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Functional brain responses in the maintenance of energy balance

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CHAPTER 10

Summary, conclusions and future perspectives



The primary aim of this thesis was to gain more insights into the brain function in the maintenance of energy balance by determining the effects of several aspects of our modern day diet and the effects of a disrupted energy balance on functional brain responses. With the goal to further elucidate both normal and disrupted central regulation of energy consumption and feeding behavior to find neurophysiological markers aiding in the management of obesity, metabolic syndrome and eating disorders. Various factors, both internal and external, influence the maintenance of energy balance by the brain. In this thesis we focused on the effects of several of these factors. First we investigated the effects of the ingestion of different types of sugars and sweeteners on the brain. Next we determined the effects of food characteristics that play a role in the palatability of food, namely consumption temperature and flavoring. Furthermore, we determined if the functional brain response to energy ingestion could be influenced by central insulin signaling. Also, we studied which effects changes and disruption of energy balance had on the functional brain responses by investigating brain responses after glucose ingestion in patients with Anorexia Nervosa (AN) and the effects of weight loss in obese participants.

In this chapter the main findings of this thesis are summarized and overall conclusions and future research perspectives following this thesis are discussed.

Summary of findings

In **chapter 2, 3 and 4** we investigated the response of the brain to the ingestion of glucose and various other sugars and sweeteners using several different approaches. In **Chapter 2** we used an assumption free whole brain approach to study the normal response of the brain to the ingestion of glucose in healthy normal weight persons (the effects are summarized in figure 1). The results of this chapter show that after an overnight fast, ingestion of glucose leads to neuronal deactivation and decreased functional network connectivity in brain areas involved in homeostatic and reward responses, which can be associated with satiation and reward effects in the brain and a decrease in energy seeking. However, these rewarding effects could in turn also stimulate and increase future re-consumption of glucose.

As a follow up to **Chapter 2** where we found a response to glucose in homeostatic and reward areas in the brain, in **Chapter 3** we determined the effects of glucose and additional other sugars and sweeteners on the homeostatic and hedonic systems specifically. To this end, instead of investigating the whole brain, we used a region of interest based approach focusing on the hypothalamus and ventral tegmental area (VTA). Our data show that, like in **Chapter 2**, ingestion of glucose elicits a prolonged decrease in hypothalamic activity with a possible transient hedonic response from the VTA, which is associated with satiety signaling. Our data indicate that the hypothalamus

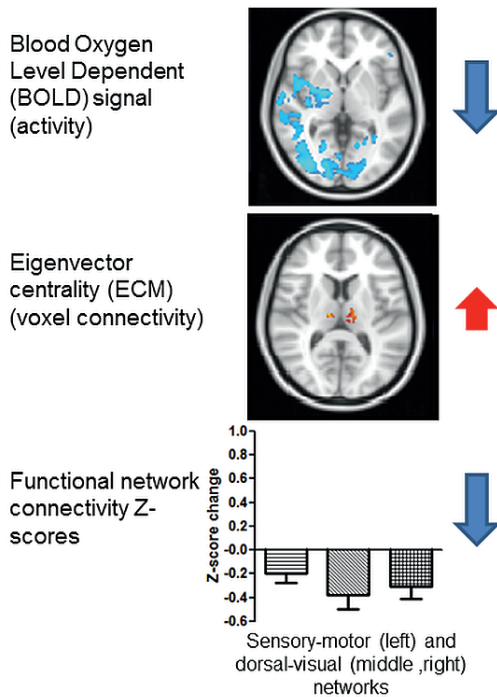


Figure 1. Whole brain functional responses to ingestion of glucose. Glucose dissolved in water leads to various functional changes in activity and connectivity throughout the brain in fasted, normal weight, healthy participants.

and VTA respond directly and readily to glucose but do not respond as efficiently and quickly to sucrose and fructose. Ingestion of the non-caloric artificial sweetener sucralose does not lead to homeostatic satiety signaling. Our findings indicate that the responses by the hypothalamus and VTA are mainly driven by energy content and that sweet taste without the corresponding energy content does not seem to elicit a lasting response from these brain areas.

Because sugars and sweeteners are most often consumed in the context of other nutrients in **Chapter 4** we determined brain responses to ingestion of different sugars and sweeteners consumed in a mixed meal together with other nutrients (fat and proteins). We again found that glucose had widespread effects on neuronal activity and connectivity in the brain and that while fructose also affects brain function, these effects are not as pronounced. The non-/low-nutritive sweeteners sucralose and allulose lead to very little functional brain responses. Similar to our findings in **Chapter 3**, we found that even in the context of other nutrients the sweet taste without the corresponding (carbohydrate) energy content of these non-nutritive sweeteners appears to have much smaller effects on the brain than nutritive sweeteners. The results of this chapter show that even in a mixed meal also containing fat and protein,

the type of sweetener and the carbohydrate energy content can affect brain responses and might thus affect reward and satiety responses and feeding behavior.

