing delay-dependent delay discounting, where higher BMI was related to increased delay discounting (lower delta values). For the beta parameter, representing delay-independent present bias, we found that it can be predicted by BMI depending on gender. Here, men and women show opposite directions of relationship between BMI and delay-independent delay discounting, where females show increased delay discounting with increasing BMI values.

Findings concerning temporal impulsivity and obesity measures are equivocal and indicate that there is a strong relationship between these variables (Weller et al., 2008; Rasmussen et al., 2010; Bickel et al., 2014; Jarmolowicz et al., 2014; Amlung et al., 2016; McClelland et al., 2016). Previous studies most often use a hyperbolic model of delay discounting (Laibson, 1997), however, we followed recommendations of Simmank et al., and used the quasi-hyperbolic model to analyse our data. In this model, the delta parameter corresponds to the *k* parameter from the hyperbolic model. Therefore, our findings are in line with previous literature predominantly showing gender-independent relationships between *k* parameter value and obesity measures. On the other hand, the beta parameter is absent in the hyperbolic discounting. To our knowledge, the only study that compared this parameter between lean and obese participants is the one by Simmank and colleagues. Here, the authors did not find significant differences. Our data indicate that there is a gender-dependent relationship between present bias and BMI. This is a new finding that suggests that males

and females differentially discount rewards just because they are delayed. In females, higher BMI correlates with lower value of present bias, which in turn means higher discounting. An opposite relationship was observed in males. To our knowledge this is the first finding showing this kind of relationship between BMI and delay-independent delay discounting. This finding is interesting in light of results shown by Weller and colleagues in 2008. Here, using the hyperbolic model of delay discounting, the authors found a significant interaction of gender and obesity status, where obese women discounted rewards more than lean women, with similar relationship being absent for men. Our study might suggest that this gender difference could be ascribed to the present bias (beta parameter), which is not directly measured by the hyperbolic model. Future studies should, however, replicate this finding, especially the gender effect, and investigate which additional factors, such as genotype, might influence delay discounting in obesity.

This study is not without its limitations. The overweight group in this sample was underrepresented, which can be seen in Figure **4.3.1**. Therefore, an improved study would investigate relationships of delay discounting and homogenously distributed BMI, potentially with a much broader range.

4.4 Study 4 – medial and dorsolateral prefrontal cortex mediate the influence of incidental priming on economical decision making in obesity

4.4.1 Rationale of the study

This study tackles the processes related to conscious decision-making using incidental priming that would allow altering those processes in an implicit manner. Using a delay discounting paradigm, we investigated whether 1) whether obese participants indeed choose more disadvantageous, immediate options more often than their lean counterparts (similar to study 3); 2) whether obese participants are more susceptible to priming and the neural underlying mechanisms of this phenomenon. To do this, we implemented a simple monetary DD paradigm, just as in study 3. Additionally, in a second part of the experiment before each of the choices, we primed participants with a food-related visual or gustatory stimulus of positive, neutral or negative valence. Visual stimuli were thought of as more distal ones representing food availability, while gustatory stimuli were more proximal ones representing actual food intake. A previous study in a similar context used only positive food-unrelated stimuli (Simmank et al., 2015). With our design we were able to not only expand this knowledge to negative stimuli, but also present a more ecologically valid approach of priming with food-related stimuli. These are often more problematic in obesity and showing how they influence general, non-food related decisions expands our knowledge about instability of decision making processes in obesity also in the economic context. Additionally, as none of the previous studies have explored what the neural mechanisms of priming in obesity are, our study aims to fill this research gap. Based on a previous study, we expected that negative cues would elicit more priming towards delayed options, whereas positive cues would have an opposite effect (Luo et al., 2014). Based on the assumption that remote cues signal *potential* food intake, i.e. availability of food, and proximal cues signal *acute* food intake, i.e. with direct consequences to the body, we expected stronger effects in the proximal condition. Further, we hypothesised that the priming effect would be larger in obese participants (Simmank et al., 2015), and that this enhanced effect would be expressed in changes of brain activity in the dlPFC, vmPFC (increased activity for delayed choices) and

striatal areas (increased activity for immediate choices (McClure et al., 2004; Kable and Glimcher, 2007; Hare et al., 2009). This hypothesis was also based on previous literature showing changes in the dlPFC and vmPFC activity in similar paradigms utilising incidental cues in DD paradigms (Murawski et al., 2012; Luo et al., 2014). In line with previous reports showing differences between obese and lean participants in the dlPFC activity in a number of tasks, we expected different engagement of this brain region in incidental priming, dependent on weight status. Moreover, since the priming effect was hypothesized to change the subjective value of delayed rewards, we expected that it would be associated with changes in activity of and connectivity between reward valuation regions.

4.4.2 Materials and Methods

4.4.2.1 Participants

56 healthy lean and obese participants aged 18-35 years took part in our experiment (29 men in total. subsample 1: 30 lean, mean BMI = 22.14 kg/m^2, SD 1.81; subsample 2: 26 obese, mean BMI = 34.32 kg/m^2, SD 3.37; group differences in BMI: t(54)=-16.499, p=0.019; lean: mean age = 25.83 years, SD = 3.14, obese: mean age = 27.42, SD = 4.16, group differences in age: t(54)=-1.627, p=0.110). BMI criteria for inclusion in the lean group were as follows: 18-25 kg/m^2, obese group: BMI above 30 kg/m^2. The majority of our participants were registered in the Institute's database (51 participants) and had previously participated in other studies carried out in the Institute. This database includes a large number of predominantly healthy participants willing to participate in various studies. It predominantly includes students at the University of Leipzig, but also other well-educated individuals of all ages. Unfortunately, the number of individuals with obesity included in the database is comparably low, hence, it was necessary to recruit additional participants with obesity for this study. In total, we recruited 5 new participants, 4 of which were included in the obese sample. These participants were recruited through an online advertisement specific for this study. Given that no participant previously participated in experiments using the same task, and a mixture of more and less experienced participants is common practice in most fields (in particular those requiring samples with specific features), we have no reason to believe that it affected our results in any way. Our sample size was based on a

similar behavioural research (e.g., Simmank et al., 2015; Murawski et al., 2012; Luo et al., 2014). However, given that we had to accept some drop-out for our fMRI analysis, which is unfortunately a common problem in studies of this kind, it is possible that there were subtle effects that we might have not been able to detect. Participants met the following *a priori* inclusion criteria: no history of neurological/psychological diseases, no drug, cigarette or alcohol addiction, no hypertension or diabetes, no MRI-related contraindications. The full fMRI sample was reduced to 51 participants due to technical problems during the fMRI session (for exclusions see section 4.4.2.4). Volunteers were compensated for taking part in the experiment with 7 Euro/hour for behavioural sessions and 8 Euro/hour for MRI sessions. The study was conducted according to the Declaration of Helsinki and approved by the Ethics Committee at the University of Leipzig. All participants gave their written informed consent prior to their participation in the study.

4.4.2.2 Procedures overview

4.4.2.2.1 Behavioural task

Behavioural task was identical to the one described in section 4.3.2.2.

4.4.2.2.2 fMRI task

The fMRI part of the experiment consisted of 'primed delay discounting' trials and 'perception only' trials mixed and presented in a random order (see Figure 4.4.1). The total number of trials per experiment was 384. Participants indicated their choices by pressing buttons on single button boxes that were placed in each of their hands. This part of the MRI experiment lasted approximately 54 minutes and was divided into four blocks. Participants were offered breaks between the blocks. After completing the experiment, we asked participants to evaluate the priming stimuli (described below) on a visual analogue scale from 0-100 (negative-positive). To make the hypothetical choices more realistic, we offered our participants a 1/6 chance of winning one of the rewards they chose during the 'primed delay discounting' trials. The reward was chosen at random, and the monetary amount was either added to the participants' reimbursement (immediate choice), or transferred to their bank account after a delay (2 months) corresponding to their choice.

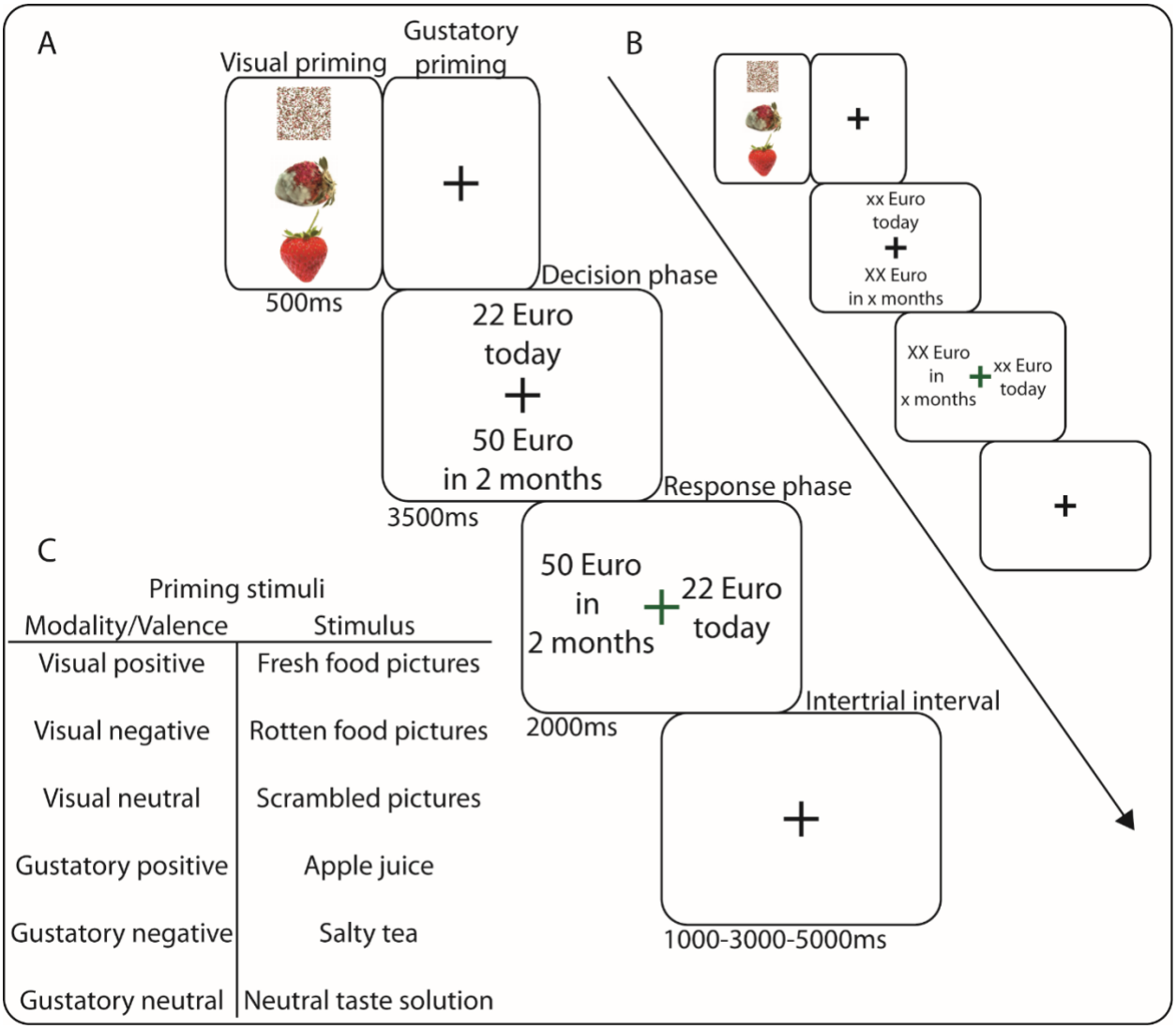

Figure 4.4.1 Overview on the experimental paradigm. A Delay Discounting (DD) and B Perception (P) trial outline. Each trial consisted of a priming period (500ms), task screen (3500ms), response screen (2000ms) and a jittered intertrial interval (1000-3000-5000ms, logarithmic distribution). During the priming period, a picture (visual conditions) or a fixation cross (gustatory conditions) was presented on the screen. In the gustatory conditions, taste liquids were delivered to participants simultaneously, for 500ms. The task screen consisted of a fixation cross and the two hypothetical rewards presented above and beneath it (random placement). For the response screen, the fixation cross turned green and the rewards appeared on its left and right sides (random placement). Visual stimulation

during the intertrial interval consisted of a fixation cross. C: list of priming stimuli used in our experiment.

- **Primed delay discounting trials**

Before making each DD decision, we presented participants with one of six different food-related stimuli (DD conditions, Figure 4.4.1). We used visual and gustatory stimuli of positive, negative and neutral valence, thus introducing 6 different DD conditions (gustatory positive – G_{pos}, gustatory neutral – G_{neu}, gustatory negative – G_{neg}, visual positive – V_{pos}, visual neutral, V_{neu}, visual negative – V_{neg}). Positive and negative food pictures were acquired from the FRIDa database (Foroni et al., 2013). We chose positive and negative food pictures according to their ratings and content, creating six pairs of valence-matched images with the same content (e.g. positive bread – negative bread, Table 4.4.1). To create neutral visual prime stimuli, the valenced pictures were divided into a matrix of 53x53 100-pixel squares and subsequently randomly scrambled. This step was performed to preserve the colour composition of visual stimuli and at the same time erasing their content. To administer the gustatory stimuli, three PVC tubes were placed directly in participants' mouth. The liquid delivery was performed using a computer-controlled, MRI compatible gustometer (Multistimulator OG001, Burghart Messtechnik, Wedel, Germany). The flow rate was set at 500µl/s, which means that during the entire experiment volunteers received 50 ml of liquids. The stimuli were apple juice (positive), salty tea (negative) and neutral taste solution (neutral, O'Doherty et al., 2001). To reduce the duration of the experiment we used only one temporal delay for all trials (2 months) in combination with 12 pairs of SIR and LDR (corresponding to 12 *r*s). Each of the pairs was repeated four times per condition. Thus, the number of trials in the DD conditions was 288.

Table 4.4.1 . List of pictures used as stimuli in the primed delay discounting task. Pictures were taken from the FoodCast Research Images Database (Foroni et al., 2013). The table comprises official database picture names and the content of each image.

Positive food pictures	Negative food pictures
Natural Food 009 - orange	Rotten Food 003 - orange
Natural Food 026 - cucumber	Rotten Food 009 - cucumber
Natural Food 051 - cheese	Rotten Food 013 - cheese
Natural Food 037 - strawberry	Rotten Food 014 - strawberry
Natural Food 055 - apple	Rotten Food 018 - apple
Natural Food 089 - bread	Rotten Food 025 - bread

- **Perception only trials**

To control for perception-related activity in priming-related brain activity, we introduced six analogous 'perception only' conditions with the same priming stimuli as in the DD conditions. Here, instead of the hypothetical rewards and a delay, participants were shown letters X or x and were asked to press a button corresponding to the side on which the capital letter X appeared (P conditions, Figure 4.4.1). Each P condition was repeated 16 times, which amounted to 96 trials.

4.4.2.2.3 Questionnaires

After the experiment, participants filled in a set of questionnaires: Beck's Depression Inventory (BDI; Beck et al., 1996), Three Factor Eating Questionnaire (TFEQ; Stunkard and Messick, 1985), Behavioural Inhibition System and Behavioural Activation System (BIS/BAS; Carver and White, 1994), Zaubermann Time Perception Scale (ZTPS; Zauberman et al., 2009). We used BDI as a screening tool to potentially exclude participants with depression. The cut-off value was 18 points (Hautzinger, 2006) and none of our participants reached it. TFEQ assesses eating behaviour on three dimensions: disinhibition (DI), cognitive restraint (CR) and hunger (H). BIS/BAS captures how a person's behaviour is driven by reward and punishment. These features often differ between obese and lean participants and may impact on performance in the current task. Additionally, secondary school education,

professional qualifications and household income were assessed using a short questionnaire.

4.4.2.3 Neuroimaging

The neuroimaging data were acquired using a 3T Siemens PRISMA scanner with a 32-channel head coil. 1520 T2* images were collected using an EPI sequence (TE=22ms, FA=90^{o}, TR=2110ms, 40 slices, voxel size: 3x3x3mm) over a time of 54 minutes. Each image was acquired in an ascending fashion. For 31 participants, whose anatomical images were not available in the Institute's database, we acquired high-resolution MPRAGE images (TE=2.98ms, FA=9^{o}, TR=2300ms, TI=900ms, voxel size: 1x1x1mm). There were 25 participants whose anatomical images were available through the Institute's database. For those participants the time between anatomical image acquisition and the current experiment was: 3 years for 2 participants, 2 years for 8 participants, 1 year for 8 participants, and images were acquired the same year as the current experiment for 7 further participants. This sample of 25 participants included 18 lean and 7 obese individuals.

