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Functional brain responses in the maintenance of energy balance

Opstal, A.M. van

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Author: Opstal, A.M. van
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CHAPTER 1

General introduction

The regulation of feeding behavior and energy balance is crucial for maintaining health. Various modern day health problems like obesity, metabolic syndrome, diabetes type 2 and eating disorders are all linked to a combination of disrupted feeding behavior and energy balance. In addition to the well-known endocrinological aspects in this, recently it was recognized that the brain is very important in regulation of our feeding behavior, both on a conscious and sub-conscious level.
In the regulation of feeding behavior, various internal and external factors play a role. Hunger and the basic need for energy for both the body and brain are the main driving factor to start eating. Energy intake is regulated by the homeostatic system. The most important brain area of this system is the hypothalamus, which uses objective signal from the periphery to determine the energy status of the body and combines these with signals of hunger and satiety. However, besides caloric need, the pleasure and reward of eating and drinking may also lead to the intake of more energy than strictly necessary. Unfortunately, highly palatable food is often high in carbohydrates, high in fats and usually strongly flavored. All of these characteristics can be very stimulating and elicit strong rewarding responses from the brain. Other factors such as memory and learned habits, social circumstances, personal preference and inhibitory control can also influence hedonic feeding. The hedonic regulation is mainly determined by the limbic and executive control systems of the brain, which can inhibit or override the homeostatic system. If so, this often leads to energy intake that is not in line with homeostatic need. Altogether, the central regulation of energy balance by the brain is a very complex, but is important in maintaining health. Extending knowledge on how these process are influenced and disrupted is crucial for a better understanding of feeding behavior and effects of diet on the brain, and for the development of markers aiding in the management of obesity, metabolic syndrome and eating disorders.
In this chapter the neuronal brain systems involved in central regulation of energy balance will be explained in more detail. The differences in function and responses of these systems when energy balance is disrupted will also be introduced. Furthermore, the effects that different food characteristics can have on the functional responses of the brain in the maintenance of energy balance will be described. And a short introduction of Magnetic Resonance Imaging techniques to investigate these functions and responses will be given. Finally, the overall aim of this thesis and the aim of the various chapters will be discussed.

Central regulation of energy balance by the homeostatic and hedonic systems
In the last decades the regulatory role of the brain in directing energy balance, glucose homeostasis, and eating behavior, is increasingly being recognized [1-3]. Energy

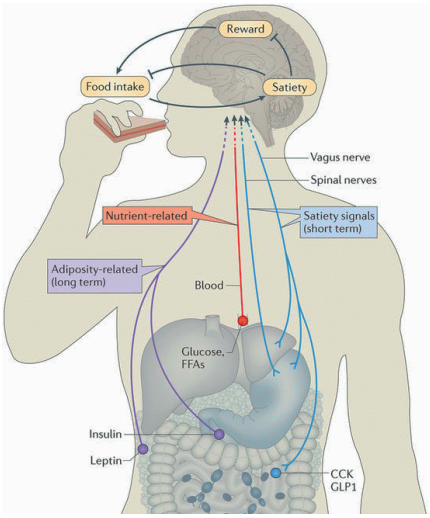


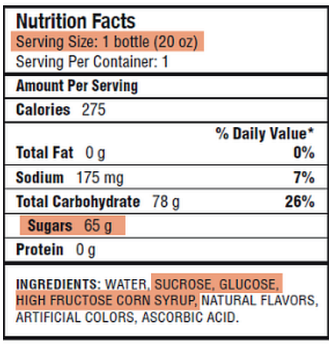
Figure 1. Central regulation of energy balance. The brain coordinates food intake based on various homeostatic (satiety) signals from the periphery and gut combined with reward signals. CCK, cholecystokinin; FFAs, free fatty acids; GLP1, glucagon-like peptide 1. Adapted from Morton, G.J., et al. Nat. Rev. Neurosci, 2014. 15(6)

