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Modulation of brain activity by hormonal factors in the context of ingestive behaviour

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ABSTRACT

Introduction: Metabolic and hormonal signals have been shown to be associated with brain activity in the context of ingestive behaviour. However, this has mostly been seen in studies using external administration of hormones or glucose. We therefore studied endocrine-brain interaction in a physiological setting with hormone levels determined by metabolic conditions such as normal food intake vs. prolonged fasting.
Methods: 24 healthy, normal weight men participated in two sessions, one involving a 38-hour fasting period and one a non-fasting control condition with standardized meals. Functional magnetic resonance imaging was performed at the end of the experiment with participants being required to rate pictures of food. Brain activation was compared between conditions in predefined regions of interest (ROIs). Multiple blood samples were taken to determine levels of insulin, C-peptide, cortisol, ACTH, glucose and adiponectin. These were used as a predictor variable in a regression analysis on brain activations in the different ROIs.
Results: Food pictures were rated as more desirable in the fasting condition. Univariate analysis of ROI activations revealed mainly effects of food rating and no significant effects of the metabolic state. Multiple regression analysis revealed associations between orbitofrontal cortex activation and blood glucose in the non-fasting condition. In the fasting condition adiponectin was associated with the signal from the caudate nucleus and insulin and C-peptide were associated with functional activity of orbitofrontal regions.
Discussion: Associations of endocrine signals and functional neural regions could be demonstrated in a realistic setting without external administration of hormones. As the current approach was correlational, further studies need to address the causal role of hormonal signals.

1. Introduction

Obesity and associated conditions of the metabolic syndrome can be considered as one of the pandemic health problems of our time with one third of the world population already being overweight [1–3]. A number of theories have been proposed that might explain the cause and origin of growing levels of body weight. On the neural level, energy intake and its regulation is commonly assumed to rely on two main neural systems: A hypothalamic homeostatic system [4,5] and a more extended system including other cortical and subcortical structures that integrates hedonic and reward related processes associated with food intake and obesity [6,7].

The brain is equipped with receptors and sensors for insulin [8], adiponectin [9,10], as well as numerous other hormonal signals [11–13]. Glucose levels seem to be primarily sensed in the portal vein from where neural signals are transmitted to the brain stem and hypothalamus [14–16]. Thus, there are receptors in place that could in principle modulate brain activity as a function of metabolic state. Indeed, previous studies that have externally administered insulin (transnasally) [17–19], leptin [20–23] or glucose ([24–27] have found marked alterations of the neural processing of food items (see also review by Zanchi et al. [28] who discusses further hormones).

The homeostatic hypothalamic system is influenced by peripheral endocrine signals relaying information about the energy status of the body and food intake [29]. Endocrine signals derived, e.g. from the gut or adipose tissue, may modulate a number of cortical and subcortical sites besides the hypothalamus [30–32]. For example, insulin alters

Abbreviations: AUC, area under the curve; Cd, caudate nucleus; CNS, central nervous system; FDG, fluorodeoxyglucose; NAcc, nucleus accumbens; Ncl., nucleus; OFC, orbitofrontal cortex; ROI, region of interest.

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the activation of brain regions like the fusiform gyrus, right hippocampus, right superior temporal cortex and mid frontal cortex after intranasal administration [33]. This shows that the networks regulating hunger and satiety interact with other cortical and subcortical brain systems, e.g. those supporting attention processes [7,34]. Glucose, as the primary source of energy of the brain, has also been found to alter the fMRI signal of cortical regions after being infused in human subjects [27]. Furthermore, the adipokine leptin interferes with the activation of brain regions such as the striatum [20]. Less knowledge is available for other adipokines, such as adiponectin whose role as a beneficial factor for insulin sensitivity and anti-inflammatory acting agent makes it a promising target for research ([35,36]; Wang & [37]). Higher peripheral levels of adiponectin correspond to higher levels in the central nervous system with adiponectin receptors being expressed in the CNS. Intraventricular injection of adiponectin leads to weight loss and higher energy expenditure [38–40]. Of note, most studies have been carried out in rodents and human imaging studies have used external application of substances intravenously, intranasally or in the intraventricular system. Consequently, very little is known about the interaction of endocrine and metabolic parameters with the central nervous system in a physiological context, i.e. during different metabolic conditions such as hunger and satiety. One of the few exceptions is a PET study that did not find an association of between the glucose and physiological insulin levels [41]. Also, electrophysiological experiments in rodents showed an influence of insulin-mediated signals arising from the ventral tegmental area to various sites of the brain that are considered to be part of the central functional reward system [42].

We chose a number of endocrine parameters associated with glucose metabolism (insulin, C-peptide, cortisol, ACTH, serum glucose) for this first experiment. Adiponectin was also included as it supports the crosstalk between fat tissue and nervous system in the regulation of food intake. We limited the range of endocrine parameters for this experiment because of the novelty of the approach and the available means.

Peripheral hormones derived from gut and adipose tissue as well as metabolites are one avenue by which the energy status of the body is affecting central brain activation, which differs for example in fasting and normally nourished individuals [43]. The brain regions affected by these metabolic and energy level differences depend on the paradigm of the study. While some areas such as the hippocampus, ventromedial prefrontal cortex, amygdala, parahippocampal gyrus and fusiform gyrus appear to be more affected by presentation of visual food cues [43,44], regions like the insula appear to be especially responsive when individuals are asked to rate visual cues, again modulated by metabolic condition [45,46].

Here, we attempted to find associations of the mentioned endocrine parameters and central activation in a physiological context of varying metabolic conditions over a longer period of time.

We hypothesised that hormones and serum parameters measured either after 38 h of fasting or 38 h of a controlled eating condition would be associated with the activity of brain regions involved in ingestive behaviour. Brain regions of interest (ROI) were selected a priori from the pertinent literature as being relevant for food intake regulation. Furthermore, it was hypothesised that these ROIs are modulated by the rating of food cues during the fMRI scan, the metabolic condition (fasting vs. non-fasting) or a combination of both.

2. Methods

2.1. Participants

Male, healthy and normal weight participants without metabolic diseases were enrolled for the study (mean age [SD] 24.3 [1.3] years; mean BMI [SD] 23.4 [1.4] kg/m^2). The sample size of 24 participants was based on pilot studies of our group as well as previous papers which compared the brain activity in different metabolic states [1,47–50]. All participants completed the whole experiment, but the data of one subject had to be discarded due to motion artefacts. All subjects underwent a medical examination and history prior to inclusion in the study and were excluded if they suffered from any chronic or acute medical condition, took any medication or drugs including cigarettes or drank >5 standard drinks per week (>50 g alcohol per week). Subjects were required to have a normal sleep-wake cycle (no shift workers), to not engage in high performance sports defined as training for >12 h a week and to not follow any particular diet (including vegan and vegetarian lifestyles). All subjects gave written informed consent. The study was approved by the Ethics Committee of the University of Lübeck and abided by the declaration of Helsinki.