4.4.2.4 Data analyses

4.4.2.4.1 Sample sizes

The full sample size for analysis of behavioural, baseline delay discounting and questionnaire data was n=56. The final fMRI sample for analysis of perceptual-related, choice value-related and task-related choice-independent brain activity was n=51. For behavioural and fMRI priming analyses and task-related choice-dependent fMRI analyses we had to exclude participants who chose either exclusively immediate or delayed rewards (*post hoc* exclusion criterion), and outliers concerning the cumulative priming effect for each of the four non-neutral priming conditions. The outliers were *a priori* defined as values lying more than 1.5 interquartile range above/below Tukey's hinges (H1 and H2). This resulted in a final sample size of n=36 participants (19 lean, 17 obese).

4.4.2.4.2 Behavioural data

Behavioural data were analysed using SPSS 22 (IBM, Armonk, New York, United States, statistical analysis of behavioural data) and MATLAB 2012b (The MathWorks, Inc., Natick, Massachusetts, United States, modelling of delay discounting data using quasi-hyperbolic model). To investigate between-group differences in the ratings of the priming stimuli, we used an ANOVA with weight status as a between subject variable. To test for rating differences between stimuli of different modalities and valences, we used a repeated measures ANOVA with modality and valence as within subject factors. Baseline and primed delay discounting data were plotted using ggplot2 toolbox for R in RStudio (Wickham, 2009).

4.4.2.4.3 Delay discounting data modelling

Delay discounting data modelling was performed using procedures described in section 4.3.2.3.1.

4.4.2.4.4 Primed delay discounting data modelling

In order to obtain a trial-by-trial measure of the priming effect, we calculated the probability of choosing the delayed reward during each trial by fitting a generalized linear model with a logit link function to the data. Here the 12 *r* values represented a predictor variable, and the dependent variable was denoted by the actual probability of choosing the LDR extracted from the data. We then extracted individual probabilities of choosing LDR for each *r* from the model. To obtain a comparable measure of the priming effect, we subtracted the probabilities for neutral conditions from the positive and negative conditions within respective modalities, thus obtaining four separate measures, one for each non-neutral priming condition.

To investigate whether probabilities of choosing the LDR were different for each *r*, we entered the priming effect values for all *r*'s into a repeated-measures general linear model as a within subject, dependent factor. This was done separately for each of the four non-neutral priming conditions.

Further, we aimed to establish whether the priming effect for different conditions, independent of *r,* was different from 0 and different between groups. For this, we calculated

a cumulative priming effect for each condition by adding all the individual probabilities of choosing the LDR. We then used a one-sample t-test to investigate whether the cumulative priming effect in each condition was different from zero. This would indicate a significant change of probability of choosing the LDR from a neutral condition to the corresponding positive or negative priming conditions. We used a two-sample t-test to investigate whether there were any between-group differences between priming conditions.

Following our findings on the behavioural level and to mimic our neuroimaging analysis (GLM 6), we decided to investigate whether BMI and BMI^2 influence *r*-dependent priming in the G_{neg} condition. To this end we entered priming effect values for all *r*'s into a repeated-measures general linear model as a within-subject, dependent factor, and BMI and BMI^2 as covariates (Brambor et al., 2006).

4.4.2.4.5 Questionnaire data

Questionnaire data were tested for group differences using a two-sample t-test. The income and education assessment questionnaire data were tested for group differences using a chi square test. Moreover, following Simmank et al. (2015), we tested for within-group correlations between delay discounting factors and subscales of the Three Factor Eating Questionnaire using Spearman's correlation.

4.4.2.4.6 Neuroimaging data analysis

We used FSL 5.0.8 (The University of Oxford, Oxford, United Kingdom), SPM 12 (Wellcome Department of Cognitive Neurology, London, United Kingdom) and MATLAB R2012b to pre-process and statistically analyse the functional imaging data. Brain figures were plotted using Nilearn. Anatomical structures corresponding to peak voxels were identified using the xjView toolbox (http://www.alivelearn.net/xjview). To enable further pre-processing steps, structural images were skull-stripped using FSL's brain extraction tool (Smith, 2002) and SPM12 segmentation tool. Functional data were motion corrected using McFLIRT (Jenkinson et al., 2002), slice-timed, and smoothed with a 6mm FWHM Gaussian Kernel, and normalised to MNI space using FSL. To remove motion and physiological noise-related artefacts, we used an automatized independent component analysis approach (ICA-AROMA; Pruim et al.,

2015). Prior to statistical analysis on an individual level, the data were high-pass filtered with a filter of 128s.

4.4.2.4.7 Analysis of BOLD response

A two-level group random effects analysis was performed using SPM12. Single subject regressors were entered into a univariate general linear model and convolved with a double-gamma hemodynamic function. Individual contrast files were then entered into a second level analysis (GLM1: flexible factorial model, remaining GLMs: one- or two-sample t-tests). In this step, BMI, age and gender were entered as covariates-of-no-interest, in order to control for variance in those variables. Additionally, for analysis of priming effects in the G_{neg} condition, we added BMI^2 as a covariate of interest (see results section 4.4.3.5). Unless stated otherwise, presented results were thresholded at a whole-brain voxel level with a threshold of $p<0.005$ and corrected for multiple comparisons on a cluster level with $p<0.05$ (family-wise error, FWE). The FWE p-value was Bonferroni corrected for the number of GLMs used in the study, resulting in an effective p-value threshold of 0.007.

First, we modelled brain activity related to perception and priming-independent choice (GLM 1, GLM 2 and GLM 3) in order to replicate findings already reported in the literature. GLM 4 and GLM 5 were the models of main interest, as they investigated how brain activity is related to priming effects that we observed on the behavioural level. GLM 6 and GLM 7 were parts of a *post-hoc* analysis to elucidate mechanisms behind the main effects.

Including all regressors of interest in one GLM would have required including more than 200 regressors. Hence, some of the analyses needed to be separated into different models. Moreover, this approach allowed us to maximise statistical power for our analyses, as some analyses (without finer distinctions between conditions) could be conducted within the full fMRI sample (51 participants, GLM 1 and GLM 2), instead of with the priming sample (36 participants, GLMs 3-7).

- **GLM 1: Perception-related brain activity**

We investigated how brain activity changed with respect to the priming stimulation. 14 regressors were entered into the single subject analysis: 12 priming regressors representing

the 3 visual and 3 gustatory priming conditions for two trial types (DD and P), and 2 regressors representing the task phase and the response phase (independent of the condition). The priming regressors were time-locked to the onset of each trial, and the duration of each event was set to 500ms (priming length). On the second level, contrasts for individual regressors were entered into a flexible factorial model, with modality and valence as factors. We contrasted gustatory and visual related brain activity against each other (visual > gustatory; visual < gustatory). Moreover, we investigated brain activity related to positive and negative valence (positive > negative; negative < positive; positive > neutral; negative > neutral), independent of modality. In this analysis the results concerning gustatory and visual brain activity were thresholded at an FWE-corrected whole brain level of 0.05 and with an extent cluster threshold of 200 voxels, while all remaining results were thresholded at a whole-brain voxel level $p<0.005$ and FWE-corrected on a cluster level ($p<0.05$).

- **GLM 2: Choice value- and task-related brain activity**

To investigate whether brain activity was modulated by the value of the chosen reward on a trial-by-trial level, we entered the choice value on single subject-level as a parametric modulator of a single regressor containing all DD trials. The model also included a regressor representing task phase for P trials, and two regressors representing priming phase and response phase (independent of conditions). Here (and in the following models) the task regressors were time-locked to the onset of the task screen and the duration of each event was set to 3500ms. We contrasted DD and P trials against each other, as well as investigated where brain activity correlated with choice value. Because of high statistical significance, the results in the DD>P contrast were thresholded at an FWE-corrected whole brain threshold of 0.05 and with an extent cluster threshold of 400 voxels.

- **GLM 3: Choice-dependent brain activity**

We investigated whether brain activity was modulated by whether participants chose delayed or immediate rewards. To this end, we entered 5 regressors into the single subject analysis: 2 regressors representing DD task phases – one for delayed and one for immediate

choices (independent of priming conditions) – 1 regressor representing task phase for P trials, and 2 regressors representing priming and response phases (independent of condition and trial type). Moreover, the first two regressors were parametrically modulated by the choice value on each trial (following the approach described in Hare et al., 2014). Brain activity for immediate choices was compared with brain activity for delayed choices.

- **GLM 4: Priming related changes in brain activity**

We investigated whether behavioural priming effects were reflected in changes in brain activity. For this analysis we entered 14 regressors into the first level analysis: 12 reflecting 12 different priming conditions, irrespective of the delayed or immediate choice, and 2 regressors reflecting the response phase and the priming phase (independent of the condition). This analysis was mainly used to investigate how brain activity in the G_{neg} condition differed from the other conditions, since we only found significant behavioural effects in this. This was based on a priori assumptions that we would only investigate brain activity differences in conditions for which behavioural effects were significant.

- **GLM 5: Trial-by-trial priming effect modulation of brain activity**

To investigate whether brain activity was modulated by the trial-by-trial priming-effect (the probability of choosing the LDR in a priming condition minus the probability of choosing the LDR in a respective neutral condition) in the G_{neg} condition, we entered the priming effect as a parametric modulator of a regressor containing all DD trials within this condition (unlike GLM 4). As described above, this regressor was obtained by modelling *r*-dependent probabilities of choosing delayed rewards for each individual trial. Additionally, we entered 13 other regressors – 11 for each of the remaining conditions (in which no significant priming effect was found), and two other regressors representing the priming phase and the response phase (independent of the condition). The contrast of interest was the parametric regressor.

- **GLM 6: Psychophysiological interaction (PPI) analysis**

In order to better understand the mechanisms underlying the observed priming effect, we performed a PPI analysis. This analysis describes how contributions of different brain areas

to each other change within a psychological context (Friston et al., 1997). Since those interactions occur on a neural level, not on the hemodynamic level, PPI involves steps such as deconvolution of the BOLD signal, calculating interaction term with the psychological variable, and reconvolution of this interaction with the hemodynamic response function. Here, we tested whether the dlPFC (identified in GLM 4) would change its connectivity with other brain regions depending on the trial-by-trial probability of choosing the LDR that we entered as a parametric modulation into the model. For this analysis, we used peak voxel coordinates from the GLM 4 contrast of the gustatory negative conditions versus other conditions (as this condition revealed the strongest results), and defined a 6mm radius sphere around it as a volume of interest. We then created a separate GLM, which consisted of 16 regressors: time course of the VOI (physiological factor), values of parametric modulation (trial-wise probability of choosing the delayed reward; psychological factor), the PPI term, and 13 remaining regressors representing 11 priming conditions (without G_{neg}) and response and priming phases of the experiment (independent of condition). This was done according to recommendations by O'Reilly and colleagues (O'Reilly et al., 2012). In comparison to the GLM 5, GLM 6 includes three additional regressors specific for the PPI analysis, and no regressor representing the G_{neg} condition. The contrasts of interest included the PPI interaction regressor, and the BMI regressor, as we tested for correlation of functional connectivity and BMI.

- **GLM 7: PPI analysis: group differences in G_{neg} condition**

In this model we aimed to investigate general group differences in connectivity between gustatory negative and gustatory neutral conditions independent of choice difficulty (based on behavioural group differences). To do that, we used the same seed regions as in the GLM 6 analysis and created three PPI regressors: time course of the VOI, main effect regressor (G_{neg} > G_{neu}, psychological factor), and the PPI term. Similarly to GLM 6, we added 10 regressors to the model representing the remaining priming conditions and 2 representing response and priming phases of the experiment. Here, contrast of interest was the PPI interaction regressor.

4.4.3 Results

4.4.3.1 Income and education

Using a short questionnaire we assessed participants' secondary school education, professional qualifications and household income (Table 4.4.2). The only significant difference between groups concerned the professional degree. This analysis revealed that lean participants had higher academic education than obese participants. Moreover, individual income group differences were on the verge of significance, indicating that obese participants earned more than lean participants. Differences in income might influence delay discounting behaviour, however, in a way where participants earning more money should have lower delay discounting (Reimers et al., 2009). This was not true for our sample, where obese participants earned more and were steeper discounters.

Table 4.4.2 Income and education group differences between lean and obese participants. Lean and obese groups differed significantly concerning their professional degree with lean participants having a higher professional degree. Total income differed at trend-level between groups with obese individuals having a higher income.

Variable	Test statistic (Pearson chi-square)	Exact p-value	Phi coefficient
Total income	14.367	0.055	0.507
Money available to spend	7.456	0.544	0.365
Satisfaction with the income	4.439	0.346	0.282
Parents' income	9.787	0.179	0.418
Highest school degree	4.045	0.113	0.269

Professional degree	**17.026**	**0.001**	**0.551**

4.4.3.2 Priming stimuli ratings

4.4.3.2.1 Between group differences

There were no group differences in evaluation of the gustatory stimuli. Within the visual modality, lean participants rated the negative stimuli as more negative compared to obese participants (main effect for group: $F(1,54)=4.817$, $p=0.032$; Table 4.4.3).

Table 4.4.3 Priming stimuli ratings for lean and obese groups. Lean participants rated the negative visual stimuli as more negative than the obese participants.

Condition	Mean		Standard deviation		F value (1,54)	p value	Effect size |d|
	Lean	Obese	Lean	Obese			
Gustatory positive	76.53	79.62	22.12	20.07	0.294	0.590	0.148
Gustatory neutral	62.50	56.00	22.96	20.65	1.225	0.273	0.302
Gustatory negative	19.4	16.73	21.58	16.76	0.261	0.611	0.139
Visual positive	76.47	73.10	11.74	15.71	0.840	0.363	0.250
Visual neutral	48.27	53.21	13.67	8.87	2.491	0.120	0.431
Visual negative	12.82	21.31	12.08	16.76	**4.817**	**0.032**	**0.599**

4.4.3.2.2 Within modality and valence differences

As expected, significant differences were observed across participants for the rating of the stimuli in relation to both valence and modality. Positive, negative and neutral stimuli were evaluated differently, and visual and gustatory stimuli were evaluated differently (main effects: Modality: $F(1,55)=8.372$, $p=0.005$, Valence: $F(2,1)=260.003$, $p<0.001$; for further details see Table 4.4.4).

Table 4.4.4 Ratings for stimuli of different valences and modalities across participants. Table represents results of a repeated measures ANOVA with modality and valence of stimuli as dependent variables

Modality	Valence	Mean	Standard deviation	Modality			Valence		
				F value (1,55)	p value	Partial η^2	F value (2,54)	p value	Partial η^2
Gustatory	Positive	77.96	21.06	**8.372**	**0.005**	**0.132**	**260.003**	**<0.001**	**0.861**
	Neutral	59.48	21.96						
	Negative	18.16	19.36						
Visual	Positive	74.90	13.70						
	Neutral	50.56	11.85						
	Negative	16.76	14.93						

4.4.3.3 Sensitivity to reward and punishment, eating behaviour and subjective time perception

We observed significant group differences between lean and obese participants for the disinhibition and cognitive restraint subscales of the TFEQ questionnaire. These results show that obese participants had higher scores on both of those subscales. There were no significant group differences for other questionnaires (cognitive restraint: t(43.195)=-2.864, p=0.006, disinhibition: t(39.688)=-2.191, p=0.034, for further details see Table 4.4.5). Further, we did not observe any significant correlations between subscales of the TFEQ and delay discounting parameters (Obese: CR/β: r=0.116, p-0.542; DI/β: r=0.167, p=0.378; H/β: r=0.186, p=0.324; CR/δ: r=0.115, p=0.544, DI/δ: r=0.207, p=0.273, H/δ: r=0.230, p=0.221; Lean: CR/β: r=0.375, p=0.059; DI/β: r=-0.236, p=0.247; H/β: r=-0.188, p=0.358; CR/δ: r=0.039, p=0.849, DI/ δ: r=0.-272, p=0.179, H/δ: r=-0.012, p=0.952;).

Table 4.4.5 Group differences in questionnaire outcomes. Significant differences between groups were observed in the disinhibition and cognitive restraint subscales of the TFEQ.