In **Chapter 5 and 6** we study the effects of characteristics of food that are related to palatability rather than energy content as these factors could affect energy consumption through their influence on the homeostatic and hedonic systems. In these chapters we determined the effects of consumption temperature and flavoring on the homeostatic and hedonic responses from the hypothalamus and VTA. Our results in **Chapter 5** show that after intake of both cold water and glucose containing drinks, the neuronal activity in the hypothalamus immediately decreases, whereas the activity increases after intake of water at room temperature. This indicates that consumption temperature can elicit or enhance the homeostatic response from the hypothalamus. In **Chapter 6** we determined the effect of added flavor by using ethyl butyrate (EB), a commonly used food flavoring with a fruity taste, to flavor both a glucose solution and plain water. The results of **Chapter 6** show that in the VTA the combination of glucose with EB flavoring led to a significant decrease in activity, which was threefold stronger than to glucose alone. The addition of EB flavoring to plain water (no caloric content) does not have any effect on the VTA. In the hypothalamus, only the ingestion of glucose, and not EB, was associated with changes in neuronal activity. Our results suggest that the hedonic response by the VTA is strongest to a combination of both flavor and energy and that the homeostatic satiety response of the hypothalamus is mainly driven by energy ingestion.

Deficits in central insulin action in diabetes type 2 are theorized to play a role in defective hypothalamic responses to glucose. Therefore, in **Chapter 7** we determined whether insulin, when centrally applied via the nose, influences the homeostatic response after glucose ingestion. Insulin signaling is an important factor in functional hypothalamic and whole brain response after glucose ingestion [1-4]. We found that centrally administered insulin augmented the decrease in neuronal activity of the hypothalamus in response to glucose ingestion in normal weight and healthy subjects. This indicates that central insulin can affect the hypothalamic function to maintain glucose homeostasis and that intranasally applied insulin might have the potential to strengthen the defective response that was observed in patients with type 2 diabetes [2, 3].

In **Chapter 8** we determined whether the hypothalamic response to glucose ingestion was disrupted in patients with anorexia nervosa. Like in diabetes type 2 and obesity, energy homeostasis along with various other hypothalamic functions are severely disrupted in patients with anorexia nervosa. However, the results presented in **Chapter 8** shows that the hypothalamic response to glucose ingestion is not different between patients with anorexia nervosa and healthy controls. Despite the fact that the hypothalamic response to energy ingestion is not different these patients still manage

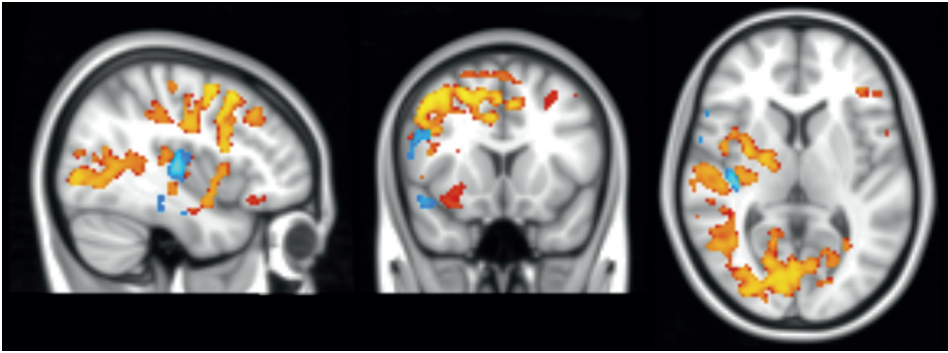


Figure 2. Brain areas showing changes in neuronal activity to both the ingestion of glucose and weight loss. Weight loss in obesity led to decreased activity in brain areas involved in feeding behavior, reward processing, and satiety after weight loss (indicated in blue, results from **Chapter 9**). These areas overlap with areas responding to the ingestion of glucose in normal weight subjects (indicated in orange, results from **Chapter 2**).

to refrain from eating, indicating that patients with anorexia nervosa might be overriding the hypothalamic signaling. Additionally we found that the volume of the cingulate cortex is decreased in anorexia nervosa. The cingulate cortex is a region known to be involved in emotion, attention, pain, and memory [5]. Together, these findings indicate that in anorexia nervosa direct hypothalamic nutrient sensing is not different but that reward and higher-order cognitive processes might be influencing and/or suppressing the hypothalamic signaling.

In **Chapter 9** we determined the effects of weight loss on the (altered) brain function in obesity by studying brain activity before and after a weight-loss intervention. Our data show that an 8-week weight loss intervention significantly decreased neural activity in parts of the insula, orbito-frontal cortex and in areas of several frontal gyri. These brain areas have previously been shown to have an increased activity in obesity [6-10] and are known to be involved in regulation of energy balance and feeding behavior [11]. We found that the neuronal activity in these areas was correlated with leptin, a marker of stored energy in the body. Interestingly, the areas that responded to weight loss, overlap with areas that showed decreased brain activity after glucose ingestion in **Chapter 2** (Figure 2). This suggest that maintaining the functional responses to glucose ingestion found in **Chapter 2** could be important for maintaining energy and glucose homeostasis. Taken together, these results indicate that alterations in neural activity in obesity are involved in glucose and energy homeostasis and that these alterations might be reversible by weight loss.