2.2. Experimental setting

All participants underwent two conditions spaced 7 days apart (order randomized across participants): a fasting condition without any energy intake for 38 h and a non-fasting condition in which standardized meals were given at specific times. The basic experimental procedures are described in Fig. 1A. Subjects appeared in the sleep laboratory of the Department of Psychiatry of the University of Lübeck on the first study day of each condition at 8:00 a.m. They stayed in single rooms and 13 blood samples were taken in both conditions over the time course of each condition out of an inserted antecubital peripheral vein catheter (at 08:45 a.m., 10:00 a.m., 12:45 p.m., 02:00 p.m., 04:00 p.m., 06:00 p.m., 06:45 p.m., 08:00 p.m. and 10:00 p.m. on the first day and 08:45 a.m., 10:00 a.m., 11:45 a.m., 01:00 p.m. on the second day in both conditions). For the fasting condition, participants were instructed to refrain from eating from 11 p.m. on the evening before the start of the experiment. In the non-fasting condition participants received standardized meals on the first day at 9:00 a.m. (breakfast: 2240 kcal, 14% protein, 46% fat and 40% carbohydrates), at 1:00 p.m. (lunch: 1204 kcal, 17% protein, 31% fat and 52% carbohydrates) and 7:00 p.m. (dinner: 1199 kcal, 16% protein, 31% fat and 53% carbohydrates) and on the second day the same breakfast at 9:00 a.m. and lunch at 12:00 a.m. (1174 kcal 18% protein,31% fat and 50% carbohydrates). The fMRI scan was performed in a 25-minute session at 1:00 p.m. on the second day of the experiment and concluded the study.

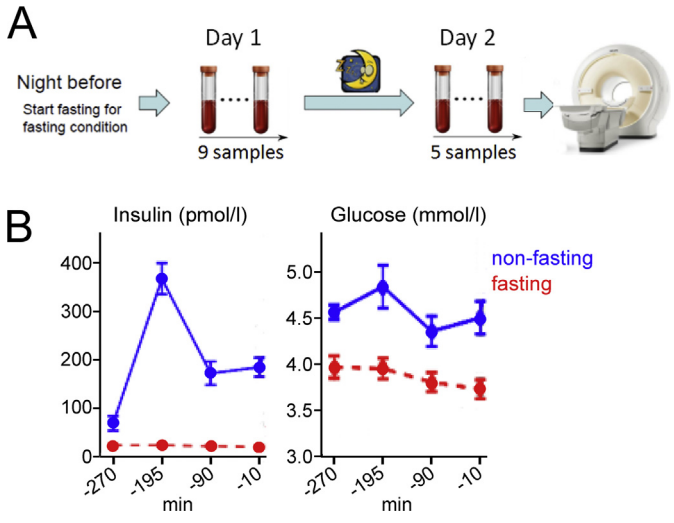

Fig. 1. A: Illustration of the general experimental setting. In each session the participants stayed in the sleep lab of the Dept. of Psychiatry and either received 3 meals per day (non-fasting condition) or fasted for 38 h. Blood samples were taken repeatedly prior to the MRI session. B: As an example for the time course of serum levels, the results for insulin and glucose are shown. The time points are given with reference to the beginning of the fMRI session.

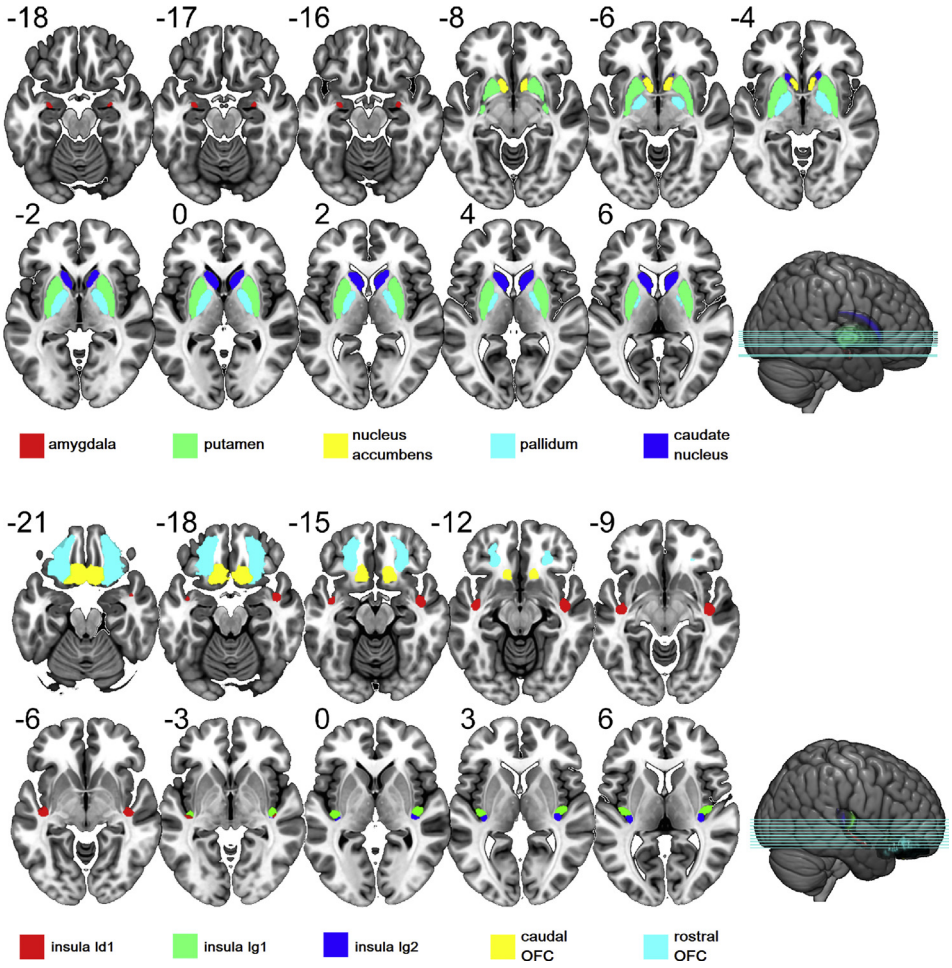

Fig. 2. Illustration of the different regions of interest used in the present study.