Questionnaire	Subscale	Mean		Standard deviation		t value	p value	Effect size |d|
		Lean	Obese	Lean	Obese			
TFEQ	Cognitive restraint	5.93	8.65	2.79	4.09	**t(43.195)=-2.864**	**0.006**	**0.872**
	Disinhibition	3.93	5.62	2.05	3.42	**t(39.688)=-2.191**	**0.034**	**0.599**
	Hunger	5.03	4.46	2.05	3.46	t(48.081)=0.667	0.508	0.2
BIS/BAS	BAS drive	12.07	12.08	1.68	2.26	t(45.638)=-0.19	0.985	0.005
	BAS fun seeking	11.37	12.19	1.85	2.58	t(44.599)=-1.359	0.181	0.365
	BAS reward responsivity	15.83	16.27	1.93	2.03	t(52.005)=-0.819	0.416	0.222
	BIS	19.27	18.12	2.02	2.37	t(49.408)=1.941	0.058	0.522
ZTPS	2 months	45.77	43.96	32.06	26.73	t(53.931)=0.230	0.819	0.061
	4 months	61.87	61.85	36.26	27.33	t(53.041)=0.002	0.998	0.001
	12 months	88.20	82.50	30.28	30.48	t(52.778)=0.700	0.487	0.188

TFEQ – Three Factor Eating Questionnaire, BIS/BAS – Behavioural Inhibition/Behavioural Activation System, ZTPS – Zauberman Time Perception Scale (subjective time perception rated on a scale 0-100 corresponding to 'not long at all - very long').

4.4.3.4 Baseline delay discounting and group differences

Using a general linear model we investigated whether there were group differences regarding delay discounting parameters for the random choice task. We included weight status and gender as between group factors, β and δ parameters as dependent variables, and obtained professional degree as a covariate (since we found significant group differences in this aspect). Our analysis revealed a significant main effect of weight status on the β parameter (delay-independent bias towards immediate rewards), showing that obese participants had higher delay-independent delay discounting (Figure 4.4.2). Moreover, we found a significant weight status by gender interaction for the δ parameter, which is the delay-dependent discount factor (β: weight status main effect: $F(1,51)=4.140$, $p=0.047$; δ:

weight status * gender interaction: F(1,51)=5.736, p=0.020, for further details see Table 4.4.6). This indicates that differences in delay-dependent delay discounting between lean and obese participants were gender-specific (Table 4.4.6). Obese females showed higher delay-dependent delay discounting than lean females, while an inverse relationship was observed for males.

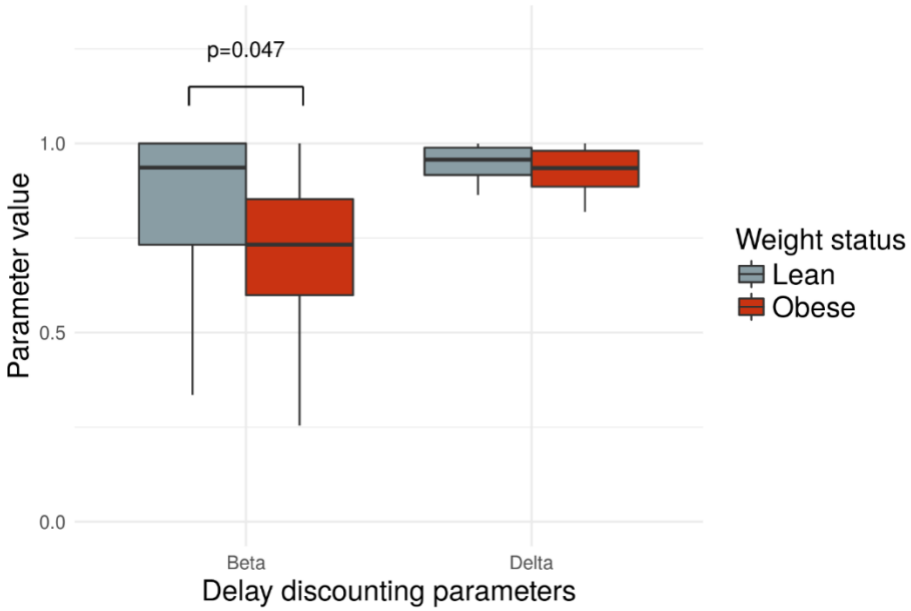

Figure 4.4.2 Delay discounting parameters β (delay-independent) and δ (delay-dependent) plotted separately for lean and obese group (n=56). We found a significant group difference between lean and obese participants in the beta parameter of delay discounting representing the present bias (p=0.047).

Table 4.4.6 Group and gender differences for the DD parameters. This analysis revealed significant group differences for the β (delay-independent) factor for the pooled sample, and β and δ (delay-dependent) parameters differences between obese and lean group for females only. DD – Delay Discounting, β – present bias, δ – discount factor

	Descriptive						Statistical analysis								
DD parameter	Weight status	Mean	Standard deviation	Gender	Mean	Standard deviation	Weight status			Gender			Weight status * gender		
							t value	p value	Partial η^2	t value	p value	Partial η^2	t value	p value	Partial η^2
β	Lean	0.86	0.21	Male	0.79	0.26	**F(1, 51)=4.140**	**0.047**	**0.075**	F(1,51) = 0.560	0.458	0.011	F(1,51) = 2.097	0.154	0.039
				Female	0.93	0.12									
	Obese	0.72	0.23	Male	0.74	0.29									
				Female	0.70	0.14									
δ	Lean	0.94	0.06	Male	0.92	0.07	F(1,51) =0.964	0.331	0.019	F(1,51) = 0.798	0.376	0.015	**F(1,51) = 5.736**	**0.020**	**0.101**
				Female	0.97	0.03									
	Obese	0.93	0.05	Male	0.94	0.06									
				Female	0.92	0.04									

4.4.3.5 Primed delay discounting

We observed a significant priming effect dependent on the *r* parameter (indexing choice difficulty) in the G_{neg} condition only (Main effect of group within the G_{neg} condition: $F(11,19)=2.222$, $p=0.048$; Table 4.4.7). This result points to the fact that choice difficulty (difference between SIR and LDR) is a factor influencing priming effects within the Gneg condition. Moreover, the cumulative effect of priming was different from zero only for the obese group in the G_{neg} condition ($t(16)=2.263$, $p=0.038$; Table 4.4.8, Figure 4.4.3). This indicates that the obese group was primed towards more delayed choices during this condition relative to G_{neu} condition. Further, there was a significant difference in the priming effect in the G_{neg} condition between the lean and obese groups ($t(34)=2.080$, $p=0.045$; Table 4.4.8). Following up on this, we tested for a direct relationship between BMI and the cumulative priming effect in the G_{neg} condition. Previous studies showed quadratic associations of responsivity to reward and the physiology of the reward system with BMI (Davis and Fox, 2008; Dietrich et al., 2014; Horstmann et al., 2015; Dietrich et al., 2016b; Verdejo-Román et al., 2017). Hence, we additionally tested for a quadratic relationship between the priming effect and BMI. Indeed, there was a quadratic relationship between BMI and the cumulative priming effect ($R^2=0.208$, $p=0.021$, see supplementary Figure S1 for details). Due to this, we added BMI^2 as a covariate in the fMRI analyses involving priming effects in the G_{neg} condition (GLM4-7). Additionally, to mimic our neuroimaging analysis, we performed a *post hoc* repeated measures ANOVA with *r*-dependent priming effect values within the gustatory negative conditions as dependent variables and BMI and BMI^2 as covariates. This analysis showed that BMI and BMI^2 are significant predictors of choice difficulty-dependent priming in the full sample, including both lean and obese participants, in the G_{neg} condition (BMI: $F(11, 23)=3.035$, $p=0.012$, BMI^2: $F(11, 23)=4.254$, $p=0.002$).

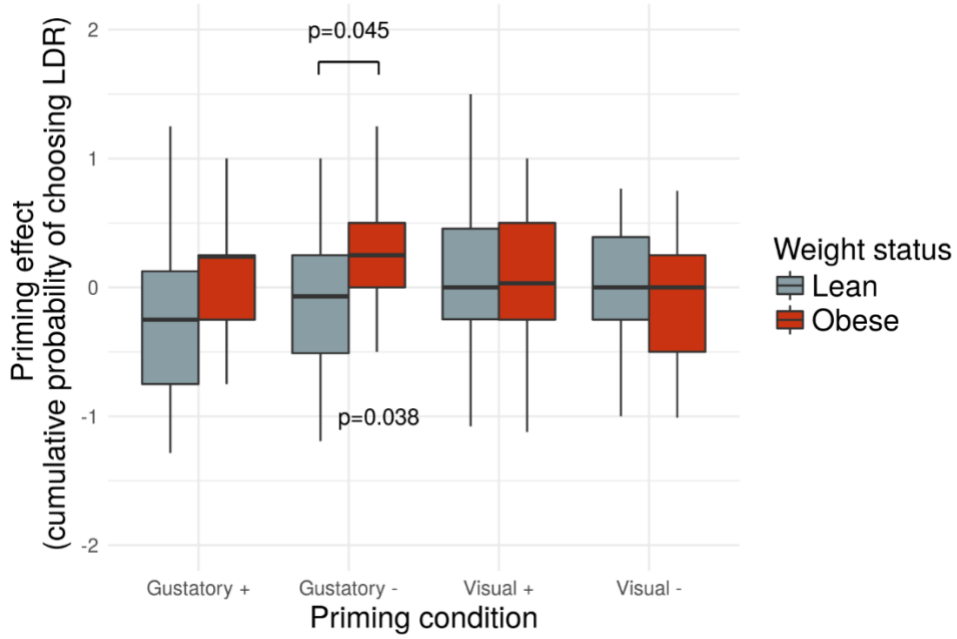

Figure 4.4.3 Condition dependent priming effects plotted separately for lean and obese group (n=36). We found that the cumulative priming effect in the gustatory negative condition was significantly different from zero in the obese group (p=0.038), which means that here participants chose more delayed options than in the gustatory neutral condition; additionally, we observed group differences in the gustatory negative condition (p=0.045), indicating that obese people were primed more towards delayed choices than lean people.

Table 4.4.7 Multivariate statistics showing differences in priming effect depending on the *r* parameter.

Condition	F value	p value	Partial η^2
Gustatory positive	F(11,19)=1.648	0.146	0.420
Gustatory negative	**F(11,19)=2.222**	**0.048**	**0.494**
Visual positive	F(11,19)=1.065	0.425	0.319
Visual negative	F(11,19)=1.188	0.344	0.343
Gustatory negative with BMI and BMI^2 as covariates	**BMI: F(11, 23)=3.035** **BMI^2: F(11,23)=4.254**	**BMI: p=0.012** **BMI^2: p=0.002**	**BMI: 0.592** **BMI^2:**

			0.670

Table 4.4.8 Cumulative effect of priming (independent of *r*). One-sample t-test against zero and two sample t-test for group comparison. The cumulative effect of priming was different from zero within the gustatory negative condition for the obese group. Obese participants showed more delayed choices than lean participants in the G_{neg} condition.

Condition	Lean		t(18) value	p value	Effect size |d|	Obese		t(16) value	p value	Effect size |d|	Lean vs. Obese		
	Mean	Standard deviation				Mean	Standard deviation				t(34) value	P value	Effect size |d|
Gustatory positive	-0.21	0.76	-1.186	0.251	0.276	0.08	0.47	0.730	0.476	0.170	-1.357	0.184	0.453
Gustatory negative	-0.13	0.63	-0.921	0.369	0.206	0.25	0.46	**2.263**	**0.038**	**0.544**	**-2.080**	**0.045**	**0.683**
Visual positive	0.09	0.62	0.635	0.534	0.145	0.01	0.66	0.119	0.907	0.015	0.333	0.741	0.125
Visual negative	-0.03	0.61	-0.205	0.840	0.049	-0.09	0.52	-0.205	0.493	0.173	0.314	0.755	0.105

4.4.3.6 Neuroimaging results

4.4.3.6.1 Brain activity related to perceptual processing

To assess differential perceptual brain activity we contrasted gustatory stimulation versus visual stimulation. For the gustatory stimulation > visual stimulation contrast, we observed higher activity in five clusters: the bilateral Rolandic operculum and insula, the supplementary motor area, and the superior frontal and cingulate gyri (Figure 4.4.4). The visual stimulation > gustatory stimulation contrast elicited higher brain activity in three clusters over the bilateral fusiform gyri and calcarine fissure (Figure 4.4.5).

We then contrasted negative and positive stimulation, regardless of modality, versus neutral stimulation. We found that negative stimulation elicited higher activation in four distinct clusters, including the superior and middle frontal gyri, thalamus, amygdala, insula, cingulate gyrus and the bilateral inferior occipital gyri. Positive stimulation elicited higher brain activation in five distinct clusters, including the bilateral inferior occipital gyrus, bilateral insula and amygdala, bilateral inferior orbital frontal gyrus, and the midbrain, including the ventral tegmental area. Clusters surviving a more stringent voxel-wise threshold of 0.001 are denoted in Table 4.4.9. Additionally, we directly contrasted positive and negative stimulation-related brain activity against each other. This analysis revealed that brain activity in the postcentral gyrus and left dorsolateral prefrontal and orbitofrontal cortex was higher for negative than for positive stimulation. We found no significant brain activations for the opposite contrast (Table 4.4.9).

4.4.3.6.2 Choice value-related brain activity

This analysis aimed at identifying brain regions, which tracked monetary values chosen in the DD task. For this, we investigated how brain activity was parametrically modulated by this chosen value on a trial-by-trial basis. In line with previous findings, the value of the chosen reward was reflected in brain activity in a single cluster with its maximum in the left medial frontal gyrus (Table 4.4.10, Figure 4.4.6).

4.4.3.6.3 Task-related brain activity

We investigated which brain regions were activated during performance of the delay discounting task in general, irrespective of the priming conditions. To control for possible perceptual confounds related to priming stimulation, we contrasted DD trials with P trials. We found a number of significant clusters, including the bilateral visual cortex, left middle and superior frontal gyri, right precentral gyrus, and right superior parietal lobule. Further, we investigated whether brain activity differed for immediate and delayed choices. We identified significant clusters for the immediate > delayed choices contrast only. These included the bilateral visual cortices along with parts of the cerebellum, the right middle frontal gyrus, and the precuneus (Table 4.4.11). Clusters surviving a more stringent voxel-wise threshold of 0.001 are denoted in Table 4.4.11.

4.4.3.6.4 Priming-related brain changes

This analysis was aimed at investigating how brain activity differed during priming. Since the behavioural differences were found only for the G_{neg} condition and in the obese group, we only investigated group differences in this condition. Using a two sample t-test we found that brain activity (DD trials > P trials) in the left superior frontal gyrus was lower for obese than for lean participants in the G_{neg} condition in relation to all other conditions (Table 4.4.12, Figure 4.4.7). Specifically, we computed single subject contrasts by assigning a positive weight to the G_{Neg} condition and negative weights to other conditions. Here, our findings imply a role for this region in mediating the priming effect.

4.4.3.6.5 Trial-by-trial priming effect modulation of brain activity

In this analysis we investigated whether brain activity in the gustatory negative condition was parametrically modulated by the priming effect. For this analysis we did not find any statistically significant results.

4.4.3.6.6 Priming-related PPI connectivity changes

While the general analysis for trial-by-trial priming effects was not significant, another possibility was that not the average activation but functional connectivity of priming related regions was modulated by the priming effect. We further hypothesised that such connectivity

changes might additionally be modulated by BMI. This logic is in line with our behavioural results, where priming effect in the G_{Neg} condition is related to different BMI values. Our PPI analysis confirmed this hypothesis and showed a negative correlation of BMI with connectivity modulated by the trial-wise priming effect between the left superior frontal gyrus (as the seed region) and regions of the left middle and superior frontal gyri, precuneus and medial frontal gyrus (Table 4.4.13, Figure 4.4.8, supplementary Figures S2-S7). Clusters surviving a more stringent voxel-wise threshold of 0.001 are denoted in Table 4.4.13. These results imply that for the G_{neg} condition higher BMI and higher priming effects were related to lower connectivity between left superior frontal gyrus and these regions. They are also in line with our behavioural results showing that BMI is a predictor of *r*-dependent priming effect.

We observed no general group differences in PPI analysis of G_{neg} and G_{neu} conditions (GLM 7).

Figures depicting contrast estimates and 95% confidence intervals for peak voxels in each fMRI analysis can be found in supplementary Figure S8.