balance is centrally regulated by the brain through several interacting neuronal systems. The homeostatic system and the hedonic system are mainly involved in maintaining energy balance [2, 4]. The homeostatic system, consisting of the hypothalamus and several nuclei in the brainstem, regulates energy intake by combining satiety signals with metabolic and hormonal cues from the periphery [4, 5]. In this system, the hypothalamus is the most important structure. It regulates energy balance by integrating information from glucose and insulin trajectories with varying levels of hormones and peptides from the gut and stomach [6-10]. Circulating metabolic cues that are related to the energy status of the body, such as ghrelin, leptin and insulin, all influence the homeostatic regulation by initiating signals of hunger and satiety [11, 12]. This information is than integrated with signals from the reward system [13]. A schematic depiction of these interactions between the periphery and homeostatic satiety and reward signalling is shown in figure 1. The reward pathway is responsible for the hedonic response to food. The ventral tegmental area (VTA) and other areas of the limbic system, such as the amygdala and nucleus accumbens, are brain areas that are important in this hedonic response [14]. The VTA is the origin of dopaminergic signaling in the mesolimbic reward system, which is a key substrate for reward prediction and response [15]. The VTA is anatomically and functionally connected to the hypothalamus and integrates homeostatic signals with reward responses [16-18]. Hedonic processes can, completely without awareness, override the homeostatic system and lead to disrupted energy balance, eating behavior and finally to obesity [14, 19].

Understanding of homeostatic and hedonic functional brain responses yields insights into satiety signaling, nutrient sensing, energy seeking and feeding behavior. Moreover, it may aid in the development of neurophysiological markers for (de)regulation of these systems in obesity, eating disorders or type 2 diabetes.

Effects of food characteristics and different nutrients on functional brain responses regulating energy balance

The palatability of food and beverages plays an important role in the consumption of energy. Various food characteristics can influence palatability and therefore influence regulation of energy intake. Several aspects of food and beverages such as taste, smell, visual cues and energy content have been found to elicit or influence functional brain responses [20-22]. The ingestion of different mixtures of macro nutrients, fats, proteins and carbohydrates, which all have specific effects on the brain, can elicit various brain responses [23, 24]. Circulating glucose is the primary source of energy for the brain, and its metabolism is kept under tight regulation to maintain optimal (brain) physiology [25, 26]. Both homeostatic and mesolimbic pathways in the brain have glucose sensing neurons and respond readily to glucose ingestion [25, 27, 28]. Glucose has been shown to elicit a homeostatic satiety response from the hypothalamus almost immediately after ingestion indicated by a decrease in hypothalamic neuronal activity [8, 29-31].
Glucose is a commonly consumed natural sugar and is used a sweetener in various foods and beverages. In addition to glucose, various other mono- and di-saccharides, such as fructose and sucrose, and low or non-caloric sweeteners are increasingly being used to sweeten foods and beverages [32, 33]. The metabolic pathways of these sweeteners is all different. For instance; in contrast to glucose, fructose cannot be used directly as a source of energy but first has to be metabolized by the liver before it can be taken up in the blood and recognized by the brain [7, 34, 35]. The metabolic effects of non-caloric sweeteners are less straightforward. Although, non-caloric sweeteners are expected to decrease caloric intake and might therefore be useable to control obesity [36], epidemiological studies have found that non-caloric sweeteners might have the opposite effect and could actually lead to increased energy intake [9, 37]. The increased ingestion of glucose, fructose or non-caloric or low caloric sweeteners over the last decades, coincides with increased prevalence of obesity [38, 39]. This increases the particular interest of investigating the homeostatic and hedonic aspects of these substances [9, 32, 39, 40].
An important contributor to the overall increased intake of sugars and sweeteners in the modern diet is the increased consumption of sweetened beverages [40]. Generally, sugar sweetened beverages have a very high sugar content and are sweetened with a combination of several sugars (a typical nutrition label for a sugar sweetened beverages



Nutrition Facts
Serving Size: 1 bottle (20 oz)
Serving Per Container: 1

Amount Per Serving	
Calories 275	
	% Daily Value*
Total Fat 0 g	**0%**
Sodium 175 mg	**7%**
Total Carbohydrate 78 g	**26%**
Sugars 65 g	
Protein 0 g	

INGREDIENTS: WATER, SUCROSE, GLUCOSE, HIGH FRUCTOSE CORN SYRUP, NATURAL FLAVORS, ARTIFICIAL COLORS, ASCORBIC ACID.