2.3. Serum parameters

Blood samples were used to measure blood glucose levels with the HemoCue® Glucose 201 DM Analyser (Radiometer, Brønshøj, Denmark) directly after the blood samples were taken. Blood samples were centrifuged (15 min with 2000 ×*g*) and the supernatant was stored at −80 °C until analysis. All hormones were measured at the same time with immunoassays to avoid interassay variability (Insulin, C-peptide, Cortisol, ACTH: Roche Diagnostics, ECLIA, Indianapolis, IN, USA; Adiponectin: Immundiagnostik AG, Adiponectin total ELISA Kit, Bensheim, Germany).

2.4. fMRI task

A slow event-related design was used with 72 pictures presented via monitor goggles one after another in a randomized order for each participant to reduce bias for beginning vs. end of scan session. The images are part of a high-resolution picture database of the Department of Neurology of the University of Lübeck. The pictures were rated in terms of their caloric content and sweet and savoury qualities by four expert raters and selected to show high and low calorie, sweet and savoury food. A new picture was presented every 20 s for 2 s. After the picture had disappeared the subjects had time to rate the depicted food on a scale of 1 to 8

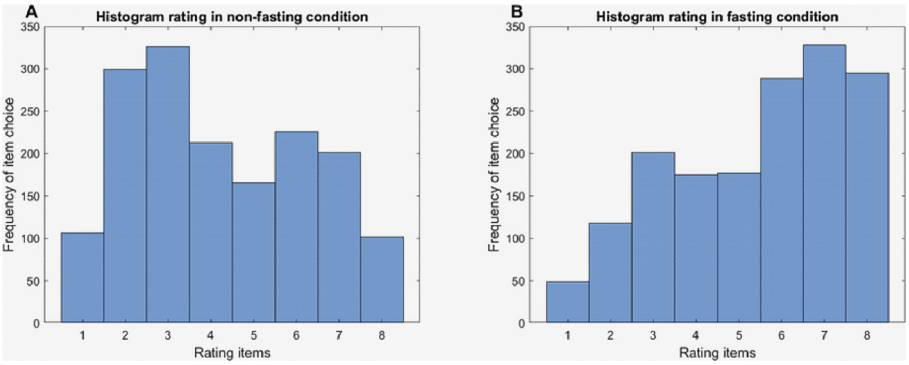

Fig. 3. Rating of food images during the fMRI measurement. Histograms of the distribution of the rating are shown in A for the non-fasting condition and B for the fasting condition.

regarding their craving for the particular food item by pressing a button on a keyboard. No time-limit was imposed for the rating, however after 20 s the next picture was shown and the next rating iteration was started.

2.5. MRI acquisition

A 3 Tesla Philips Achieva MR-scanner equipped with an 8 channel head-coil was used. A structural T1 weighted 3D turbo gradient Echo sequence with SENSE was performed with 180 sagittal slices of 1 mm, a 240 × 240 matrix and a flip angle of 9°. The echo time was 3.04 milliseconds (ms) with a repetition time of 6.72 ms. The functional session followed subsequently and consisted of 366 volumes. T2* weighted images were acquired with an Echo-planar pulse frequency with SENSE factor 2. Sagittal slices of 3 mm in a 64 × 64 matrix and a field of view of 192 mm and a flip angle of 80° were measured. The repetition time was 2 s and the echo time 25 ms.

2.6. Statistics and fMRI analysis

Matlab R2015b, SPSS 22 and R 0.99.902 were used for data analysis. Differences in hormone levels in between the conditions were assessed with repeated measures ANOVAs. For the non-parametric food rating data, the Wilcoxon test was used while *t*-tests were calculated for reaction times. A 2 × 2 factorial ANOVA was carried out with the factors rating (median split) and study condition for the percent signal change values of the ROI analysis. The percent signal change values of the 10 bilateral ROIs were defined as dependent variables for a multivariate multiple regression, in which the same AUC values of the serum parameters were used as a predictor variable as in the multiple regression. AUC values were chosen to represent a measure of the overall activity of an endocrine parameter during the experiment, being applicable due to the high level of standardisation in food intake and timing of the experiment.

Analysis of fMRI data was carried out with SPM 8 (Wellcome Trust Centre for Neuroimaging, UCL, UK). Preprocessing of the functional data comprised slice time correction with Fourier phase shift interpolation, followed by realignment and coregistration of functional and structural T1- to the mean functional image. The DARTEL algorithm was used to adjust T1 images to the Montreal Neurological Institute (MNI) template [51]. Functional images were spatially normalized to MNI space by applying the normalization parameters of the structural DARTEL normalization procedure to the functional data. In a final step functional data were smoothed with an 8 mm full width at half maximum (FWHM) Gaussian kernel and then analysed in a comparative fasting > control paradigm. A general linear model was designed according to the within study design with two conditions with the SPM 8 canonical hemodynamic response function, restricted maximum likelihood and an additional regressors for movement artefacts. An uncorrected factorial design of paired *t*-tests for the contrast in between the activation parameters was used with a threshold of $p < 0.001$ and a minimal Cluster size of 10 voxels (270 mm^3). Percent signal change values were calculated for the most significant cluster with the function Rfxplot for SPM8 with Matlab 2015b [52].

From a literature review of fMRI studies addressing food intake and fasting, the following regions of interest (ROI) were defined (Fig. 2 for illustration): amygdala, caudate nucleus, insula (3 different regions), nucleus accumbens (NAcc), orbitofrontal cortex (OFC, 2 different regions), pallidum and putamen [48–50,53–55]. The OFC and insular regions were defined according to the Jülich histological atlas [56]. The Harvard-Oxford subcortical atlas was used for all other brain regions [57]. The means of the percent signal change values were calculated individually for the subjects for each condition and the grouping according to high and low rating of the pictures.

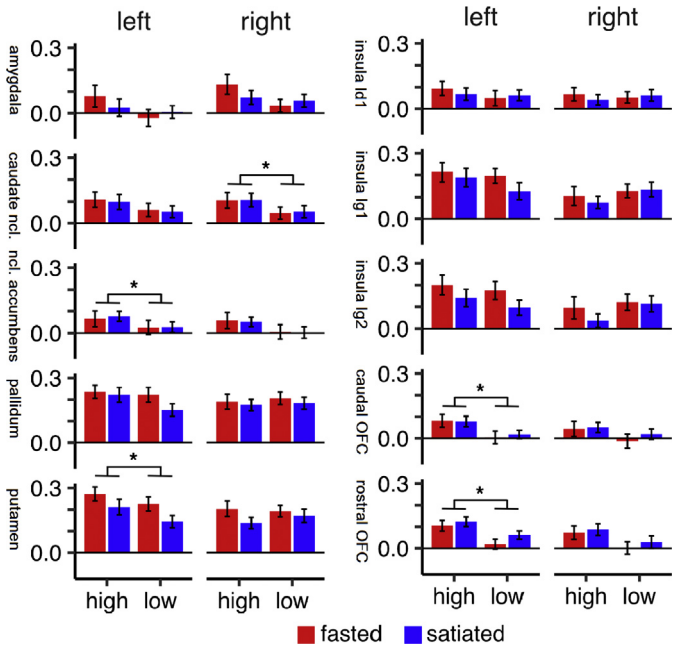

Fig. 4. Region of interest analysis. Depicted is the percent signal change in the different conditions per ROI. The significant effects are indicated for each bar graph ($p < 0.05$, Bonferroni corrected).