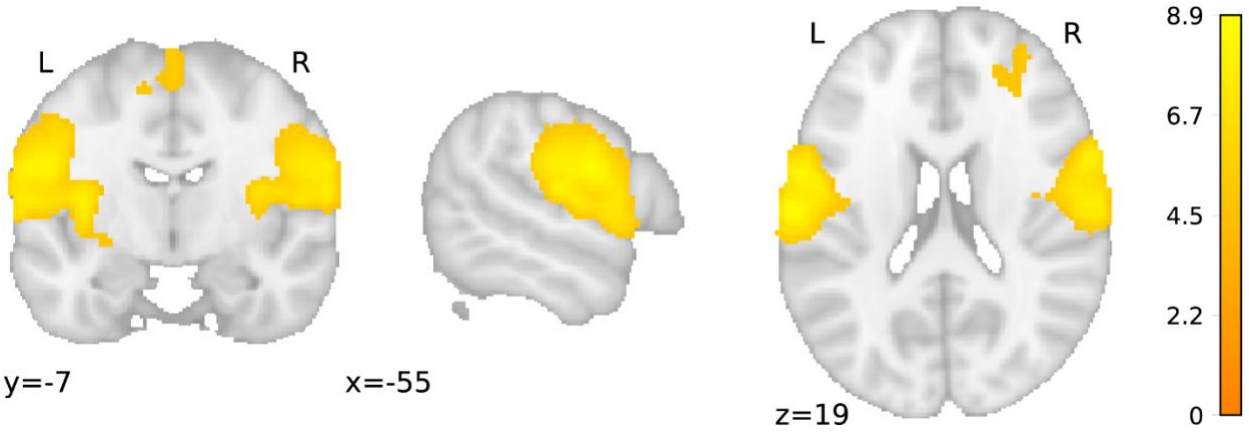

Figure 4.4.4 Brain regions showing higher activity for trials using gustatory stimulation (priming phase, independent of DD or P trial type) compared to trials using visual stimulation. L – left, R – right. T-values are plotted on a standard brain

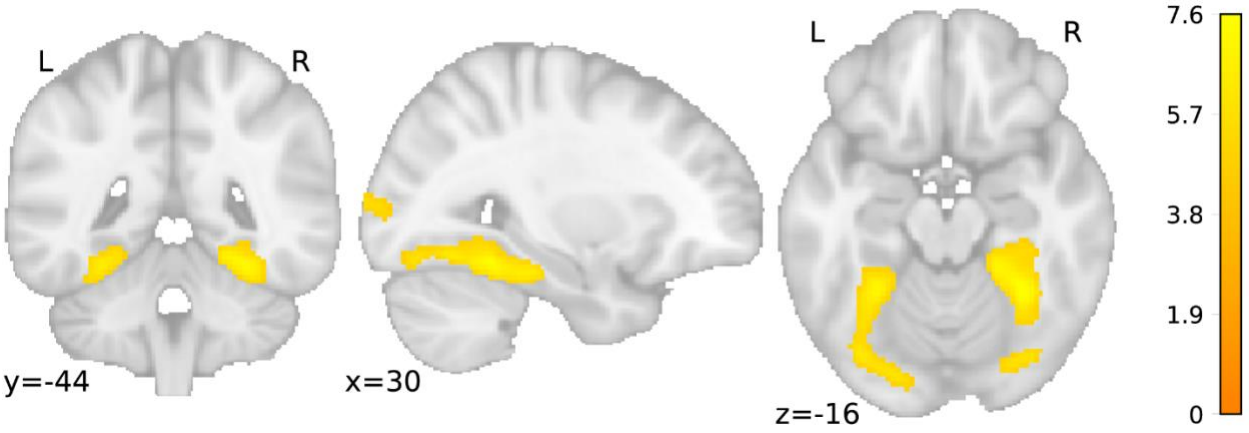

Figure 4.4.5 Brain regions showing higher activity for trials using visual stimulation (priming phase, independent of DD or P trial type) compared to trials using gustatory stimulation. L – left, R – right. T-values are plotted on a standard brain

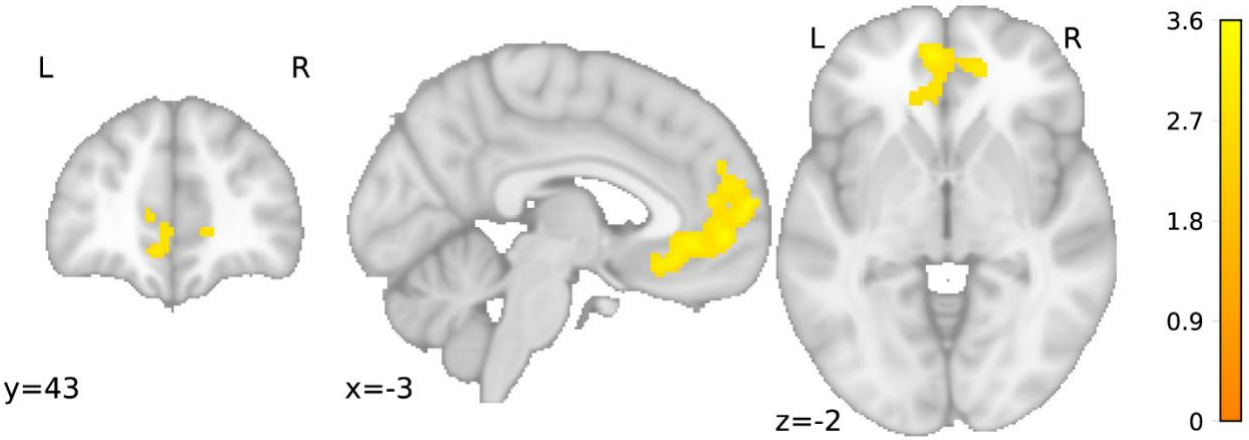

Figure 4.4.6 Brain regions where the trial-wise choice value parametrically modulated brain activity during DD trials. L – left, R – right. T-values are plotted on a standard brain

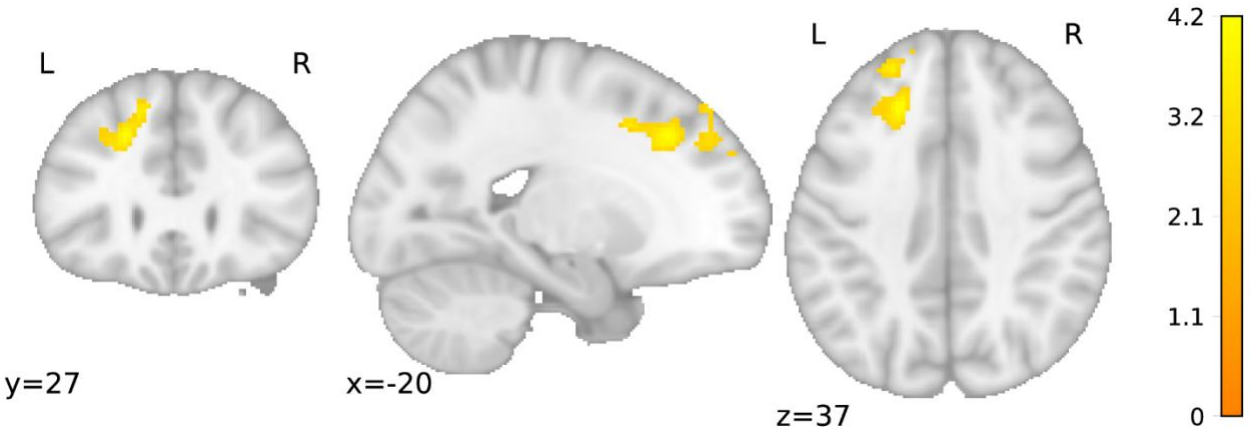

Figure 4.4.7 Brain region where brain activity during gustatory negative priming is higher for lean than for obese participants. L – left, R – right. T-values are plotted on a standard brain

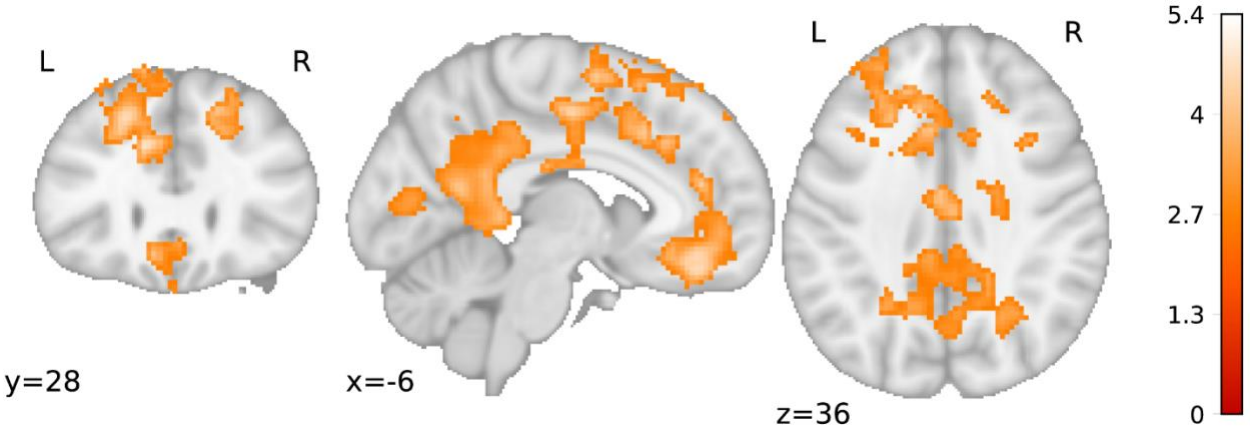

Figure 4.4.8 Brain regions where PPI connectivity from the dlPFC modulated by the trial-wise priming effect correlates negatively with BMI. L – left, R – right. T-values are plotted on a standard brain

Table 4.4.9 Brain regions showing significant effects for the perceptual analysis.

Contrast	Region of the peak voxel	Cluster size [voxels]	Coordinates (MNI)			Peak z score	Peak t score
Gustatory>Visual**	Postcentral gyrus L	4443	-62	-16	16	-	8.92
	Precentral gyrus R	3260	60	4	24	7.67	8.16
	Medial frontal gyrus R	1457	2	-2	60	6.15	6.40
	Cingulate gyrus R	568	6	12	36	5.65	5.84
	Superior frontal gyrus R	265	28	44	12	5.32	5.47
Visual>Gustatory**	Fusiform gyrus R	1046	34	-50	-18	7.18	7.57
	Calcarine Fissure R	626	18	-98	2	6.86	7.20
	Fusiform gyrus L	746	-30	-50	-16	6.74	7.07
Negative>Neutral	Insula L*	25940	-36	8	-10	6.96	7.32
	Middle occipital gyrus L*	1730	-48	-82	-12	6.73	7.05
	Inferior occipital gyrus R*	987	50	-80	-12	5.52	5.69
	Precuneus*	931	0	-74	40	4.21	4.29
Positive>Neutral	Middle occipital gyrus L*	2922	-48	-82	-12	7.28	7.69
	Insula L*	3779	-36	6	-10	6.64	6.95
	Insula R*	2805	38	4	-10	6.02	6.25
	Middle occipital gyrus R*	2208	52	-78	-12	5.87	6.08
	Superior frontal gyrus R	832	16	10	72	3.79	3.84
Negative>Positive	Middle frontal gyrus L	3616	-36	56	2	4.59	4.13

R – right, L – left; * denotes clusters surviving 0.001 voxel-wise threshold and further FWE correction (0.007); ** this analysis was performed using an FWE-corrected voxel-wise threshold of 0.05

Table 4.4.10 Brain region modulated by the single trial monetary choice value on the delay discounting task.

Contrast	Region of the peak voxel	Cluster size [voxels]	Coordinates (MNI)			Peak z score	Peak t score
Parametric modulation choice value	Medial frontal gyrus L	1056	-4	62	10	3.37	3.61

R – right, L - left

Table 4.4.11 Brain regions showing higher activity for the delay discounting task conditions vs. perception only conditions and for the immediate vs. delayed choices.

Contrast	Region of the peak voxel	Cluster size [voxels]	Coordinates (MNI)			Peak z score	Peak t score
DD>P**	Calcarine fissure L	8108	-16	-96	-6	-	12.42
	Middle occipital gyrus R	2017	32	-98	-4	-	12.38
	Medial frontal gyrus L	2321	-6	-2	58	6.21	7.78
	Precentral gyrus R	1573	30	-24	62	6.21	7.78
	Inferior frontal gyrus L	809	-46	10	30	5.83	7.11
	Precuneus L	815	-26	-64	38	5.65	6.81
	Superior parietal lobule R	615	34	-54	50	5.48	6.53
Immediate choices > Delayed choices	Middle frontal gyrus R*	4889	26	70	10	5.01	6.25
	Cerebellum R*	12183	2	-86	-20	4.54	5.43

	Cingulate Gyrus L	1200	-6	-8	28	3.97	4.56
	Medial frontal gyrus R	1079	6	18	48	3.89	4.44

DD – delay discounting, P – perception only, L – left, R – right; * denotes clusters surviving 0.001 voxel-wise threshold and further FWE correction (0.007); ** this analysis was performed using an FWE-corrected voxel-wise threshold of 0.05

Table 4.4.12 Brain region associated with priming effects in the gustatory negative condition

Contrast	Region of the peak voxel	Cluster size [voxels]	Coordinates (MNI)			Peak z score	Peak t score
Obese < lean for G_{neg} condition versus all other conditions	Superior frontal gyrus L	738	-20	28	38	3.70	4.21

R – right, L - left

Table 4.4.13 Brain regions whose connectivity to the left superior frontal gyrus correlates negatively with BMI and is modulated by the trial-wise priming effect within the gustatory negative condition

Contrast	Region of the peak voxel	Cluster size [voxels]	Coordinates (MNI)			Peak z score	Peak t score
BMI correlation with connectivity modulated by the trial-wise priming effect	Middle frontal gyrus L*	4023	-24	22	44	4.50	5.40
	Cerebellum R	1315	42	-76	-32	4.14	4.85
	Occipital lobe L*	5580	-36	-66	-2	4.08	4.74
	Medial frontal gyrus L*	939	-6	40	-14	3.97	4.57
	Postcentral gyrus L	688	-54	-22	56	3.89	4.46

R – right, L – left; * denotes clusters surviving 0.001 voxel-wise threshold and further FWE correction (0.007)

4.4.4 Discussion

In this study we investigated whether 1) obese participants showed higher delay discounting than lean participants, and 2) whether they were more susceptible to incidental priming on the delay discounting paradigm than lean people. In a second step, we then investigated the neural correlates of any significant behavioural effects. We hypothesised that participants with obesity would show higher DD, and that they would also show higher susceptibility to priming. We further hypothesised that this higher susceptibility to priming would be reflected in differences in brain regions involved in valuation (vmPFC), cognitive control (dlPFC), and reward perception (striatum). We showed higher baseline delay discounting for obese compared to lean individuals independent of delay. Moreover, group differences in delay-dependent discounting differed by gender. We also demonstrated a higher susceptibility to incidental priming on the delay-discounting task in obese participants (albeit only for one group of negative stimuli). Thus, our findings are in line with the most important findings regarding intertemporal decision-making in obese people. In addition, the priming effect was associated with modulation of brain activity in the left dorsolateral prefrontal cortex (dlPFC) and, indirectly, its connectivity to the medial prefrontal cortex (mPFC).

Here, we replicated previous results showing higher delay discounting in obese compared to lean participants (for a meta-analysis and review see: Amlung et al., 2016; McClelland et al., 2016). We showed this for males and females by using a delay-independent discounting parameter δ. For a delay-dependent parameter, resembling the widely used *k* parameter of the hyperbolic discounting model, we found a significant interaction between weight status and gender. This differential effect of gender is in line with some previous studies showing changed DD only for females (Weller et al., 2008; Rasmussen et al., 2010), and in contrast to others (Bickel et al., 2009; Jarmolowicz et al., 2014; Lawyer et al., 2015; Simmank et al., 2015; Amlung et al., 2016; Price et al., 2016b). Here, we used a quasi-hyperbolic delay discounting model which is different to most of the previous studies. It is conceivable that differences in

parameter estimations between these models explain why others mostly did not find gender differences in their studies. Differences between individuals might also contribute to these finer differences in effects. There is no homogenous population of "obese people", and hence fluctuations in variables not measured here, such as impulsivity, genotype or obesity duration, might have contributed to discrepancies in results between studies. However, given the diversity of findings so far, a systematic investigation focused on gender with large sample sizes would constitute a valuable future research program.

Taken together, our behavioural results provide evidence that obese people were more impulsive in their financial decisions than their lean control counterparts, but when primed by a negative food-related gustatory stimulus, this effect reversed. Simmank and colleagues (2015) interpreted their findings as evidence that obese people would be, more than others, biased in their general decision-making by different types of tempting, positive stimuli. As the decisions were not related to food, and the priming stimuli not related to the financial decisions, this could indeed point toward a general impulse control deficit in decision systems. Our results add to this view as we again show an effect of incidental stimuli on decisions in obese people, but this time reversed: While negatively valenced gustatory stimuli could be expected to delay the desire to consume food, these stimuli again had a transfer effect to delaying the desire to receive monetary rewards. Hence, our findings complement previous reports by showing that effects of incidental cues on decision-making might generalise, even for aversive stimuli.