Figure 2. Typical nutrition label of a sugar sweetened beverage. Sugar sweetened beverages are often very high in sugar and sweetener content, often containing various other sugars or added artificial sweeteners besides glucose such as sucrose and high fructose corn syrup.

is shown in figure 2). In the palatability and rewarding aspects of consumption of sugar sweetened beverages several factors are involved. In addition to the high energy content and sweetness, the refreshment and thirst quenching features are also important [41]. Drinks consumed at low temperatures have been shown to be more thirst quenching than drinks consumed at room temperature [42], indicating that the relatively low consumption temperature, at which sugar sweetened beverages are generally consumed, could have effects on reward and homeostatic brain responses. In addition to sweetness and energy content and consumption temperature, the pleasantness of food is also affected by factors such as flavor and texture. Flavor can have a direct influence on feeding behavior by making food palatable and attractive and thereby eliciting a reward response in the brain [16, 43, 44]. Taste and flavor are an important part of the palatability and pleasantness of food and have been shown to have an effect on the consumption volume and rewarding effects of food and might cause overeating [43, 45, 46]. Energy ingestion combined with a pleasant flavor has been shown to enhance the rewarding properties of energy ingestion. For instance, when glucose is paired with a congruent flavoring, the perception of flavor is enhanced, and results in a greater feeling of satiety [47-49]. Furthermore, sweet taste that is rated as pleasant has been shown to elicit an insulin response when applied to the oral cavity only [50]. Although the evidence for the effect of taste perception on the insulin response is limited, these results suggest that the taste of food, independent of energy content, might influence the central regulation of energy intake and the peripheral energy metabolism.

Taken together, current scientific evidence indicates that various ingredients and other aspects of food and beverages as consumed in our modern day diet could influence and/or alter functional brain responses important for the maintenance of energy balance. Therefore, investigating these effects is important for our understanding of how they might affect regulation of energy consumption and feeding behavior and what role they could play in the disruption of energy balance.

Altered brain function in disrupted energy balance

Knowledge of the regulation of the energy balance by the brain is also important because various modern day health problems and chronic diseases can be led back to a disrupted energy balance, feeding behavior and altered brain function. One of the most important and most prevalent public health concerns is obesity and its subsequent co-morbidity [51]. Obesity is generally marked by a disrupted energy balance and increased storage of energy (fat) often coinciding with disturbed eating behavior [52]. The regulatory role of the brain in obesity is essential since it has unequivocally been shown that in obese persons the function of homeostatic and hedonic brain areas is altered [53-57]. Generally, in obese persons, brain connectivity and activity is increased compared to lean persons [53, 56-58], especially in brain areas that are involved in reward processes [53-55, 57]. Furthermore, brain responses to fasting but also to food intake are different between lean and obese persons [59]. In diabetes type 2, a common co-morbidity of obesity, the hypothalamus demonstrates a decreased homeostatic response after glucose ingestion [29, 30]. This lack of response can be caused by disrupted insulin sensitivity and signaling. Insulin is a hormone that gives negative feedback to hypothalamic nuclei that control energy and glucose homeostasis, and is vital in the regulation of glucose and energy metabolism [60-63]. Hypothalamic functioning is also important on the other end of the spectrum of a disrupted energy balance. For instance, in patients with anorexia nervosa, who demonstrate a severe negative energy balance and disrupted feeding behavior, the hypothalamic-pituitary-adrenal axis is hyperactive [64-66].

Taken together, disrupted brain function plays an important role in several diseases and conditions associated with a disrupted energy balance. Investigating these alterations in brain function and how they could be influenced and/or normalized is therefore important to determine potential targets for the treatment of obesity, metabolic syndrome and eating disorders.