3. Results

3.1. Rating of food pictures

This analysis was performed to assess the behavioural changes in the participants in response to the fasting manipulation. Ratings differed significantly between the conditions (median fasting: 6; non-fasting: 4 $Z = -16.1$, $p < 0.001$, see Fig. 3 for histogram). Subjects were faster in the fasting condition (fasting 3313 ± 1094 ms; non-fasting 3574 ± 1208 ms, $t(22) = 2.6$, $p = 0.016$). 41 ratings (1.2%) were missing as subjects failed to respond and these ratings were therefore excluded from analysis.

3.2. fMRI Region of Interest

Significant clusters are defined with $p < 0.001$ (uncorrected) with a minimum cluster size of 10 voxels. The BOLD signal of two clusters differed significantly in between the fasting and the control condition (fasting > eating). These clusters are anatomically located bilaterally in the insula/operculum (Brodmann area 48). Details can be found in Table 1.

ROI analysis was performed to assess how brain activation changes in response to food stimuli and to fasting. A 2 (fasting vs. non-fasting) × 2 (low vs. high rating) factorial ANOVA was performed with the percent signal change values for every single ROI (Fig. 4). Bonferroni-corrected significant results were found for five ROIs for the main effect

Table 1
Statistical values for the fasting > eating analysis. Two clusters were found to be significantly different in between the conditions when applying a threshold of $p < 0.001$ and a minimal cluster size of 10 voxels.

Area	Brodmann area	Cluster size [mm^3]	Uncorrected *p*-value cluster	Peak z-value	Uncorrected *p*-value peak voxel	Coordinates x,y,z
Left insula/operculum	48	10,233	0.001	3.98	<0.001	−45, −18, 21
Right insula/operculum	48	4077	0.023	3.74	<0.001	42, 9, 15

Table 2
Significant results of multivariate multiple regression of the non-fasting condition with the endocrine AUC-values as predictors for the percent signal change activation of the ROIs.

Region of Interest	Endocrine parameter	β-coefficient	Standard error	T-value	*p*-Value
Left rostral OFC	Blood glucose	2.34E−04	1.10E−04	2.12	0.05
Right rostral OFC	Blood glucose	3.18E−04	1.50E−04	2.12	0.05

Table 3
Significant results of the multivariate multiple regression of the fasting condition with the endocrine AUC-values as predictors for the percent signal change activation of the ROIs.

Region of interest	Endocrine parameter	β-Coefficient	Standard error	T-value	*p*-Value
Left caudate nucleus	Adiponectin	7.83E−04	2.85E−04	2.74	0.014
Right caudate nucleus	Adiponectin	6.47E−04	3.03E−04	2.14	0.049
Left caudal OFC	Insulin	4.09E−04	1.88E−04	2.17	0.045
Right caudal OFC	Insulin	5.41E−04	1.91E−04	2.84	0.012
Right caudal OFC	C-peptide	−4.67E−02	2.11E−02	−2.22	0.042

rating including the right caudate nucleus (signal change low rating: 5%, high rating: 10.7%; $F(1,22) = 22$; $p < 0.001$; $\eta_p^2 = 0.5$), left NAcc (low rating: 2.6%, high rating: 7.1%; $F(1,22) = 12.35$; $p = 0.002$; $\eta_p^2 = 0.36$), left caudal OFC (low rating: 1.1%, high rating: 8%; $F(1,22) = 17.9$; $p < 0.001$; $\eta_p^2 = 0.45$), left rostral OFC (low rating: 4%, high rating: 11.4%; $F(1,22) = 23.2$; $p < 0.001$; $\eta_p^2 = 0.513$) and left putamen (low rating: 18.5%, high rating: 24.2%; $F(1,22) = 16.1$; $p = 0.001$; $\eta_p^2 = 0.422$). No other main effects or interactions were significant after correction for multiple testing.

3.3. Relationship between ROI activations and serum parameters

The following analyses were performed to get insight into the relationship between the fasting-related dynamics of hormonal/metabolic parameters and brain activations. A multivariate multiple linear regression was calculated for each condition with the percent signal change of the ROI as dependent variables and the AUC serum parameter values as independent variables. As an example, the time course of insulin and glucose serum levels is illustrated in Fig. 1B. Differences in hormone levels were found with repeated measure ANOVAs for insulin ($F(1,22) = 352.6$, $p < 0.001$), C-peptide ($F(1,22) = 306.8$, $p < 0.001$), serum glucose ($F(1,22) = 27.1$, $p < 0.001$ whereas no differences were found for adiponectin ($F(1,22) = 2.5$, $p = 0.13$), ACTH ($F(1,22) = 2.0$, $p < 0.17$) and cortisol ($F(1,22) = 0.05$, $p < 0.81$). In the non-fasting condition (Table 2) associations were mainly found between bilateral orbitofrontal regions with the AUC-values of blood glucose measurement before the fMRI. In the fasting condition adiponectin AUC-values were associated bilaterally with the caudate nucleus (Table 3 and Fig. 5). AUC-parameters of insulin were also associated bilaterally with orbitofrontal regions and the right orbitofrontal region was associated with the AUC of C-peptide levels during the experiment.

4. Discussion

The main purpose of the current study was to get first insights into the relationship of hormonal/metabolic parameters and brain activations during the processing of food stimuli. The novel aspect of the study is that natural variations of hormonal and metabolic parameters were induced by a fasting period and compared to conditions of regular food intake. The functionality of the experiment can for example be represented in the profound differences of insulin and glucose levels as illustrated in Fig. 1B. Multivariate regression analysis revealed associations between brain activity and hormonal/metabolic parameters for orbitofrontal regions and blood glucose levels in the non-fasting condition. Expectedly, more associations were found in the fasting condition: insulin levels were associated with fMRI signal