The second important finding in our study was that obese people were more susceptible to priming by incidental cues than lean controls. Incidental cues have previously been shown to be an effective way of influencing decision making processes in the context of delay discounting (Murawski et al., 2012; van der Wal et al., 2013; Luo et al., 2014). Our results are in line with the general findings by Simmank et al. (2015). Unexpectedly, however, in our experiment this phenomenon occurred in the gustatory negative condition only, in which obese people showed stronger priming effects towards delayed choices. The direction of the effect is in line with the results of Luo et al. 2014. Simmank and colleagues (2015), on the other hand, showed a more diverse profile of obesity-gender interactions for a variety of visual stimuli. It should be noted, however, that there were several important differences

between these studies. First, Simmank and colleagues (2015) did not use gustatory stimuli, hence our results are not in conflict with their findings. Second, food-related cues were the only theme of all visual and gustatory stimuli in the present study while in the previous study a variety of positive visual stimuli, including social images, status symbols, and only a subset of food-related images, was used. This might have created strong framing and expectation effects. Third, in order to include all necessary control conditions and to maximise the number of delay discounting trials, we used only one temporal delay of two months, while Simmank and colleagues (2015) used several delays. This might have enabled participants to form expectations in our study and, in consequence, form rather stable indifference points. The resulting rather consistent choice patterns work against any potential priming effects. Supporting this conclusion, it should be noted that several participants, who had to be excluded from the analyses, exclusively chose delayed or immediate options in at least one condition, even though we initially adjusted choice options to individual indifference points. Finally, a possible explanation for observing priming effects only in the gustatory negative condition is that our design was not optimised to detect priming effects and that only the strongest primes could impact on behaviour. Therefore, it is important to note that even under these suboptimal circumstances, obese participants were primed by gustatory negative cues. Although subjective valence assessments were not statistically different, these cues had nominally the most negative values for obese participants, which might offer an explanation for why this particular condition elicited effects on delay discounting behaviour. Another difference to previous work (Simmank et al., 2015) could be that our positive stimuli were not perceived as positive as intended. We did not find brain regions responding more strongly to positive than to negative stimuli, and the positive stimuli were also rated as being closer to neutral than the negative stimuli. The absence of effects for the positive stimuli should therefore be interpreted with care.

We further investigated how the behavioural priming effect in the gustatory negative condition was reflected in brain activity. Firstly, in the parametric modulation analysis of the G_{neg} condition by priming effect we found no significant results. The effects of G_{neg} condition on a trial-by-trial basis were very small, and our analysis might not have been sensitive enough to detect changes in brain activity related to these behavioural effects. It is also

conceivable that that trial-by-trial effect on the neural level was only reflected in connectivity changes, not in changes of brain activity. Further, generally during priming with negative gustatory stimuli, activity in the left dlPFC was significantly lower for obese than for lean participants. Activity in the lateral prefrontal cortex (lPFC) has been shown to be related to more difficult choices, but also to choosing delayed rewards and exerting context-dependent control over behaviour (Monterosso et al., 2007; Shamosh et al., 2008; Weber and Huettel, 2008; Hare et al., 2009; Figner et al., 2010; Hare et al., 2011). However, opposing activation patterns (Pizzagalli et al., 2005; Boettiger et al., 2007; Cho et al., 2010; Hecht et al., 2013) or no activation patterns (Kable and Glimcher, 2007; Kable and Glimcher, 2010) have also been reported. A theory posed by Weber et al. might offer a possible explanation for these discrepancies (Weber et al., 2007). They suggested that differences in reward discounting might be related to query theory which posits that individual preferences, also in value-based decision making, are determined by sequentially answering a number of internal queries regarding choice and order thereof (Weber and Kirsner, 1997; Fischer et al., 1999; Johnson et al., 2007). Put simply, factors such as the order of reward evaluation, shift of attention to the reward's magnitude or delay, and internal goals (answers to internal queries) influence delay discounting rates (Weber et al., 2007). Applied to our results, this would mean that obese and lean participants might have differed concerning their initial internal goals, and therefore made different choices. It follows that neural mechanisms of maintaining these goals could then produce different response patterns. Different implicit goals of participants might explain differential engagement of the dlPFC in reward-related decision making. Therefore, the dlPFC might not only act as an inhibitory brain structure, constantly promoting less impulsive decision-making, but it could also promote more impulsive decision-making, provided that this is congruent with internal goals. In our study, obese compared to lean people generally gravitated towards more immediate rewards, which could reflect intrinsic differences in internal goal structures. In consequence, priming towards delayed options in obese people was related to the observed *decrease* in dlPFC activity.

The results of our connectivity analysis point to a potential mechanism for how this goal-dependent activity of the dlPFC could influence behaviour. In our behavioural analysis we

showed that BMI was a significant predictor of choice difficulty-dependent priming within gustatory negative condition. This means that, depending on how different the monetary values of available rewards were, participants were primed to a different degree depending on their BMI. We showed a similar effect in our PPI connectivity analysis. This indicated that during the gustatory negative condition connectivity of the dlPFC with the vmPFC, posterior cingulate cortex and parietal cortex was modulated by the trial-by-trial choice difficulty-dependent priming effect which, in turn, correlated negatively with BMI. These regions are discussed to be part of the default mode network (DMN) (Raichle et al., 2001). The DMN has previously been shown to be engaged in delay discounting. More specifically, in lean samples, activity within these brain structures has been shown to increase with choices of delayed rewards (McClure et al., 2004; Kable and Glimcher, 2007; Kable, 2014; Chen et al., 2017). The vmPFC has also been shown to track trial-by-trial subjective value of chosen rewards (e.g. Kable and Glimcher, 2007), an effect corroborated by our results. Thus, a modulation of the connectivity between the aforementioned brain regions might be necessary to alter decision making processes. Indeed, two studies investigating neural correlates of primed intertemporal choices showed that the mPFC was directly related to the effects of priming with incidental cues (Murawski et al., 2012; Luo et al., 2014). Hare and colleagues further showed that dlPFC increased its connectivity to the vmPFC at the time of intertemporal choice, especially in trials in which participants chose LDRs (Hare et al., 2014). Surprisingly, our findings suggest an opposite pattern for participants with higher BMI. This, however, might again be expected if one assumes that dlPFC activity depends on current individual goals. The increased connectivity in obese participants then again suggests that, by default, the dlPFC inhibits brain regions related to delayed choices and thus promotes immediate choices in obese individuals. During priming with negative gustatory cues, the brain regions promoting delayed choices may be disinhibited by means of inhibiting the dlPFC. However, it is important to note that the present PPI analysis does not include any information about the directionality of the connectivity effects between any of those brain regions. Therefore, this interpretation is speculative and warrants replication using different studies, methodology and analyses (e.g., using non-invasive brain stimulation approach).

Some potential limitations of the present study should be mentioned. Firstly, the proportion of excluded participants, in particular for some of the neuroimaging analyses, was relatively large. Some of these exclusions were necessary as we aimed to establish individual indifference points in the DD task, and for this choosing different options (as opposed to settling for one option only early in the experiment, as some people did) was necessary. As in many other decision tasks, this task feature always comes with the risk that participants do not behave as expected. "Correcting" their behaviour by using additional instructions would bias the results and render them non-interpretable and had to be avoided by all means. Hence, while we recommend using an online adjustment of indifference points using a staircase function as a potential strategy for future studies, for our study excluding participants was the only option. We note that as a consequence, our sample size was lower than initially hoped, which is a limitation of this study and has to be taken into account when interpreting the results. Further, behavioural results in the priming section of our study were obtained by performing four independent tests. Correcting p-values for multiple testing (Bonferroni correction) results in nonsignificant findings. However, our overall sample size used in the priming analysis is sufficient, as we conclude from previous reports (Murawski et al., 2012; Luo et al., 2014), thus suggesting that the results are not just due to type I error. Generally, the behavioural effects we aimed to investigate in our study are quite small. Given the presence of the aforementioned limitations and the fact that we used a very ambitious design, the fact that we were still able to find a behavioural effect in one of the conditions (before correcting for multiple comparisons) is encouraging. Finding a neural correlate of this effect (with correction for multiple comparisons – which in the case of neural data is conducted for a multitude of tests and therefore extremely strict) provides a second step of validation for this finding.

Our neuroimaging results have been thresholded on a voxel-level of 0.005, and corrected for multiple comparisons on the cluster-level. Further, most of the results have survived a more stringent voxel-wise threshold of 0.001. Clusters found in remaining analyses, related to priming, but also to reward-valuation, are highly congruent with current literature. The vmPFC, which we found to correlate with trial-by-trail choice value, has been widely implicated in reflecting values of potential rewards (Kable and Glimcher, 2007). Further, we

hypothesised that the dlPFC and its connectivity to other brain areas will be related to priming. Thus, while we are aware of studies showing that the voxel-wise threshold of 0.005 might result in a higher rate of false positives (Woo et al., 2014) we believe that the presented results are not merely due to type I error. Additionally, fMRI studies on special participant groups, such as healthy obese participants, should also be concerned with false negative results, and may therefore apply more liberal thresholding techniques, especially while having strong *a priori* hypotheses concerning locations of potential clusters (Carter et al., 2016). Altogether, we believe that our results show true effects, both on the behavioural and neuroimaging levels. We note, however, that independent replications would be desirable to confirm and expand on our results.

In conclusion, our study highlights important differences in intertemporal decision behaviour and related brain functions of obese and lean people. We hypothesised that people with obesity were more susceptible to environmental cues and that this susceptibility would be reflected in regions of the prefrontal cortex. Our results showed that priming with negative gustatory cues increased the ratio of decisions for delayed financial rewards in obese people. This was accompanied by decreased activity in the dlPFC. This region, in turn, showed a connectivity pattern with vmPFC and other regions that was negatively correlated with BMI. This pattern of results suggests that negative food-related cues can inhibit obese people's behaviour of choosing more immediate rewards. This is reflected by a disengagement of the dlPFC, which might be implicated in maintaining default internal goals. Such effects could propagate through the brain's reward system, as shown in our connectivity analysis, with increasing effects depending on BMI.

Our results also have broader implications for impulse control in obesity because they show that decision making processes, beyond dietary decisions, are more easily influenced by food-related cues in obese people as compared to people without obesity. Importantly, observing such susceptibility to environmental cues on economical choices suggests that food cues may influence general decision making processes in obesity. Economic decisions are a substantial part of everyday life, ranging from smaller purchase decisions to decisions with potentially long-term consequences, e.g., whether to overspend and to accumulate debt, which is an increasing problem in our society. Priming susceptibility is especially important

in light of today's obesogenic environment, where food cues are ubiquitous, and might strongly influence all kinds of decisions in susceptible individuals. We contribute to already existing literature on priming and delay discounting, which suggests that positive primes change behaviours towards less beneficial routines (i.e. less rational choices), while negative primes are said to have an opposite effect (Wilson and Daly, 2004; Murawski et al., 2012; van der Wal et al., 2013; Luo et al., 2014; Simmank et al., 2015). While it might be premature to draw strong conclusions from the limited number of studies showing enhanced priming effects in obesity about which primes have the strongest effects, our study nevertheless confirms the view that there is a general enhanced susceptibility to environmental cues in obese people. This finding has implications for systematically targeting obese people (or potentially even people who might be at risk) with specifically designed cues. For example, a previous study using health warnings showed that negatively framed graphic warnings promoted higher self-control in dietary decisions compared to all other warning messages, including positive messages (Rosenblatt et al., 2018b). In addition, the same cues designed to prevent unhealthy eating behaviour were also demonstrated to lead to altered brain signals associated with self-control when subsequently processing food items (Rosenblatt et al., 2018a). At this stage, it is important to further understand how eating behaviour can be altered to address the obesity epidemic, and by showing that negative gustatory priming has a positive influence on general decision behaviour in obesity, our study might inspire research into alternative cueing interventions in the future. However, our findings should also not be over-interpreted, as we neither know the specific drivers for the observed effects nor whether the effects would occur in all possible context situations. Potentially, the results of our study are also a basis for further brain stimulation studies investigating the role of the dlPFC and its connections in obesity. In light of our imaging findings, we show that current intentions of participants (e.g., dieting, stronger desire for immediate gratification), should always be taken into consideration when conducting studies concerning decision-making and cognitive control.

4.4.5 Supplementary materials

The following 7 figures depict scatter plots of relationships of BMI with other measures for all analyses where BMI was included as a continuous predictor:

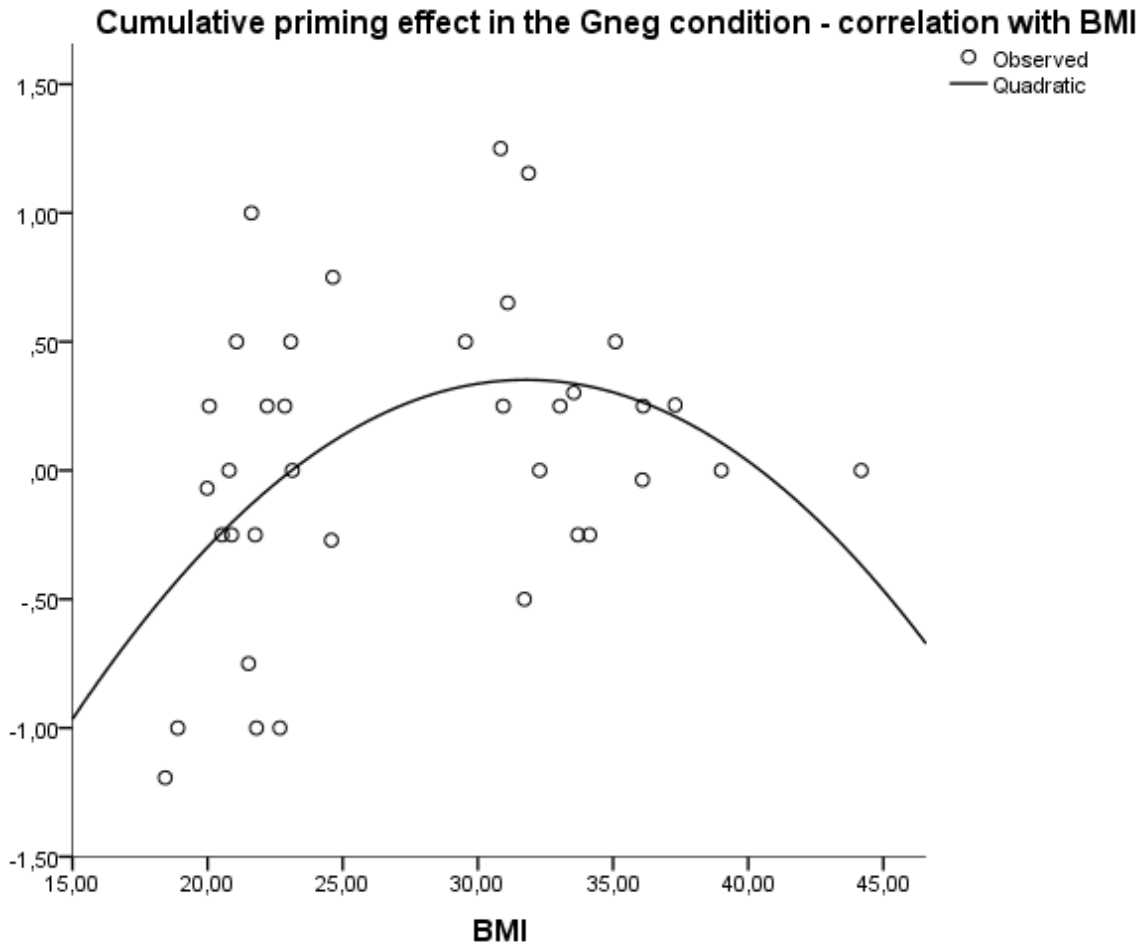

Figure S 1 Scatter plot of the relationship between BMI and the cumulative priming effect in the gustatory negative condition (R^2=0.208, p=0.021, for details see section 4.4.3.5)