Magnetic resonance imaging techniques to investigate functional brain responses

To investigate functional brain responses in regulating energy balance, functional Magnetic Resonance Imaging (fMRI) can be used to visualize and quantify both functional brain activity and connectivity. Blood oxygen level dependent (BOLD) fMRI is used as a measure of neuronal activity [67]. BOLD fMRI has been used extensively to analyses the immediate effects of nutrient ingestion on specific brain areas and throughout the brain [8, 20, 30, 31]. Beyond measurements of neuronal activity, analysis of functional connectivity can been used to provide further insights into brain areas interacting together to perform specific functions. Functional connectivity analysis

has been successfully used to identify and investigate various functional networks involved in feeding behavior, reward responses and energy balance. Changes in connectivity in these networks have been found after exposure to food cues and nutrient ingestion [54, 55, 68-70].

Aim of this thesis

The primary aim of this thesis was to gain more insights into 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.

As glucose is the preferred source of energy of the brain we first investigated the normal functional brain responses to glucose (**Chapter 2**) in healthy normal weight participants. However, in addition to glucose other sugars and sweeteners are often consumed as part of our daily diet. Therefore, to gain a better understanding of the different effects of the ingestion of other caloric and non-caloric sweeteners in addition to glucose, in **Chapter 3** we investigated the effects of several different sugars and sweeteners on the homeostatic and hedonic responses. With the exception of sugar sweetened beverages, sugars and sweeteners are usually consumed in a mixed meal together with other nutrients. Therefore, in **Chapter 4** we investigated the effects of different sugars and sweeteners throughout the brain in the context of other nutrients. To this end, we investigated the effects of the ingestion of sweetened nutrient shakes containing fats and protein and sweetened with either the nutritive natural sugars or low- /non-nutritive sweeteners. In addition to the effects of sweetness and energy content, we investigated the role of consumption temperature (**Chapter 5)** and flavoring **(Chapter 6)** of beverages on hedonic and homeostatic brain responses.

As discussed, various metabolic cues, such as circulating insulin, are known to influence homeostatic regulation of energy balance via the hypothalamus. Deficits in central insulin action in Diabetes type 2 are theorized to play a role in defective hypothalamic responses to glucose. As a proof of concept we investigated in **Chapter 7** whether centrally administrated insulin could potentiate the BOLD response in the hypothalamus after glucose ingestion in healthy normal weight subjects.

Because of the strongly disrupted energy balance and known hypothalamic dysfunction in patients with anorexia nervosa, we investigated whether the hypothalamic response to energy ingestion in these patients was disrupted (**Chapter 8**). Obesity is also be characterized by a disrupted energy balance and alter feeding behavior. The disrupted

energy balance in obesity is also associated with altered brain function, often in the form of increased connectivity and activity, compared to lean persons [53, 56-58]. However it is not known if these altered functions are the cause or a consequence of excess body weight. Therefore, in **Chapter 9** we investigated whether weight loss could reverse and/or normalize the increased brain activity in obese participants.
Overall conclusions, final remarks on the findings of this thesis and future perspectives are discussed in **Chapter 10**.