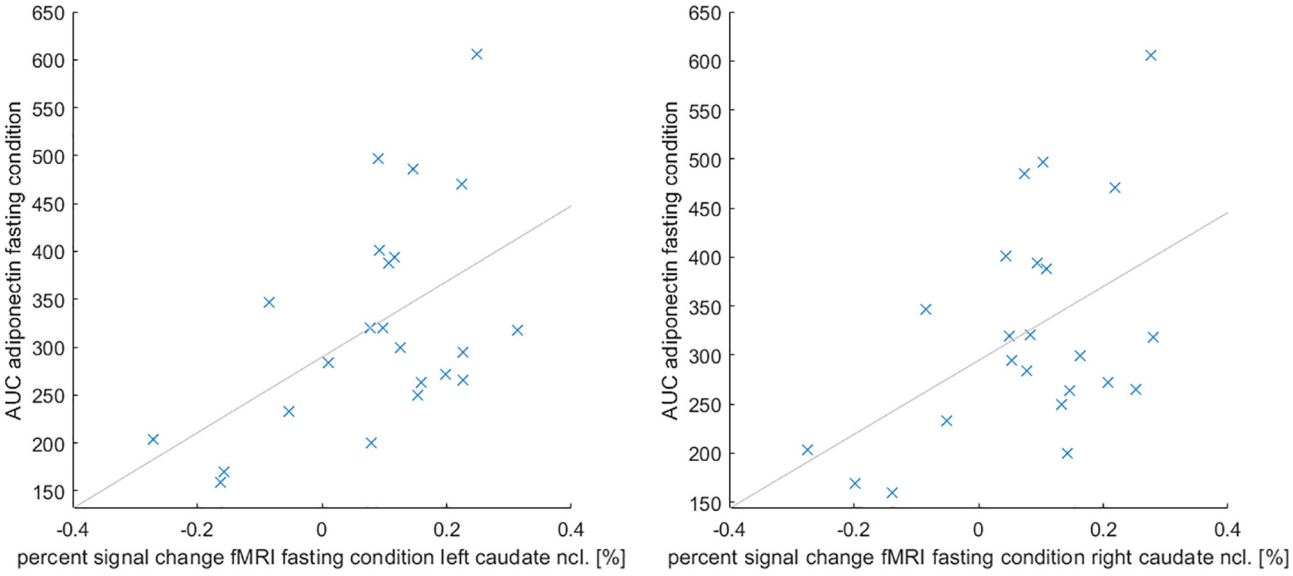

Fig. 5. Scatterplots showing the association of adiponectin and the caudate nucleus bilaterally in the fasting condition. The percent signal change is depicted in relation to the AUC of adiponectin and a line of best fit is added (least squares method) for visualising individual results of the regression analysis.

change in bilateral orbitofrontal cortex, whereas adiponectin levels were associated with activations in the left and right caudate nucleus. Finally, C-peptide levels were associated with food-related activity in right orbitofrontal regions.

Differences in the BOLD signal of the insula were found in the analysis fasting > control bilaterally in this study. Early studies exploring the activation of brain regions after a fasting intervention pointed out the significance of the insula in this context [58]. Later studies following the paradigm of fasting interventions found that the insula especially plays a role in rating processes of food cues [45]. This might be explained by the insula's role in generating salience [59]. These functions of the insula appear to demand more activity in a hungry state, supporting evidence for is potential role in food evaluation and ingestion. To increase statistical power for the fMRI-analysis we used a ROI based approach instead of a whole brain approach for the exploration of the connection between of hormonal/metabolic parameters and brain activations. Regions of interest were defined on the basis of previous studies that have investigated the processing of food items [48–50,53–55]. The statistical analysis revealed statistically significant effects for the factor rating (highly desirable vs. less desirable food items) for the right caudate nucleus, right nucleus accumbens, left putamen and left orbitofrontal cortex, i.e. regions that have been previously associated with the evaluation of items. Of note, the desirability ratings were significantly different between the fasting and non-fasting conditions which is in line with previous results [60]. Subjects rated food pictures also significantly faster in the fasting condition suggesting a heightened attention towards food in this condition [61,62]. For the fMRI analysis we performed a median split to ensure an equal number of stimuli in the two categories. Despite the overall higher desirability ratings of food stimuli, we did not obtain a stimulus category × metabolic state (fasting vs. non-fasting) interaction effect in the ROI analysis. One reason for this failure to find an interaction might be the composition of the stimulus materials. In an earlier study comparing patients with anorexia and healthy controls during the processing of visual stimuli in fasted and satiated states, we had employed pictures of objects and food items [63]. In this study, clear group × stimulus category × metabolic state interactions were observed. Thus, we argue that non-food control stimuli might have increased our ability to detect stimulus category × metabolic state interactions.

As stated above, the main purpose of the study was to reveal a relationship between brain activations and hormonal/metabolic parameters. This analysis revealed effects of insulin on the OFC. The OFC is concerned with the valuation of stimuli in general [64–67] and food in particular [68]. Suzuki et al. [68] found that food value is represented in patterns of neural activity in both medial and lateral parts of the OFC. It is interesting that insulin during the fasting condition modulated orbitofrontal brain responses to food items. Obviously, the valuation of food stimuli should be dependent on the metabolic state of an individual [69]. Insulin is a key signal for metabolic status and energy needs. While insulin receptors are abundantly expressed in prefrontal cortex [70–72], it remains unclear whether the modulating effect of insulin on orbitofrontal activity is due to a direct action or to an effect on upstream neural centres, e.g. in the hypothalamus; [71,73], which likewise express insulin receptors.

With regard to the modulating effect of adiponectin on brain activations in the left and right caudate nucleus it is important to note that adiponectin has been shown to bind and influence hypothalamic structures which in turn are functionally connected to other cortical and subcortical structures [45].

While this study thus suggests a modulation of brain activation related to ingestive behaviour by a number of hormonal/metabolic factors in a quasi-natural setting, i.e. without external application of hormones, it is important to note its limitations. First, the current approach is correlative. Therefore, further studies are needed to demonstrate a causal influence. Many other factors such as psychological or autonomous parameters may influence relevant brain areas under fasting conditions and take part in controlling their activity. Second, we only included male, healthy, normal weight subjects. Results in obese individuals might be different, as differences in brain activations to food items [46,74–77] and in hormonal levels [78–81] have been demonstrated repeatedly. Third, we have selected only a few hormones for the current study. As reviewed in Zanchi et al. [28] multiple further hormones related to ingestive behaviour have been shown to interact with brain function.

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We attest that this work has been approved by all co-authors.

Contribution statement

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Conceptualization, Data curation, Formal analysis, Investigation, Visualization, Writing – original draft, Writing – review & editing.

Jana Laupenmühlen
Data curation, Investigation, Writing – review.

Arkan Al-Zubaidi
Conceptualization, Investigation, Software, Writing – review.

Marcus Heldmann
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Kamila Jauch-Chara
Conceptualization, Formal analysis, Funding acquisition, Resources, Supervision, Writing – review & editing, Project administration.

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Declaration of Competing Interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.metabol.2019.06.014.