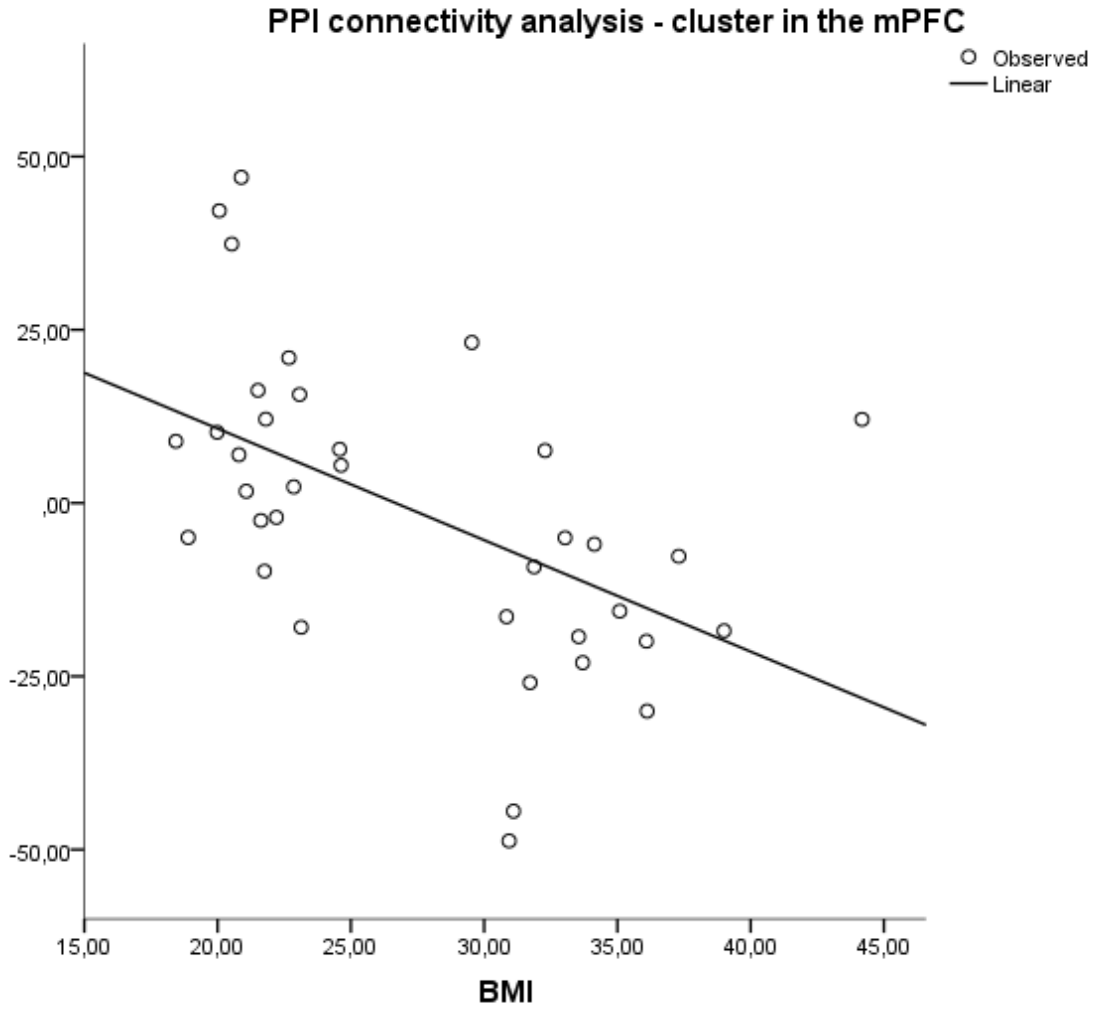

Figure S 2 Scatter plot of the relationship between BMI and the PPI connectivity (GLM 6) to the medial prefrontal cortex (mPFC) – Figure presented for illustration purposes; for details see section 4.4.3.6.6.

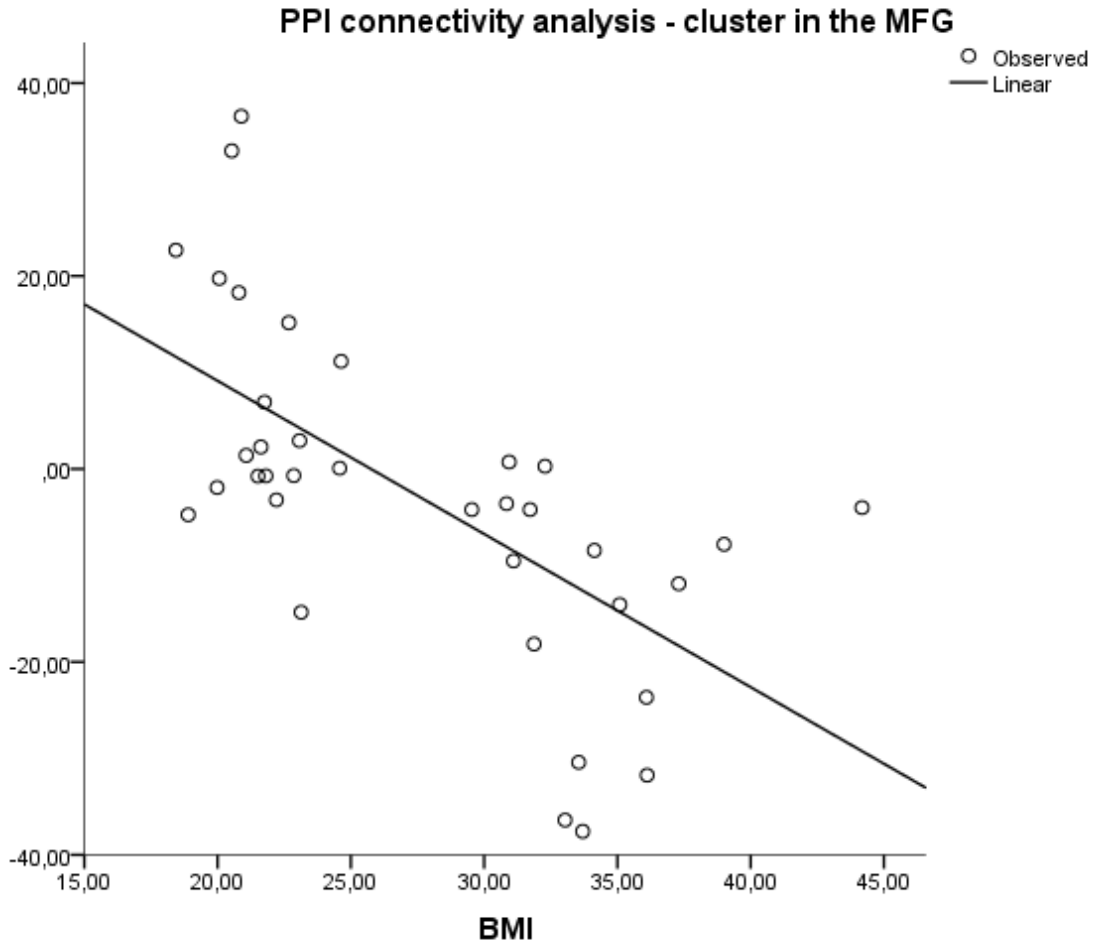

Figure S 3 Scatter plot of the relationship between BMI and the PPI connectivity (GLM 6) to the middle frontal gyrus (MFG) – Figure presented for illustration purposes; for details see section 4.4.3.6.6..

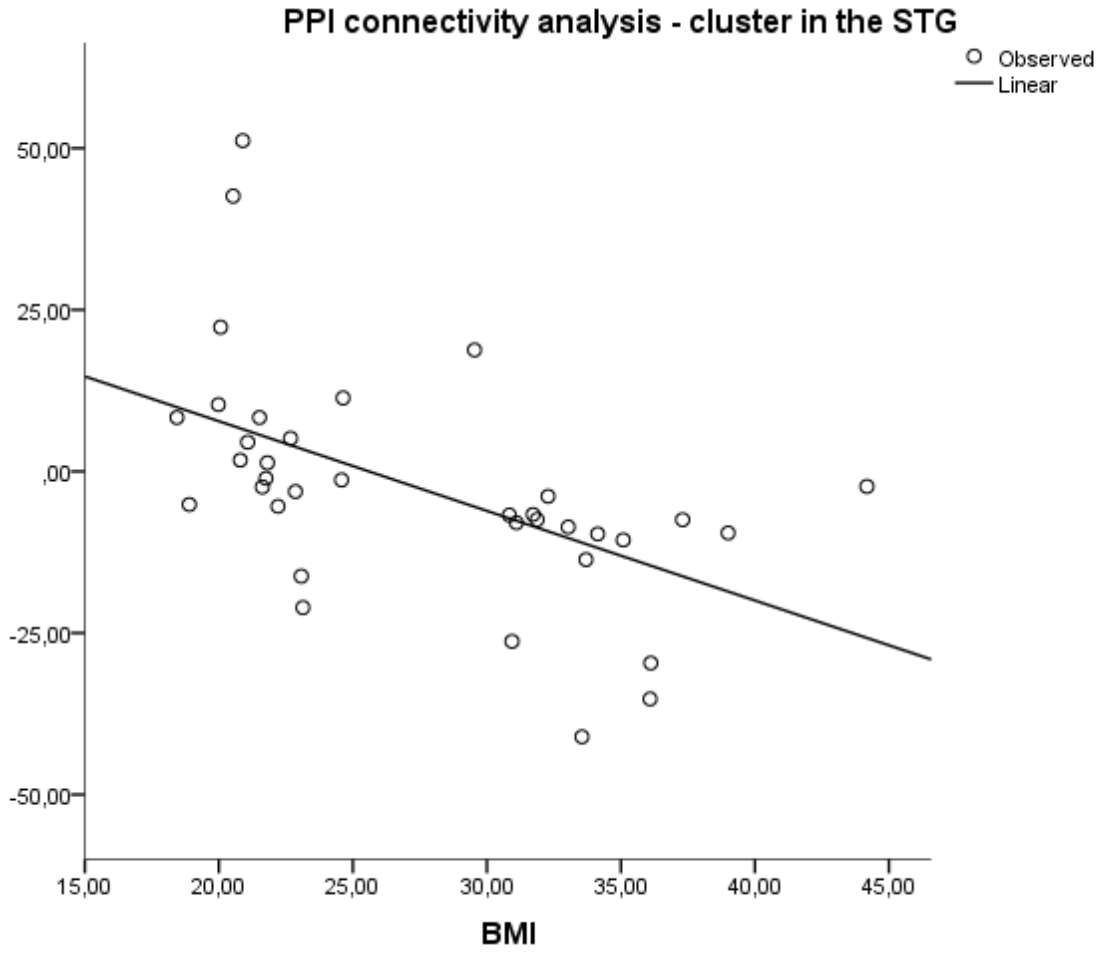

Figure S 4 Scatter plot of the relationship between BMI and the PPI connectivity (GLM 6) to the superior temporal gyrus (STG) – Figure presented for illustration purposes; for details see section 4.4.3.6.6.

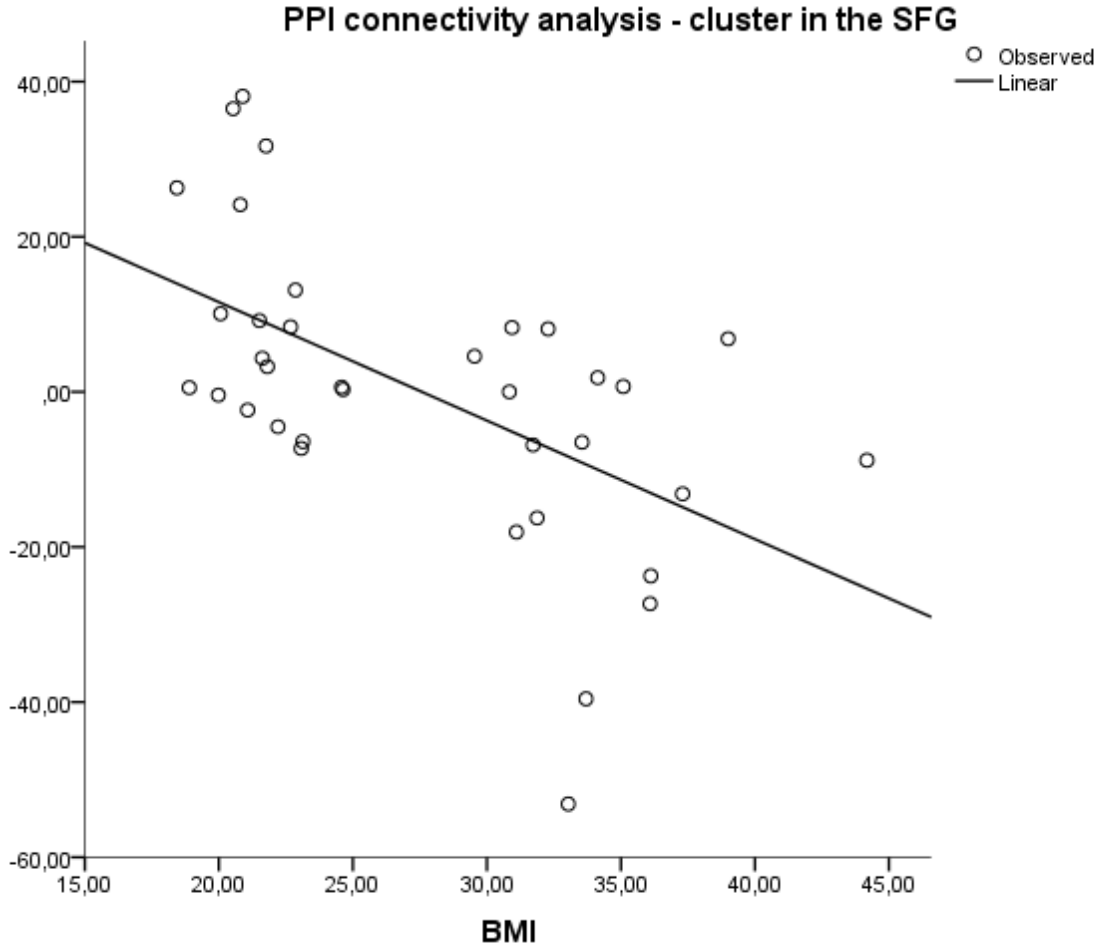

Figure S 5 Scatter plot of the relationship between BMI and the PPI connectivity (GLM 6) to the superior frontal gyrus (SFG) – Figure presented for illustration purposes; for details see section 4.4.3.6.6.

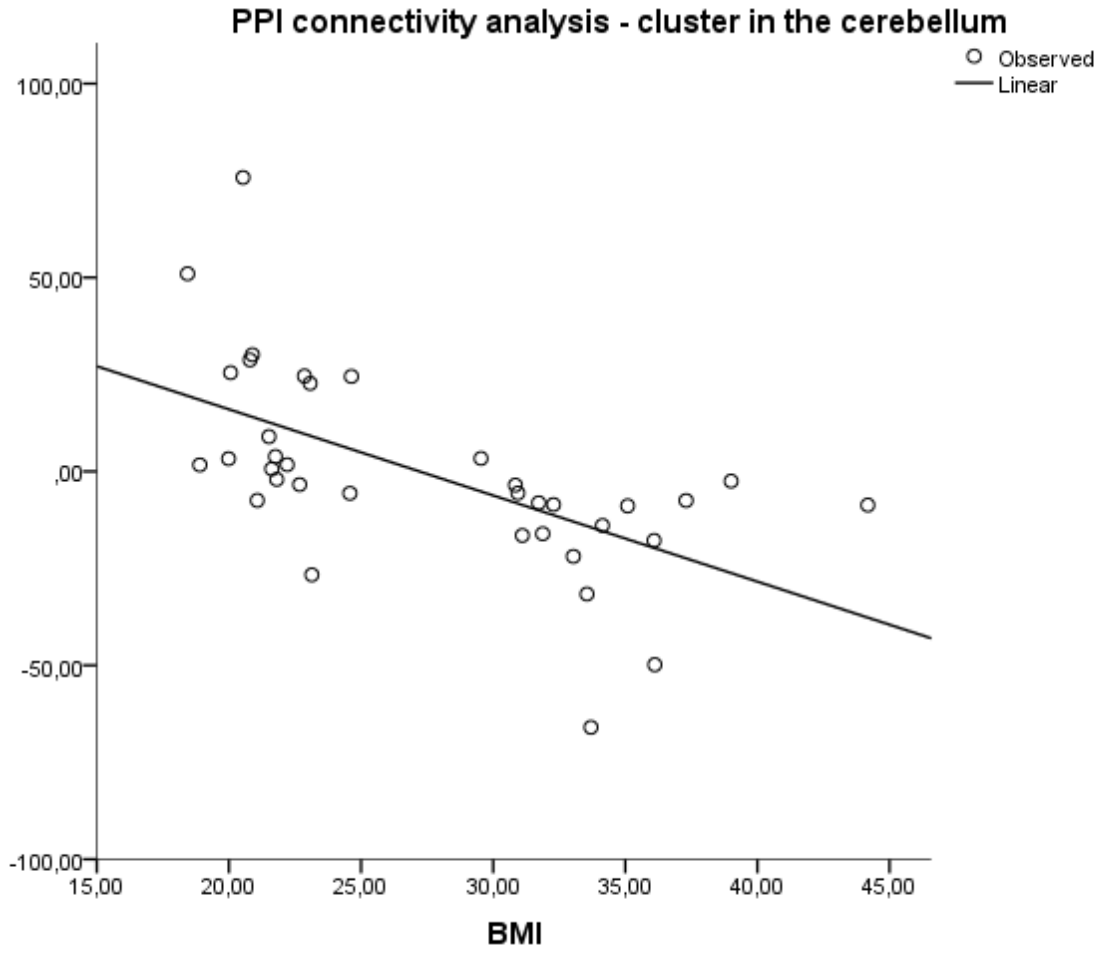

Figure S 6 Scatter plot of the relationship between BMI and the PPI connectivity (GLM 6) to the cerebellum – Figure presented for illustration purposes; for details see section 4.4.3.6.6.