REFERENCES

1. Deem, J.D., et al., *How Should We Think About the Role of the Brain in Glucose Homeostasis and Diabetes?* Diabetes, 2017. 66(7): p. 1758-1765.
2. Morton, G.J., et al., *Central nervous system control of food intake and body weight.* Nature, 2006. 443(7109): p. 289-295.
3. Schwartz, M.W., et al., *Central nervous system control of food intake.* Nature, 2000. 404(6778): p. 661-671.
4. Morton, G.J., T.H. Meek, and M.W. Schwartz, *Neurobiology of food intake in health and disease.* Nat. Rev. Neurosci, 2014. 15(6): p. 367-378.
5. Kim, K.S., R.J. Seeley, and D.A. Sandoval, *Signalling from the periphery to the brain that regulates energy homeostasis.* Nat. Rev. Neurosci, 2018. 19(4): p. 185-196.
6. Ochoa, M., et al., *Dietary sugars: their detection by the gut-brain axis and their peripheral and central effects in health and diseases.* Eur. J. Nutr, 2015. 54(1): p. 1-24.
7. Page, K.A., et al., *Effects of fructose vs glucose on regional cerebral blood flow in brain regions involved with appetite and reward pathways.* JAMA, 2013. 309(1): p. 63-70.
8. Smeets, P.A., et al., *Functional MRI of human hypothalamic responses following glucose ingestion.* Neuroimage, 2005. 24(2): p. 363-368.
9. Steinert, R.E., et al., *Effects of carbohydrate sugars and artificial sweeteners on appetite and the secretion of gastrointestinal satiety peptides.* Br. J. Nutr, 2011. 105(9): p. 1320-1328.
10. Pan, W.W. and M.G. Myers, Jr., *Leptin and the maintenance of elevated body weight.* Nat. Rev. Neurosci, 2018. 19(2): p. 95-105.
11. Lam, C.K., M. Chari, and T.K. Lam, *CNS regulation of glucose homeostasis.* Physiology (Bethesda.), 2009. 24: p. 159-170.
12. Schwartz, M.W. and D. Porte, Jr., *Diabetes, obesity, and the brain.* Science, 2005. 307(5708): p. 375-379.
13. Blouet, C. and G.J. Schwartz, *Hypothalamic nutrient sensing in the control of energy homeostasis.* Behav. Brain Res, 2010. 209(1): p. 1-12.
14. Volkow, N.D., R.A. Wise, and R. Baler, *The dopamine motive system: implications for drug and food addiction.* Nat. Rev. Neurosci, 2017. 18(12): p. 741-752.
15. Schultz, W., P. Dayan, and P.R. Montague, *A neural substrate of prediction and reward.* Science, 1997. 275(5306): p. 1593-1599.
16. Meye, F.J. and R.A. Adan, *Feelings about food: the ventral tegmental area in food reward and emotional eating.* Trends Pharmacol. Sci, 2014. 35(1): p. 31-40.
17. Nieh, E.H., et al., *Inhibitory Input from the Lateral Hypothalamus to the Ventral Tegmental Area Disinhibits Dopamine Neurons and Promotes Behavioral Activation.* Neuron, 2016. 90(6): p. 1286-1298.
18. Sheng, Z., et al., *Metabolic regulation of lateral hypothalamic glucose-inhibited orexin neurons may influence midbrain reward neurocircuitry.* Mol. Cell Neurosci, 2014. 62: p. 30-41.
19. Berthoud, H.R., H. Munzberg, and C.D. Morrison, *Blaming the Brain for Obesity: Integration of Hedonic and Homeostatic Mechanisms.* Gastroenterology, 2017. 152(7): p. 1728-1738.
20. Haase, L., B. Cerf-Ducastel, and C. Murphy, *Cortical activation in response to pure taste stimuli during the physiological states of hunger and satiety.* Neuroimage, 2009. 44(3): p. 1008-1021.
21. Ulrich, M., et al., *Glucose modulates food-related salience coding of midbrain neurons in humans.* Hum. Brain Mapp, 2016.
22. Blouet, C. and G.J. Schwartz, *Hypothalamic nutrient sensing in the control of energy homeostasis.* Behav Brain Res, 2010. 209(1): p. 1-12.
23. Carreiro, A.L., et al., *The Macronutrients, Appetite, and Energy Intake.* Annu Rev Nutr, 2016. 36: p. 73-103.
24. Tulloch, A.J., et al., *Neural responses to macronutrients: hedonic and homeostatic mechanisms.* Gastroenterology, 2015. 148(6): p. 1205-18.
25. Mergenthaler, P., et al., *Sugar for the brain: the role of glucose in physiological and pathological brain function.* Trends Neurosci, 2013. 36(10): p. 587-597.
26. Steinbusch, L., G. Labouebe, and B. Thorens, *Brain glucose sensing in homeostatic and hedonic regulation.* Trends Endocrinol. Metab, 2015. 26(9): p. 455-466.
27. Grayson, B.E., R.J. Seeley, and D.A. Sandoval, *Wired on sugar: the role of the CNS in the regulation of glucose homeostasis.* Nat Rev Neurosci, 2013. 14(1): p. 24-37.
28. Galgani, J. and E. Ravussin, *Energy metabolism, fuel selection and body weight regulation.* Int J Obes (Lond), 2008. 32 Suppl 7: p. S109-19.
29. Teeuwisse, W.M., et al., *Short-term caloric restriction normalizes hypothalamic neuronal responsiveness to glucose ingestion in patients with type 2 diabetes.* Diabetes, 2012. 61(12): p. 3255-3259.
30. Vidarsdottir, S., et al., *Glucose ingestion fails to inhibit hypothalamic neuronal activity in patients with type 2 diabetes.* Diabetes, 2007. 56(10): p. 2547-2550.