References

[1] Abarca-Gómez L, Abdeen ZA, Hamid ZA, Abu-Rmeileh NM, Acosta-Cazares B, Acuin C, et al. Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128·9 million children, adolescents, and adults. The Lancet 2017;390(10113):2627–42. https://doi.org/10.1016/S0140-6736(17)32129-3.
[2] Ng M, Fleming T, Robinson M, Thomson B, Graetz N. Global, regional and national prevalence of overweight and obesity in children and adults 1980–2013: a systematic analysis. Lancet 2014;384(9945):766–81. https://doi.org/10.1016/S0140-6736(14)60460-8.Global.
[3] Stevens GA, Singh GM, Lu Y, Danaei G, Lin JK, Finucane MM, et al. National, regional, and global trends in adult overweight and obesity prevalences. Popul Health Metr 2012;10(1):1. https://doi.org/10.1186/1478-7954-10-22.
[4] Anand BK, Brobeck JR. Hypothalamic control of food intake in rats and cats. Yale J Biol Med 1951;24(2):123–40.
[5] Hetherington AW, Ranson SW. Hypothalamic lesions and adiposity in the rat. Anat Rec 1940;78:149–72.
[6] Kenny PJ. Reward mechanisms in obesity: new insights and future directions. Neuron 2011;69(4):664–79. https://doi.org/10.1016/j.neuron.2011.02.016.
[7] Van Der Klaauw AA, Farooqi IS. The hunger genes: pathways to obesity. Cell 2015;161(1):119–32. https://doi.org/10.1016/j.cell.2015.03.008.
[8] Gralle M. Insulin in the brain IR signaling IR in Alzheimer's disease. J Neurochem 2017;140:359–67. https://doi.org/10.1111/jnc.13909.
[9] Thundyil J, Pavlovski D, Sobey CG, Arumugam TV. Adiponectin receptor signalling in the brain; 2012; 313–27. https://doi.org/10.1111/j.1476-5381.2011.01560.x.

[10] Weisz F, Piccinin S, Mango D, Ngomba RT, Mercuri NB, Nicoletti F, et al. The role of adiponectin receptors in the regulation of synaptic transmission in the hippocampus, (November 2016); 2017; 1–8. https://doi.org/10.1002/syn.21964.

[11] Gao Y, Tschöp MH, Luquet S. Hypothalamic tanycytes: gatekeepers to metabolic control. Cell Metab 2014;19:173–5. https://doi.org/10.1016/j.cmet.2014.01.008.

[12] Sarmento-cabral A, Peinado JR, Halliday LC, Malagon MM. Adipokines (leptin, adiponectin, resistin) differentially regulate all hormonal cell types in primary anterior pituitary cell cultures from two primate species. *Nature Publishing Group*; 2017; 1–13. https://doi.org/10.1038/srep43537 [January].

[13] Wada N, Hirako S, Takenoya F, Kageyama H. Leptin and its receptors. J Chem Neuroanat 2014;61–62:191–9. https://doi.org/10.1016/j.jchemneu.2014.09.002.

[14] Adachi A, Shimizu N, Oomura Y, Kobáshi M. Convergence of hepatoportal glucose-sensitive afferent signals to glucose-sensitive units within the nucleus of the solitary tract. Neurosci Lett 1984;46:215–8.

[15] Niijima A. Glucose-sensitive afferent nerve fibres in the hepatic branch of the vagus nerve in the guinea-pig. J Physiol 1982:315–23.

[16] Soty M, Gautier-stein A, Rajas F, Mithieux G. Perspective gut-brain glucose signaling in energy homeostasis. Cell Metab 2017;25(6):1231–42. https://doi.org/10.1016/j.cmet.2017.04.032.

[17] Guthoff M, Grichisch Y, Canova C, Tschritter O, Veit R, Hallschmid M, et al. Insulin modulates food-related activity in the central nervous system are there any sensitive and specific sex steroid markers for polycystic ovary syndrome?, *151*(September), 2456289; 2018.

[18] Kullmann S, Heni M, Veit R, Scheffler K, Machann J, Häring HU, et al. Intranasal insulin enhances brain functional connectivity mediating the relationship between adiposity and subjective feeling of hunger. Sci Rep 2017;7(1):1–10. https://doi.org/10.1038/s41598-017-01907-w.

[19] Tiedemann LJ, Schmid SM, Hettel J, Giesen K, Francke P, Büchel C, et al. Central insulin modulates food valuation via mesolimbic pathways. Nat Commun 2017;8(May):1–10. https://doi.org/10.1038/ncomms16052.

[20] Farooqi IS, Bullmore E, Keogh J, Gillard J, O'Rahilly S, Fletcher PC. Leptin regulates striatal regions and human eating behavior. Science (New York, NY) 2007;317(5843):1355. https://doi.org/10.1126/science.1144599.

[21] Hinkle W, Cordell M, Leibel R, Rosenbaum M, Hirsch J. Effects of reduced weight maintenance and leptin repletion on functional connectivity of the hypothalamus in obese humans. 2013;*8*(3). https://doi.org/10.1371/journal.pone.0059114.

[22] Kroemer NB, Wuttig F, Bidlingmaier M, Zimmermann US, Smolka MN. Nicotine enhances modulation of food-cue reactivity by leptin and ghrelin in the ventromedial prefrontal cortex; 2014; 832–44. https://doi.org/10.1111/adb.12167.

[23] Rosenbaum M, Sy M, Pavlovich K, Leibel RL, Hirsch J. Leptin reverses weight loss-induced changes in regional neural activity responses to visual food stimuli. J Clin Investig 2008;118(7):2583–91. https://doi.org/10.1172/JC135055.

[24] Heni M, Schöpfer P, Peter A, Sartorius T, Fritsche A, Synofzik M, et al. Evidence for altered transport of insulin across the blood-brain barrier in insulin-resistant humans. Acta Diabetol 2014;51(4):679–81. https://doi.org/10.1007/s00592-013-0546-y.

[25] Lennerz BS, Alsop DC, Holsen LM, Stern E, Rojas R, Ebbeling CB, et al. Effects of dietary glycemic index on brain regions related to reward and craving in men. 2013; 1–4(4):641–7. https://doi.org/10.3945/ajcn.113.064113.INTRODUCTION.

[26] Page KA, Seo D, Belfort-deaguiar R, Lacadie C, Dzuira J, Naik S, et al. Circulating glucose levels modulate neural control of desire for high-calorie foods in humans. 2011;*121*(10). https://doi.org/10.1172/JCI57873DS1.

[27] Purnell JQ, Klopfenstein B a, Stevens a a, Havel PJ, Adams SH, Dunn TN, et al. Brain functional magnetic resonance imaging response to glucose and fructose infusions in humans. Diabetes Obes Metab 2011;13(3):229–34. https://doi.org/10.1111/j.1463-1326.2010.01340.x.