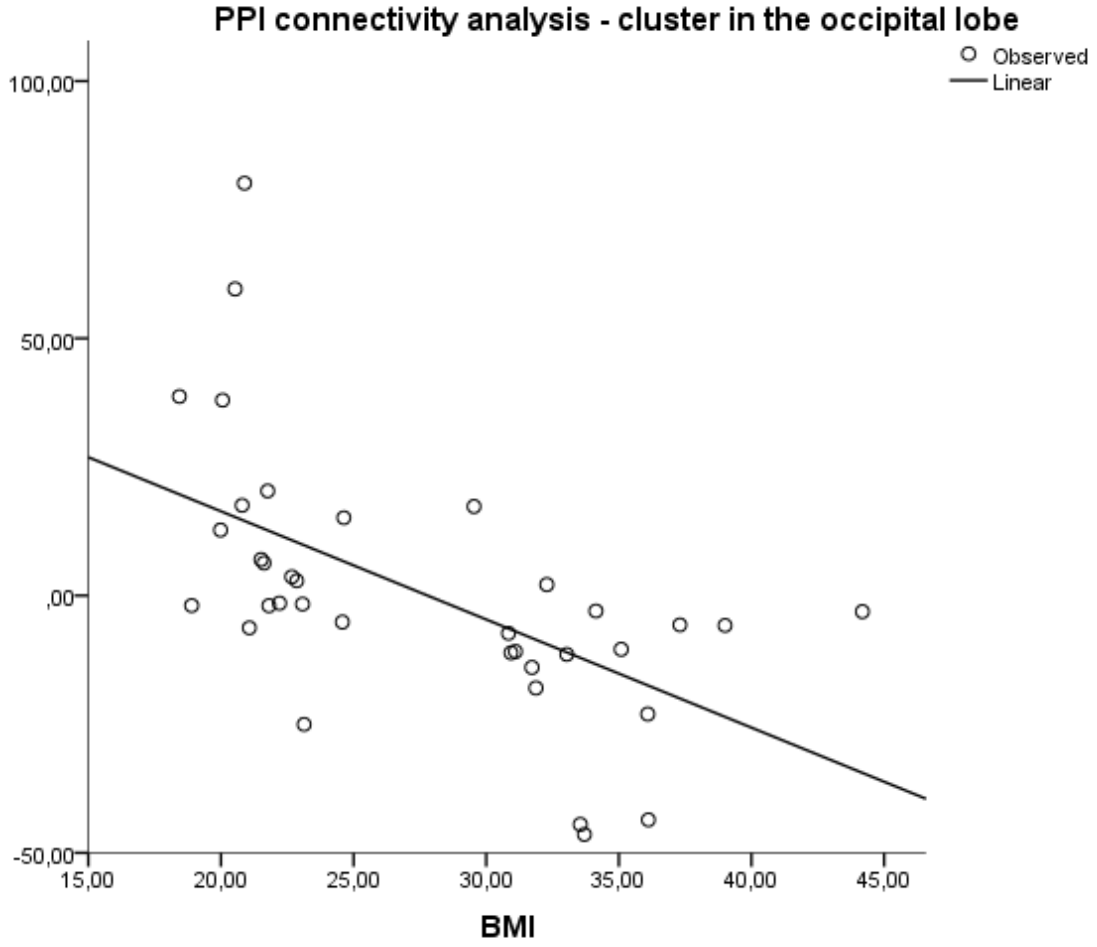

Figure S 7 Scatter plot of the relationship between BMI and the PPI connectivity (GLM 6) to the occipital lobe – Figure presented for illustration purposes; for details see section 4.4.3.6.6.

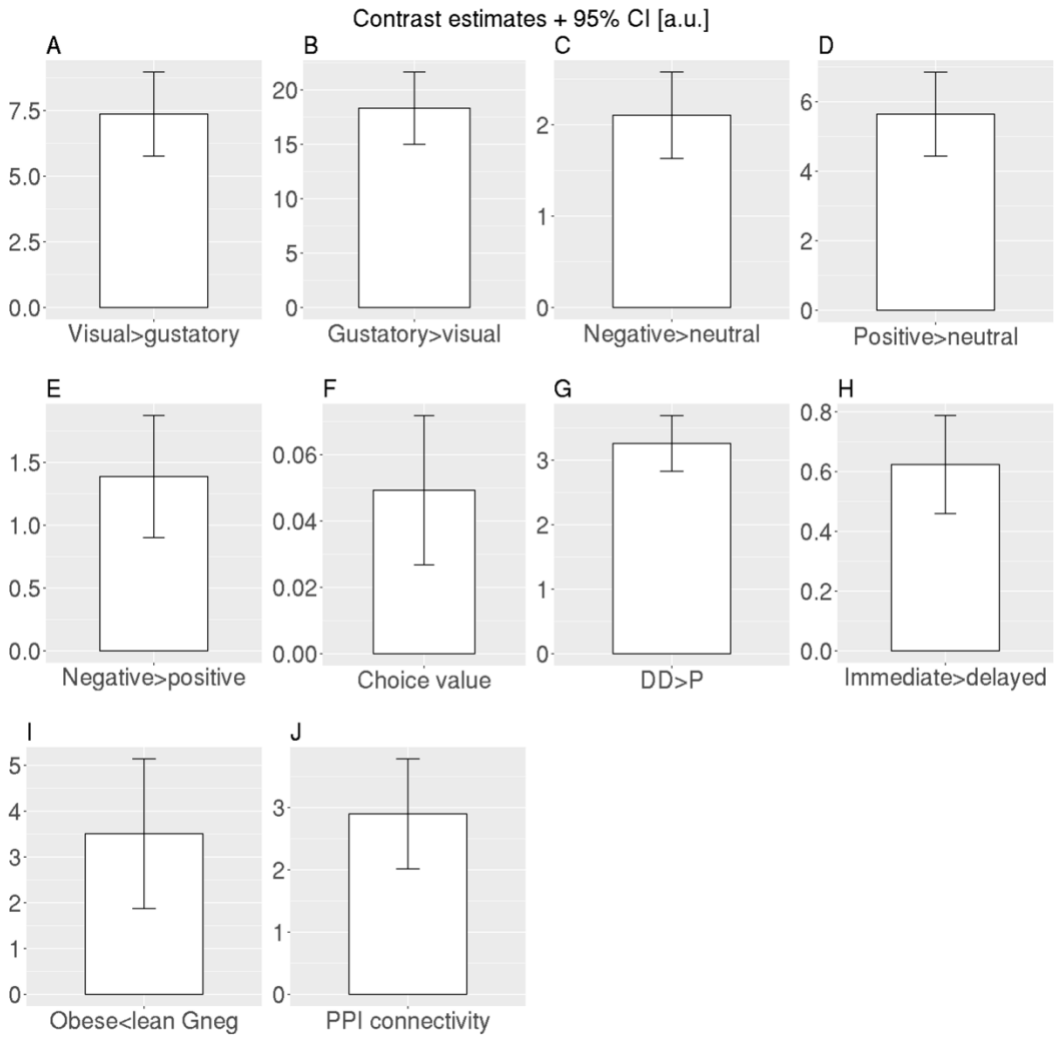

Figure S 8 Figure depicting contrast estimates and 95% confidence intervals for peak voxels of each of the fMRI analyses. **A** analysis contrasting gustatory and visual stimulation; **B** analysis contrasting visual and gustatory stimulation; **C** analysis contrasting negative and neutral stimulation; **D** analysis contrasting positive and neutral stimulation; **E** analysis contrasting negative and positive stimulation; **F** analysis investigating modulation of brain activity by choice value during the delay discounting task; **G** analysis contrasting delay discounting trials with perception only trials; **H** analysis contrasting immediate choices with delayed choices on delay discounting trials; **I** analysis contrasting brain activity during the gustatory negative condition in the obese and in the lean group; **J** PPI analysis. Please note different y-axis scales for each subplot.

5 General discussion and outlook

Discussed in this thesis are: 1) behavioural maladaptive tendencies related to obesity and their underlying neural correlates, and 2) possible ways to alter these tendencies, along with their mechanisms. An extended summary of findings can be found in chapter 6 of this thesis. Briefly, in study 1 we showed that approach/avoidance behaviour is indeed associated with hemispheric asymmetry, which can be measured using EEG and fMRI. This asymmetry, however, was not associated with increased BMI or altered self-reported eating behaviour. Study 2 showed that obese participants show approach tendencies towards both healthy and unhealthy foods. Further, we showed that food avoidance is a potentially conflicting process, which activates the right angular gyrus – a brain region related to stimulus-conflict resolution and cognitive control. We also found that the approach bias towards unhealthy foods can be decreased by means of cognitive bias modification using an approach-avoidance task. This is related to decreases in the right angular gyrus and changes in task-related and task-unrelated connectivity within brain's inhibitory regions, such as the middle frontal gyrus or insula. This suggests that short-term CBM in obesity is related to improving executive functions (response inhibition) rather than changing the value of unhealthy foods within the reward system. Study 3 confirmed previous findings that increased BMI is related to higher delay discounting, which is a proxy for executive functioning. A new finding in this study allows to better interpret previous results showing gender differences in delay discounting and obesity, as we found those only for the delay-independent delay discounting parameter. Finally, study 4 confirmed our hypothesis that participants with obesity are more susceptible to environmental cues and that those cues can influence choices within a food unrelated decision-making paradigm – delay discounting in monetary context. This influence was related to decreased activity in the dlPFC, the brain's cognitive control hub, which suggests that altering maladaptive decisions requires disconnection of this structure, because normally it drives behaviour towards more impulsive choices. This was also related to decreased connectivity to the brain's valuation regions, such as the vmPFC or the ventral striatum. This shows that priming might work by disengaging the dlPFC from valuation structures, which in turn allows participants to make choices that are incongruent with their current goals.

In general, we show that obesity is indeed related to a number of maladaptive behaviours that constitute potential targets for future interventions. This is line with Marteau's claims who suggests to use those kind of interventions instead of the ones targeting explicit knowledge, such as food education, or general lifestyle interventions, e.g. increasing amounts of physical activity (Marteau et al., 2012). These traditional interventions usually have short-term effects and relatively small reductions in BMI (Jeffery et al., 2000; Curioni and Lourenço, 2005; Franz et al., 2007; Barte et al., 2010; Kirk et al., 2012). Studies presented in this thesis show that maladaptive tendencies related to obesity are rather automatic – such as implicitly approaching unhealthy foods – or are related to decreased inhibitory abilities – such as choosing immediate gratification, instead of waiting for a more rewarding one in the future. Our findings are in line with previous literature showing relationships between temporal impulsivity and obesity (Weller et al., 2008; Amlung et al., 2016; McClelland et al., 2016), as well as approach bias and obesity (Mehl et al., 2018).

Neural systems implicated in those maladaptive tendencies include two systems of the appetitive network, namely the reward/motivational system, and the executive system (Dagher, 2012). Contrary to what the right-brain theory of obesity posits (Alonso-Alonso and Pascual-Leone, 2007), alterations in those systems in our samples are not related to hemispheric asymmetries. Behavioural interventions that we used to target maladaptive tendencies alter brain activity within the two systems. Benefits of investigating neural underpinnings of those interventions are twofold. Firstly, this approach gives us insight into mechanisms thereof – such as CBM working by means of increasing inhibitory abilities. This can be further used to inform obesity therapies that could potentially focus on increasing inhibitory tendencies in participants. Secondly, it provides information for future potential non-invasive brain stimulation studies, which could focus on specific structures identified by our studies. This is a possible way of supporting behavioural therapies and increasing their effectiveness.

In the obesogenic environment, priming can be a negative process. But our study shows that it can also be used to obese people's advantage in the context of temporal impulsivity. This has important implications for future obesity therapies, as environmental stimuli might be used to alter behaviour towards more advantageous routines. This could potentially be used

in two ways – preventing food companies from advertising campaigns that increase unhealthy food intake (Kemps et al., 2014a), but also increasing the number of environmental stimuli that could potentially decrease food intake. For example, a previous study showed that negative health warnings promoted higher self-control in dietary decisions compared to remaining warning messages, including positive messages (Rosenblatt et al., 2018b). In addition, the same cues designed to prevent unhealthy eating behaviour were also demonstrated to lead to altered brain signals associated with self-control when subsequently processing food items (Rosenblatt et al., 2018a). Altogether, using incidental priming, possibly in the form of health warnings, is a promising tool and might be used as prevention, but also intervention, in obesity.

Our findings regarding CBM in the context of approach bias are a very promising glimpse into to its potential use in obesity. This type of easy training can be implemented in all kinds of settings, from kindergartens, schools, using smartphones or online and web-based applications. It can also target participants in a variety of demographic groups, such as children, adolescents and adults. CBM has a lot of potential in the context of obesity, as certain adjustments can be made to make it even more effective. They could include identifying individual problematic foods and targeting the training specifically towards those foods. It might also be used as a preventive measure for people at risk of obesity. Those ideas, however, need to be tested in a laboratory context first.

A general limitation to the studies performed as parts of this thesis concerns their ecological validity. None of the studies have been performed in a natural context, therefore more research is needed to state whether these can also be effective in natural settings. One idea concerning CBM is to create a smartphone application that could be used by people easily during the day for a prolonged period of time. With this it would be possible to test whether CBM has long-term effects and if longer exposure to it results in more pronounced effects. Concerning the incidental priming findings, as mentioned before, it can be used to investigate in depth whether health warnings are an effective tool for changing behaviour, especially in obesity.

An additional and important limitation is the fact that we did not investigate how the two interventions influence actual food intake. This should be the ultimate goal of all

interventions, as obesity is most often related to increased food intake. Decreasing it is a long-term aim that all the interventions should pursue. Hence, with our promising results, the next step would be to try and translate the findings into an everyday context and investigate, whether they can alter eating behaviour.

Altogether, results presented in this thesis constitute a basis for future research concerning altering disadvantageous behaviours and tendencies in obesity, as well as a guide for possible directions of future studies in similar contexts.

6 Summary of the dissertation

Zusammenfassung der Arbeit

Dissertation zur Erlangung des akademischen Grades Dr. rer. med.

Characterising and altering disadvantageous behaviours and tendencies in obesity

Eingereicht von Filip Morys

Angefertigt am Max-Planck-Institut für Kognitions- und Neurowissenschaften, Leipzig

Betreut von Prof. Dr. Arno Villringer & Dr. Annette Horstmann

September 2018

Investigating neural mechanisms of certain disadvantageous behaviours and tendencies in obesity provides an opportunity to understand how and why those behaviours come about. Furthermore, investigation of possible strategies to alter these behaviours and mechanisms by which those strategies work might give an exciting opportunity for new obesity interventions. This is what research in this thesis focuses on. In general, maladaptive behaviours in obesity are mainly constrained to the domains of executive functions and responsivity to food cues/food motivation (Vainik et al., 2013). Executive functions regulate behaviour based on abstract goals and include inhibitory abilities, working memory and behavioural flexibility (Diamond, 2013). Food motivation describes people's behaviour in the food context (e.g. food choice). For this reason we focused our main research on two tasks tackling behaviours in the domain of executive functioning (i.e. behavioural inhibition and impulsivity), and food motivation (i.e. unhealthy food approach bias). In this framework, a subdomain of impulsivity – temporal impulsivity – can be described by a preference towards small immediate rewards in the presence of larger delayed rewards. Temporal impulsivity is consistently shown to be associated with obesity (Amlung et al., 2016; McClelland et al., 2016). Unhealthy food approach bias, on the other hand, is a tendency to

approach unhealthy foods, rather than avoid them. Both of these behaviours, impulsivity and unhealthy food approach, could lead to increased food consumption and therefore to obesity.