31. Smeets, P.A., et al., *Functional magnetic resonance imaging of human hypothalamic responses to sweet taste and calories.* Am. J. Clin. Nutr, 2005. 82(5): p. 1011-1016.
32. Imamura, F., et al., *Consumption of sugar sweetened beverages, artificially sweetened beverages, and fruit juice and incidence of type 2 diabetes: systematic review, meta-analysis, and estimation of population attributable fraction.* Br. J. Sports Med, 2016. 50(8): p. 496-504.
33. Lohner, S., I. Toews, and J.J. Meerpohl, *Health outcomes of non-nutritive sweeteners: analysis of the research landscape.* Nutrition Journal, 2017. 16: p. 55.
34. Tappy, L. and K.A. Le, *Metabolic effects of fructose and the worldwide increase in obesity.* Physiol Rev, 2010. 90(1): p. 23-46.
35. Purnell, J.Q. and D.A. Fair, *Fructose ingestion and cerebral, metabolic, and satiety responses.* JAMA, 2013. 309(1): p. 85-86.
36. Rogers, P.J., et al., *Does low-energy sweetener consumption affect energy intake and body weight? A systematic review, including meta-analyses, of the evidence from human and animal studies.* Int. J. Obes. (Lond), 2016. 40(3): p. 381-394.
37. Swithers, S.E., *Artificial sweeteners produce the counterintuitive effect of inducing metabolic derangements.* Trends Endocrinol. Metab, 2013. 24(9): p. 431-441.
38. Malik, V.S., et al., *Sugar-sweetened beverages and weight gain in children and adults: a systematic review and meta-analysis.* Am. J. Clin. Nutr, 2013. 98(4): p. 1084-1102.
39. Malik, V.S., M.B. Schulze, and F.B. Hu, *Intake of sugar-sweetened beverages and weight gain: a systematic review.* Am. J. Clin. Nutr, 2006. 84(2): p. 274-288.
40. Kit, B.K., et al., *Trends in sugar-sweetened beverage consumption among youth and adults in the United States: 1999-2010.* Am. J. Clin. Nutr, 2013. 98(1): p. 180-188.
41. Eccles, R., et al., *Cold pleasure. Why we like ice drinks, ice-lollies and ice cream.* Appetite, 2013. 71: p. 357-360.
42. Brunstrom, J.M. and A.W. MacRae, *Effects of temperature and volume on measures of mouth dryness, thirst and stomach fullness in males and females.* Appetite, 1997. 29(1): p. 31-42.
43. Bellisle, F., et al., *Sweetness, satiation, and satiety.* J. Nutr, 2012. 142(6): p. 1149S-1154S.
44. Berthoud, H.R. and C. Morrison, *The brain, appetite, and obesity.* Annu. Rev. Psychol, 2008. 59: p. 55-92.
45. Rolls, E.T., *Taste, olfactory, and food texture processing in the brain, and the control of food intake.* Physiol Behav, 2005. 85(1): p. 45-56.
46. Szalay, C., et al., *Gustatory perception alterations in obesity: an fMRI study.* Brain Res, 2012. 1473: p. 131-140.
47. AR, F. and B. J, *Taste-smell interactions are tastant and odorant dependent.* Chem. Senses, 1988. 13: p. 445-455.
48. Green, B.G., et al., *Enhancement of retronasal odors by taste.* Chem. Senses, 2012. 37(1): p. 77-86.
49. Yin, W., et al., *Effects of aroma and taste, independently or in combination, on appetite sensation and subsequent food intake.* Appetite, 2017. 114: p. 265-274.
50. Just, T., et al., *Cephalic phase insulin release in healthy humans after taste stimulation?* Appetite, 2008. 51(3): p. 622-627.
51. Withrow, D. and D.A. Alter, *The economic burden of obesity worldwide: a systematic review of the direct costs of obesity.* Obes. Rev, 2011. 12(2): p. 131-141.
52. Spiegelman, B.M. and J.S. Flier, *Obesity and the regulation of energy balance.* Cell, 2001. 104(4): p. 531-543.
53. Garcia-Garcia, I., et al., *Reward processing in obesity, substance addiction and non-substance addiction.* Obes. Rev, 2014. 15(11): p. 853-869.
54. Garcia-Garcia, I., et al., *Alterations of the salience network in obesity: a resting-state fMRI study.* Hum. Brain Mapp, 2013. 34(11): p. 2786-2797.
55. Kullmann, S., et al., *Functional network connectivity underlying food processing: disturbed salience and visual processing in overweight and obese adults.* Cereb. Cortex, 2013. 23(5): p. 1247-1256.
56. Lips, M.A., et al., *Resting-state functional connectivity of brain regions involved in cognitive control, motivation, and reward is enhanced in obese females.* Am. J. Clin. Nutr, 2014. 100(2): p. 524-531.
57. Wijngaarden, M.A., et al., *Obesity is marked by distinct functional connectivity in brain networks involved in food reward and salience.* Behav. Brain Res, 2015. 287: p. 127-134.
58. Zhang, B., et al., *Altered baseline brain activity differentiates regional mechanisms subserving biological and psychological alterations in obese men.* Sci. Rep, 2015. 5: p. 11563.
59. Matsuda, M., et al., *Altered hypothalamic function in response to glucose ingestion in obese humans.* Diabetes, 1999. 48(9): p. 1801-1806.
60. Leibowitz, S.F. and K.E. Wortley, *Hypothalamic control of energy balance: different peptides, different functions.* Peptides, 2004. 25(3): p. 473-504.
61. Obici, S., et al., *Decreasing hypothalamic insulin receptors causes hyperphagia and insulin resistance in rats.* Nat. Neurosci, 2002. 5(6): p. 566-572.
62. Obici, S., et al., *Hypothalamic insulin signaling is required for inhibition of glucose production.* Nat. Med, 2002. 8(12): p. 1376-1382.