[28] Zanchi D, Depoorter A, Egloff L, Haller S, M?hlmann L, Lang UE, et al. The impact of gut hormones on the neural circuit of appetite and satiety: a systematic review. Neuroscience & Biobehavioral Reviews 2017;80(June):457–75. https://doi.org/10.1016/j.neubiorev.2017.06.013.

[29] Austin J, Marks D. Hormonal regulators of appetite. International Journal of Pediatric Endocrinology 2009;2009:1–9. https://doi.org/10.1155/2009/141753.

[30] Batterham RL, Ffytche DH, Rosenthal JM, Zelaya FO, Barker GJ, Withers DJ, et al. PYY modulation of cortical and hypothalamic brain areas predicts feeding behaviour in humans. Nature 2007;450(7166):106–9. https://doi.org/10.1038/nature06212.

[31] De Silva A, Salem V, Long CJ, Makwana A, Newbould RD, Rabiner EA, et al. The gut hormones PYY 3-36 and GLP-1 7-36 amide reduce food intake and modulate brain activity in appetite centers in humans. Cell Metab 2011;14(5):700–6. https://doi.org/10.1016/j.cmet.2011.09.010.

[32] Van Bloemendaal L, IJzerman RG, Ten Kulve JS, Barkhof F, Konrad RJ, Drent ML, et al. GLP-1 receptor activation modulates appetite- and reward-related brain areas in humans. Diabetes 2014;63(12):4186–96. https://doi.org/10.2337/db14-0849.

[33] Guthoff M, Grichisch Y, Canova C, Tschritter O, Veit R, Hallschmid M, et al. Insulin modulates food-related activity in the central nervous system. J Clin Endocrinol Metab 2018;151:2456289.

[34] Betley JN, Cao ZFH, Ritola KD, Sternson SM. Parallel, redundant circuit organization for homeostatic control of feeding behavior. Cell 2013;155(6):1337–50. https://doi.org/10.1016/j.cell.2013.11.002.

[35] Chaurasia B, Summers SA. Ceramides - lipotoxic inducers of metabolic disorders. Trends Endocrinol Metab 2015;26(10):538–50. https://doi.org/10.1016/j.tem.2015.07.006.

[36] Holland WL, Miller RA, Wang ZV, Sun K, Barth BM, Bui HH, et al. Receptor-mediated activation of ceramidase activity initiates the pleiotropic actions of adiponectin. Nat Med 2011;17(1):55–63. https://doi.org/10.1038/nm.2277.

[37] Wang ZV, Scherer PE. Adiponectin, the past two decades. 2016;*8*:93–100.

[38] Psilopanagioti A, Papadaki H, Kranioti EF, Alexandrides TK, Varakis JN. Expression of adiponectin and adiponectin receptors in human pituitary gland and brain. Neuroendocrinology 2009;89(1):38–47. https://doi.org/10.1159/000151396.

[39] Qi Y, Takahashi N, Hileman SM, Patel HR, Berg AH, Pajvani UB, et al. Adiponectin acts in the brain to decrease body weight. Nat Med 2004;10(5):524–9. https://doi.org/10.1038/nm1029.

[40] Ukkola O, Santaniemi M. Adiponectin: a link between excess adiposity and associated comorbidities?; 2002; 696–702. https://doi.org/10.1007/s00109-002-0378-7.

[41] Ishibashi, K., Onishi, A., Fujiwara, Y., Ishiwata, K., & Ishii, K. (2017). Effects of glucose, insulin, and insulin resistance on cerebral 18F-FDG distribution in cognitively normal older subjects. PLoS ONE [Electronic Resource], 12 (7) no(e0181400), 1–12. https://doi.org/10.1371/journal.pone.0181400

[42] Labouèbe G, Liu S, Dias C, Zou H, Wong JCY, Karunakaran S, et al. Insulin induces long-term depression of ventral tegmental area dopamine neurons via endocannabinoids. Nat Neurosci 2013;16(3):300–8. https://doi.org/10.1038/nn.3321.

[43] LaBar KS, Gitelman D, Parrish T, Kim Y-H, Nobre AC, Mesulam M-M. Hunger selectively modulates corticolimbic activation to food stimuli in humans. Behav Neurosci 2001;115(2):493–500. https://doi.org/10.1037/0735-7044.115.2.493.

[44] Killgore WDS, Young AD, Femia LA, Bogorodzki P, Rogowska J, Yurgelun-Todd DA. Cortical and limbic activation during viewing of high- versus low-calorie foods. NeuroImage 2003;19(4):1381–94. https://doi.org/10.1016/S1053-8119(03)00191-5.

[45] De Silva A, Salem V, Matthews PM, Dhillo WS. The use of functional MRI to study appetite control in the CNS. Exp Diabetes Res 2012;2012. https://doi.org/10.1155/2012/764017.

[46] Porubská K, Veit R, Preissl H, Fritsche A, Birbaumer N. Subjective feeling of appetite modulates brain activity. An fMRI study. NeuroImage 2006;32(3):1273–80. https://doi.org/10.1016/j.neuroimage.2006.04.216.

[47] García-García I, Horstmann A, Jurado MA, Garolera M, Chaudhry SJ, Margulies DS, et al. Reward processing in obesity, substance addiction and non-substance addiction. Obes Rev 2014;15(11):853–69. https://doi.org/10.1111/obr.12221.

[48] Goldstone AP, Prechtl De Hernandez CG, Beaver JD, Muhammed K, Croese C, Bell G, et al. Fasting biases brain reward systems towards high-calorie foods. Eur J Neurosci 2009;30(8):1625–35. https://doi.org/10.1111/j.1460-9568.2009.06949.x.

[49] Pursey KM, Stanwell P, Callister RJ, Brain K, Collins CE, Burrows TL, et al. Neural responses to visual food cues according to weight status: a systematic review of functional magnetic resonance imaging studies; 2014. https://doi.org/10.3389/fnut.2014.00007.

[50] Tang DW, Fellows LK, Small DM, Dagher A. Food and drug cues activate similar brain regions: a meta-analysis of functional MRI studies. Physiol Behav 2012;106(3):317–24. https://doi.org/10.1016/j.physbeh.2012.03.009.

[51] Ashburner J, Friston KJ. Unified segmentation. Neuroimage 2005;26:839–51. https://doi.org/10.1016/j.neuroimage.2005.02.018.

[52] Gläscher J. Visualization of group inference data in functional neuroimaging. Neuroinformatics 2009;7:73–82.

[53] Brooks SJ, Cedernaes J, Schiö HB. Increased prefrontal and parahippocampal activation with reduced dorsolateral prefrontal and insular cortex activation to food images in obesity: a meta-analysis of fMRI studies. https://doi.org/10.1371/journal.pone.0060393; 2013.