Overall conclusions, implications and future perspectives

In this thesis we found that different types of sugars and sweeteners elicit different functional brain responses in both the homeostatic and hedonic system. Additionally, we found that the flavoring and consumption temperature of the ingested substances can also influence these responses. Furthermore, we found that centrally administered insulin can influence the brain's response to glucose ingestion. In obese participants, with a disrupted energy balance, we found that weight loss appeared to normalize the brain activity in various areas known to be affected by obesity. However, in patients with anorexia nervosa we found that the homeostatic response to glucose remained intact despite the disrupted energy balance.

When determining the functional responses to energy ingestion, we consistently found across the different chapters that glucose ingestion elicits the strongest and most widespread functional response from the brain in healthy normal weight subjects. We found that the response to other common sugars and non/low-nutritive sweeteners (both artificial and natural sugar derived sweeteners) is much less apparent or even absent. Furthermore, we demonstrated that the type of sweetener is an important determinant of functional brain responses, even in the context of other nutrients. This thesis shows that the use of glucose as a sweetener instead of other alternatives leads to the strongest satiety response and most immediate effect on feeding behavior. Therefore, when just regarding the brain, glucose appears the most preferable sweetener as the immediate homeostatic and hedonic effects might decrease continued consumption and overconsumption of energy.

When studying the brain function in obesity, where the maintenance of energy balance is disrupted, we found that similar areas respond to changes in body weight that respond to glucose ingestion. Furthermore, we show that brain areas that respond to glucose ingestion can be influenced by metabolic signals such as leptin and insulin, either endogenous or exogenous, that are often disrupted/altered in obesity and diabetes type 2. This, along with results from various other studies [2, 3, 12-14], and our finding that glucose elicits strong responses from the brain, suggests that the functional response to glucose and carbohydrates is important in maintaining energy and glucose homeostasis. Therefore further investigation into these responses should be an area of focus when aiming to find methods to achieve and/or restore normal energy intake and feeding behavior in obesity.

The combined results of the first chapters of this thesis show that energy content of food or drinks appears to be the most important determining factor in the homeostatic brain response and to a lesser extent in the hedonic response. However, we also demonstrated that consumption temperature has an effect on the homeostatic response, whereas flavoring without corresponding energy content does not elicit a lasting homeostatic response. This can be explained by the fact that while flavor in

itself does not have effects on homeostasis, drinking liquids at a low temperature is often deemed as thirst quenching can therefore have effects on the homeostatic regulation of thirst and fluid balance by the hypothalamus [15-17]. Our findings indicate that factors that influence homeostasis, like energy content and temperature, are important in determining hypothalamic responses but factors that do not directly affect homeostasis, like flavoring, might mainly affect the hedonic response.

An important limitation of this thesis is the fact that the functional brain responses have mostly been determined in a very homogenous group of healthy lean young men. Future research should focus on investigating functional brain responses in maintaining energy balance in a more heterogeneous study population with different body weights, fat percentages and feeding habits as these could all affect the brain function and responses [18-21]. Furthermore, investigation of these brain responses in females compared to males is important as females have a different (cerebral) glucose and lipid metabolism compared to males [22, 23]. Differences in eating behavior [24, 25] and taste perception [26] and different levels of inhibitory control over feelings of hunger have been also shown [27]. All of these factors will influence, or are influenced by, the central regulation of energy balance. To extrapolate the results of this thesis to the general population studies in female subjects are therefore necessary.

Overall, this thesis adds further insights into functional brain responses to energy ingestion and in the maintenance of energy balance. We found that glucose has a strong effect on these responses, especially on the homeostatic response, where other sugars and sweeteners in our modern day diet have lesser to very little effects on the brain. And while food characteristics such as temperature and flavor can influence the functional brain responses, both homeostatic and hedonic, the most important driving factor for these response is energy content. Additionally, in this thesis we show that hypothalamic and whole brain activity can be affected by central insulin signaling and weight loss. Still, we find that a disrupted energy balance does not necessarily correlate with an altered functional homeostatic response. Highlighting that even though the homeostatic response of the brain to maintain energy balance is important, the hedonic system and its capability to override the homeostatic system should not be overlooked when investigating feeding behavior. Therefore, future research should focus on what the responses found in this thesis mean in terms of feeding behavior and whether they can be predictive for energy consumption and (maintenance of) energy balance. This is especially important to investigate in subjects with a disrupted energy balance to determine if measurements of functional responses could be used to aid in treatment of this disrupted energy homeostasis. Furthermore, it is important that future investigations into central regulation of energy balance should be done in a more heterogeneous group as it is expected that sex and body weight could lead to different responses and function of the brain in the maintenance of energy balance.

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