63. Plum, L., M. Schubert, and J.C. Bruning, *The role of insulin receptor signaling in the brain.* Trends Endocrinol. Metab, 2005. 16(2): p. 59-65.
64. Lawson, E.A., et al., *Increased hypothalamic-pituitary-adrenal drive is associated with decreased appetite and hypoactivation of food-motivation neurocircuitry in anorexia nervosa.* Eur. J. Endocrinol, 2013. 169(5): p. 639-647.
65. Bailer, U.F. and W.H. Kaye, *A review of neuropeptide and neuroendocrine dysregulation in anorexia and bulimia nervosa.* Curr. Drug Targets. CNS. Neurol. Disord, 2003. 2(1): p. 53-59.
66. Smitka, K., et al., *The role of "mixed" orexigenic and anorexigenic signals and autoantibodies reacting with appetite-regulating neuropeptides and peptides of the adipose tissue-gut-brain axis: relevance to food intake and nutritional status in patients with anorexia nervosa and bulimia nervosa.* Int. J. Endocrinol, 2013. 2013: p. 483145.
67. Forster, B.B., et al., *Functional magnetic resonance imaging: the basics of blood-oxygen-level dependent (BOLD) imaging.* Can. Assoc. Radiol. J, 1998. 49(5): p. 320-329.
68. Bolo, N.R., et al., *Functional Connectivity of Insula, Basal Ganglia, and Prefrontal Executive Control Networks during Hypoglycemia in Type 1 Diabetes.* J. Neurosci, 2015. 35(31): p. 11012-11023.
69. Seeley, W.W., et al., *Dissociable intrinsic connectivity networks for salience processing and executive control.* J. Neurosci, 2007. 27(9): p. 2349-2356.
70. Tregellas, J.R., et al., *Altered default network activity in obesity.* Obesity (Silver Spring), 2011. 19(12): p. 2316-21.