These problematic behaviours are driven by specific brain mechanisms. Generally, the appetitive brain network regulates actions related to food intake (Dagher, 2012). Previous studies show that approach bias as well as temporal impulsivity are steered by interactions of the executive system and the motivational system that both belong to the appetitive network (McClure et al., 2004; Kable and Glimcher, 2007; Cousijn et al., 2012; Wiers et al., 2014). The executive system comprises frontal areas, such as the dorsolateral prefrontal cortex and the anterior cingulate cortex. The motivational system, on the other hand, is related to the brain's dopaminergic system (including the ventral tegmental area, ventral striatum and the medial prefrontal cortex), but also to the insula, and the orbitofrontal cortex. Further underlining the interactions of the executive and motivational system is the right-brain theory of obesity, which posits that obesity, seen as a disorder of increased approach, is related to underactivation of right anterior brain areas, relative to left (Alonso-Alonso and Pascual-Leone, 2007).

To expand current knowledge on these topics, we designed four studies focusing on 1) relationships between right and left hemispheric activity with measures of approach/avoidance behaviours, eating behaviours and obesity, 2) food motivation behaviours, namely food approach bias, alterations of this bias and its neural correlates 3) measures of executive functioning, namely temporal impulsivity, and 4) alteration of temporal impulsivity and neural correlates of this process.

In study 1, we investigated how approach/avoidance behaviours, self-reported eating behaviours and BMI are related to hemispheric asymmetries. We additionally aimed to expand previous knowledge constrained to the EEG imaging domain to functional magnetic resonance imaging (fMRI). To this end, we investigated three independent samples of participants. Sample 1 included predominantly lean participants and comprised EEG and fMRI measurements. Samples 2 and 3, on the other hand, consisted of lean, overweight and obese participants, and included fMRI measurements. In sample 1, using EEG data we were able to show that higher left versus right hemispheric activity was related to approach behaviour. Using fMRI in the same sample, we showed that higher right vs. left hemispheric

activity was related to approach behaviour. This means that hemispheric asymmetries can be meaningfully measured using fMRI. We were not able to show a similar asymmetry finding in the second sample using fMRI data. Further, we found no relationships between body mass index (BMI) or self-reported eating behaviour and hemispheric asymmetries in samples 1, 2 and 3. With this study, we supported previous findings that approach behaviours are indeed related to hemispheric asymmetries. We were, however, not able to show correlations of obesity measures or eating behaviour measures with hemispheric asymmetries, and therefore could not provide support for the right-brain theory of obesity. This lack of support, however, might be related to methodological differences between studies – previous reports only used EEG measures, while we mostly used fMRI measures.

In study 2, we first investigated food approach bias and its correlates in obese participants, and second, we trained these participants to avoid unhealthy foods and approach healthy foods. This was done using the approach-avoidance task (AAT), which requires participants to respond to a number of healthy and unhealthy food pictures by pushing (avoidance) or pulling (approach) a joystick. Participants were asked to react to the format of the picture (horizontal vs. vertical), not to the content (healthy vs. unhealthy foods), which allowed us to measure implicit reactions to food cues. Further, by implementing the cognitive bias modification (CBM) into the AAT we trained participants to avoid unhealthy and approach healthy foods.

In study 2, obese participants showed higher approach bias towards both healthy and unhealthy foods. Avoiding food, was related to an increased brain activity in the right angular gyrus (rAG), a brain structure that is often related to stimulus-response conflict resolution, attentional reorientation and response inhibition (Rushworth et al., 2001; Schiff et al., 2011; Seghier, 2013; Cieslik et al., 2015; Kolodny et al., 2017). It therefore seems that approaching food in obese participants is an intuitive reaction, while its avoidance is a conflict, which activates an appropriate brain structure. The CBM in our study proved to be an effective way to decrease implicit approach towards unhealthy foods in obese participants. Compared to a sham condition group, training group significantly decreased approach bias towards unhealthy foods. This was related to a decrease in activity of the rAG, implying that avoiding food after CBM is less of a conflict. The CBM was additionally related to increased coupling

of the rAG with the right dorsal striatum, which is related to executive attention and exerting cognitive control, but also to stimulus-response learning (Balleine et al., 2007; Jankowski et al., 2009; Liljeholm and O'Doherty, 2012; Mestres-Missé et al., 2012; Robertson et al., 2015). The dorsal striatum might facilitate avoidance of unhealthy foods after CBM, which is reflected in its higher connectivity with the rAG. In addition to these task-related results, we observed resting-state changes in brain connectivity after the training. Namely, there was an increased connectivity between the left and right middle frontal gyrus (MFG), and the left anterior insula, but also between the left nucleus accumbens and the left inferior frontal gyrus (IFG). The MFG, IFG, and anterior insula are inhibitory structures (Garavan et al., 1999; Simmonds et al., 2008; Boehler et al., 2010; Cai et al., 2014), hence increased connectivity between them possibly relates to increased inhibitory abilities in the training group, which facilitates food avoidance during the AAT.

Study 2 showed that approach bias and its modification involve the executive brain system with a number of inhibitory structures involved. Previous studies in alcohol-dependent patients additionally showed engagement of the reward and motivational system. We did not find such an effect in our study. It might mean that 1) both unhealthy and healthy foods are similarly rewarding, hence there is no difference in brain activity between these reinforcers in the motivational system, and 2) our training was too short to influence valuation of food rewards, instead targeting inhibitory abilities and brain areas. However, uncovering the mechanisms by which CBM works in obesity is a promising step into applying it more effectively in the clinical context. Additionally, showing neural correlates of CBM might provide information for future non-invasive brain stimulation studies aiming at decreasing approach bias in obesity.

In study 3, we focused on temporal impulsivity in a large sample of lean, overweight and obese participants. We replicated previous findings showing that higher temporal impulsivity is related to increased BMI (Weller et al., 2008; Amlung et al., 2016). In this study we used a new model of delay discounting, which gave us more insight into the relationship between BMI and delay discounting. Namely, we showed that just the fact that a reward is delayed – independent of the actual delay – results in opposite relationships between BMI and discounting rates depending on the gender. Specifically, this means that women with

higher BMI discount future rewards more than women with lower BMI just because the rewards are delayed, while an opposite pattern was observed for men. Further, a delay discounting parameter that is dependent on the delay was related to BMI in a gender-independent way – increased BMI was related to increased delay discounting. This study additionally provided a methodological framework for study 4, where we used similar delay discounting paradigm.

In study 4, we investigated general temporal impulsivity in the monetary context in groups of lean and obese participants. Further, we aimed at altering behaviours in obesity relating to choosing more immediate rewards by incidental priming – priming with cues unrelated to the discounting process. Here, we used gustatory (proximal) and visual (distal) food cues of positive, neutral and negative valence. This was done to investigate how food cues, readily available in the environment, affect general executive processes in people with obesity.

Results of study 4 show that, consistent with previous literature, obese participants indeed have higher temporal impulsivity than lean participants. Furthermore, we were able to show that priming with gustatory negative cues decreases temporal impulsivity in obese participants, but not in lean participants. This finding has two important implications – firstly, it shows that obese participants are more susceptible to environmental cues, and secondly, it shows that maladaptive decisions can be altered.

This increased susceptibility to negative gustatory cues was related to a decreased activity in the dorsolateral prefrontal cortex (dlPFC) in obese participants. Again, this structure is a part of the executive system of the appetitive network and is often related to exerting cognitive control over behaviour (McClure et al., 2004; Hare et al., 2009; Dietrich et al., 2016b). The finding that its activity is decreased might therefore be surprising, since it was related to lower impulsivity. However, it is possible that the dlPFC steers behaviours according to current goals. In case of obese participants, the implicit goal is to choose immediate rewards, and it is promoted by higher activity in the dlPFC. It follows that altering the behaviour and acting not in sync with the internal goal requires deactivation of the dlPFC. The behavioural priming effect was found to correlate with the connectivity of the dlPFC and other brain structures, such as the ventral striatum, ventromedial prefrontal cortex (vmPFC; motivational system) and parietal areas (executive system). Here, participants with higher

BMI showed decreased connectivity of the dlPFC with these brain regions. This decrease might be necessary to overcome current internal goals and alter behaviour.

Altogether, the findings presented in this thesis do not support the right-brain theory of obesity. However, they provide evidence of altered executive functioning and food motivational behaviours in obesity, along with brain mechanisms of those alterations. Moreover, results show that targeting these maladaptive tendencies is effective and involves alterations of executive and motivational brain networks. These promising findings are in line with Marteau and colleagues (Marteau et al., 2012) who claim that interventions should tackle implicit behaviours instead of explicit knowledge.

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8 Appendix

8.1 Authors' contributions to the publications

Authors involved in study 1: Filip Morys, Lieneke Janssen, Frauke Beyer, Elena Cesnaite, Isabel Garcia-Garcia, Jana Kube, Anne Schrimpf, Deniz Kumral, Franziskus Liem, Nora Mehl, Keyvan Mahjoory, Daniel Margulies, Michael Gaebler, Arno Villringer, Jane Neumann, Vadim Nikulin, Annette Horstmann

Parts of chapter 4.1 were used in an article currently in preparation for a submission to a peer-reviewed journal.

Authors involved in study 2: Filip Morys, Nora Mehl, Arno Villringer, Annette Horstmann

Parts of chapter 4.2 were used in an article currently submitted to a peer-reviewed journal.

Authors involved in study 3: Filip Morys, Jakob Simmank, Annette Horstmann

Parts of chapter 4.3 were used in an article currently in preparation for a submission to a peer-reviewed journal.

Authors involved in study 4: Filip Morys, Stefan Bode, Annette Horstmann

Parts of chapter 4.4 were used in an article currently submitted to a peer-reviewed journal.

8.2 Declaration of authenticity

Erklärung über die eigenständige Abfassung der Arbeit

Hiermit erkläre ich, dass ich die vorliegende Arbeit selbstständig und ohne unzulässige Hilfe oder Benutzung anderer als der angegebenen Hilfsmittel angefertigt habe. Ich versichere, dass Dritte von mir weder unmittelbar noch mittelbar eine Vergütung oder geldwerte Leistungen für Arbeiten erhalten haben, die im Zusammenhang mit dem Inhalt der vorgelegten Dissertation stehen, und dass die vorgelegte Arbeit weder im Inland noch im Ausland in gleicher oder ähnlicher Form einer anderen Prüfungsbehörde zum Zweck einer Promotion oder eines anderen Prüfungsverfahrens vorgelegt wurde. Alles aus anderen Quellen und von anderen Personen übernommene Material, das in der Arbeit verwendet wurde oder auf das direkt Bezug genommen wird, wurde als solches kenntlich gemacht. Insbesondere wurden alle Personen genannt, die direkt an der Entstehung der vorliegenden Arbeit beteiligt waren. Die aktuellen gesetzlichen Vorgaben in Bezug auf die Zulassung der klinischen Studien, die Bestimmungen des Tierschutzgesetzes, die Bestimmungen des Gentechnikgesetzes und die allgemeinen Datenschutzbestimmungen wurden eingehalten. Ich versichere, dass ich die Regelungen der Satzung der Universität Leipzig zur Sicherung guter wissenschaftlicher Praxis kenne und eingehalten habe.

Leipzig, _____ 2018 _____

Filip Morys

8.3 Curriculum vitae

Name Filip Morys, M.Sc.

Date of birth 01 March 1990, born in Tarnowskie Gory, Poland

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Stephanstrasse 1a, 04103 Leipzig, Germany,
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Education & Qualifications

2013-2018 PhD student/researcher;
IFB Adiposity Diseases, Leipzig University Medical Center;
Max Planck Institute for Human Cognitive and Brain Sciences, Decision-making in obesity: neurobiology, behavior and plasticity group (Dr. Annette Horstmann), Leipzig, Germany

2011-2013 Master's Degree; International Graduate Program Medical Neurosciences; final grade: 1.9[1]
Charité – Medical University, Berlin, Germany
Master's thesis: Decoding task sets from human brain activity

2008-2011 Bachelor's Degree; Neurobiology; final grade: 5,0[2]

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[2] Results graded on a normalised scale from 2,0 – 'insufficient' ,to 5,0 – 'very good'

Jagiellonian University, Cracow, Poland
Bachelor's thesis: Neuropsychology of prospective memory

2005-2008 High School Diploma;
Tarnowskie Gory, Poland

Professional experience

2012-2013 Research master's thesis; Bernstein Center for Computational Neuroscience, Laboratory of Theory and Analysis of Large-Scale Brain Signals (Prof. Dr. John-Dylan Haynes); Berlin, Germany

2012 Laboratory Rotation; Dahlem Institute for Neuroimaging of Emotions (Prof. Dr. Felix Blankenburg); Berlin, Germany

2012 Laboratory Rotation; Charité – Medical University Berlin, Working Group Cognition, Ageing, Neurorehabilitation (Prof. Dr. Agnes Flöel); Berlin, Germany

2010 Internship; Nencki Institute for Experimental Biology, Laboratory of Preclinical Studies for Neurodegenerative Diseases (Prof. Dr. Grazyna Niewiadomska); Warsaw, Poland

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Organisational & Scientific Activities

2016-2018 Member of the Data Quality Assurance Team in the Neurology Department at the Max Planck Institute for Human Cognitive and Brain Sciences; Leipzig, Germany

2013-2015

Editor of the Charité Neuroscience Newsletter, a quarterly magazine devoted to newest topics in neuroscience

2011

Organisation of IBRO Neuroscience Forum Neuronus,
Jagiellonian University; Cracow, Poland

Awards

2012/2013 Fellowship for up-and-coming scientists by the NeuroCure Cluster of Excellence; Berlin, Germany

2017 Society for the Study of Ingestive Behavior New Investigator Travel Award for the project: 'Neural correlates of retraining automatic action tendencies in obesity'

2017 Deutsche Adipositas Gesellschaft best poster award for the project: 'Neural correlates of retraining automatic action tendencies in obesity'

Teaching

2015 Maladaptive plasticity in behavioural disorders and addictions. Lecture. Berlin School of Mind and Brain, Humboldt University Berlin, Germany

8.4 Conference contributions

Talks

Morys, F., & Horstmann, A. (2017). Dorsolateral and medial prefrontal cortex mediate influence of incidental priming on economic decisions in obesity. Talk presented at 25th Annual Meeting of the Society for the Study of Ingestive Behavior; Montréal, QC, Canada. 2017-07-18 — 2017-07-22.

Mehl, N., Morys, F., Villringer, A., Horstmann, A. (2017). 'Neural correlates of retraining automatic action tendencies in obesity'. Talk presented at 25th Annual Meeting of the Society for the Study of Ingestive Behavior; Montréal, QC, Canada. 2017-07-18 — 2017-07-22.

Posters

Morys, F., Janssen, L., Cesnaite, E., Garcia-Garcia, I., Kube, J., Schrimpf, A., et al. (2018). Hemispheric bias in resting state EEG and fMRI is related to approach/avoidance behaviors, but not BMI. Poster presented at 2018 Organization for Human Brain Mapping Annual Meeting; Singapore.

Morys, F., & Horstmann, A. (2017). Dorsolateral and medial prefrontal cortex mediate influence of incidental priming on economic decisions in obesity. Poster presented at 33rd Annual Conference of the German Association for the Study of Obesity; Potsdam, Germany.

Morys, F., Mehl, N., Horstmann, A., & Villringer, A. (2017). Neural correlates of cognitive bias modification in obesity. Poster presented at 33rd Annual Conference of the German Association for the Study of Obesity; Potsdam, Germany.

Morys, F., Simmank, J., & Horstmann, A. (2016). BMI mediates the relationship between temporal impulsivity and cognitive restraint in women. Poster presented at 32nd Annual Conference of the German Association for the Study of Obesity; Frankfurt, Germany.

Morys, F., Simmank, J., & Horstmann, A. (2016). BMI mediates the relationship between temporal impulsivity and cognitive restraint in women. Poster presented at 24th Annual Meeting of the Society for the Study of Ingestive Behaviour; Porto, Portugal.

Morys, F., Bode, S., Murawski, C., & Horstmann, A. (2015). Influence of incidental priming with visual and gustatory cues on intertemporal choice in obesity. Poster presented at LIMIOR — 1st Leipzig International Meeting for Interdisciplinary Obesity Research; Leipzig, Germany.

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