[54] García-García I, Narberhaus A, Marqués-Iturria I, Garolera M, Rădoi A, Segura B, et al. Neural responses to visual food cues: insights from functional magnetic resonance imaging. Eur Eat Disord Rev 2013;21(2):89–98. https://doi.org/10.1002/erv.2216.

[55] Huerta CI, Sarkar PR, Duong TQ, Laird AR, Fox PT. Neural bases of food perception: coordinate-based meta-analyses of neuroimaging studies in multiple modalities. Obesity 2014;22(6):1439–46. https://doi.org/10.1002/oby.20659.

[56] Amunts, K., Zilles, K., & Evans, A. (2018). JuBrain Cytoarchitectonic Atlas Viewer. Retrieved October 6, 2018, from https://bigbrain.loris.ca/main.php

[57] Desikan RS, Ségonne F, Fischl B, Quinn BT, Dickerson BC, Blacker D, et al. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. NeuroImage 2006;31(3):968–80. https://doi.org/10.1016/j.neuroimage.2006.01.021.

[58] Simmons WK, Martin A, Barsalou LW. Pictures of appetizing foods activate gustatory cortices for taste and reward. Cereb Cortex 2005;15(10):1602–8. https://doi.org/10.1093/cercor/bhi038.

[59] Menon V, Uddin LQ. Saliency, switching, attention and control: a network model of insula function; 2010; 655–67. https://doi.org/10.1007/s00429-010-0262-0.

[60] Cameron JD, Goldfield GS, Finlayson G, Blundell JE, Doucet É. Fasting for 24 hours heightens reward from food and food-related cues. PLoS ONE 2014;9(1):1–8. https://doi.org/10.1371/journal.pone.0085970.

[61] Davidson GR, Giesbrecht T, Thomas AM, Kirkham TC. Pre- and postprandial variation in implicit attention to food images reflects appetite and sensory-specific satiety. Appetite 2018;125:24–31. https://doi.org/10.1016/j.appet.2018.01.028.

[62] Piech RM, Pastorino MT, Zald DH. All I saw was the cake. Hunger effects on attentional capture by visual food cues. Appetite 2010;54(3):579–82. https://doi.org/10.1016/j.appet.2009.11.003.

[63] Santel S, Baving L, Krauel K, Münte TF, Rotte M. Hunger and satiety in anorexia nervosa: fMRI during cognitive processing of food pictures; 2006; 4. https://doi.org/10.1016/j.brainres.2006.07.045.

[64] Mcginty VB, Rangel A, Newsome WT, Mcginty VB, Rangel A, Newsome WT. Orbitofrontal cortex value signals depend on fixation location during free viewing article orbitofrontal cortex value signals depend on fixation location during free viewing. Neuron 2016;90(6):1299–311. https://doi.org/10.1016/j.neuron.2016.04.045.

[65] Murray EA, Rudebeck PH. Specializations for reward-guided making in the primate ventral prefrontal cortex. Nat Rev Neurosci 2018;19(July). https://doi.org/10.1038/s41583-018-0013-4.

[66] Rudebeck, P. H., Saunders, R. C., Lundgren, D. A., Murray, E. A., Rudebeck, P. H., Saunders, R. C., … Murray, E. A. (2017). Specialized representations of value in the orbital and ventrolateral prefrontal cortex: desirability versus availability of outcomes article specialized representations of value in the orbital and ventrolateral prefrontal cortex: desirability versus availability of outcomes. Neuron, 95(5), 1208–1220.e5. https://doi.org/10.1016/j.neuron.2017.07.042.

[67] Winston XJS, Vlaev I, Seymour B, Chater XN, Dolan RJ. Relative valuation of pain in human orbitofrontal cortex 2014;34(44):14526–35. https://doi.org/10.1523/JNEUROSCI.1706-14.2014.
[68] Suzuki S, Cross L, Systems N. Elucidating the underlying components of food valuation in the human orbitofrontal cortex. Nature Neuroscience Neuroscience 2017;20(12):1780–6. https://doi.org/10.1038/s41593-017-0008-x.Elucidating.
[69] Roefs A, Franssen S, Jansen A. The dynamic nature of food reward processing in the brain 2018:*21*(6). https://doi.org/10.1097/MCO.0000000000000504.
[70] Abbott M, Wells DG, Fallon JR. The. Insulin receptor tyrosine kinase substrate p58/53 and the insulin receptor are components of CNS synapses 1999;19(17):7300–8.
[71] Hopkins DFC, Williams G. Insulin receptors are widely distributed in human brain and bind human and porcine insulin with equal affinity. Diabet Med 1997;14(12):1044–50. https://doi.org/10.1002/(SICI)1096-9136(199712)14:12<1044::AID-DIA508>3.0.CO;2-F.
[72] Wozniak M, Raizadai MK. Commentary the cellular and physiological actions of insulin in the central nervous system 1993;22(I):1–10.
[73] Havrankova J, Roth J, Brownstein M. Insulin receptors are widely distributed in the central nervous system of the rat. Nature 1978;272(5656):827–9. https://doi.org/10.1038/272827a0.
[74] Eldor R, Daniele G, Huerta C, Al-atrash M, Adams J, Defronzo R, et al. Discordance. Between central (brain) and pancreatic action of exenatide in lean and obese subjects 2016;39(October):1804–10. https://doi.org/10.2337/dc15-2706.
[75] Führer, D., Zysset, S., & Stumvoll, M. (2008). Brain activity in hunger and satiety: an exploratory visually stimulated FMRI study. Obesity (Silver Spring, Md.), 16(5), 945–950. https://doi.org/10.1038/oby.2008.33.
[76] Kullmann S, Heni M, Veit R, Scheffler K, Machmann J, Häring H-U, et al. Selective insulin resistance in homeostatic and cognitive control brain areas in overweight and obese adults. Diabetes Care 2015;38(June):1044–50. https://doi.org/10.2337/dc14-2319.
[77] Scharmüller W, Übel S, Ebner F, Schienle A. Appetite regulation during food cue exposure: a comparison of normal-weight and obese women. Neurosci Lett 2012;518(2):106–10. https://doi.org/10.1016/j.neulet.2012.04.063.
[78] Chang C, Jian D, Lin M, Zhao J, Ho L. Evidence in obese children: contribution of, 1–13; 2015. https://doi.org/10.1371/journal.pone.0125935.
[79] Haluzík M, Matoulek M, Hilgertova J, Haas T. The influence of short-term fasting on serum leptin levels, and selected hormonal and metabolic parameters in morbidly obese and lean females. Endocr Res 2001;27(1-2):251–60.
[80] Mishra S, Gupta V, Mishra S, Sachan R, Asthana A. Serum level of orexin-A, leptin , adiponectin and insulin in north Indian obese women. Diabetes Metab Syndr Clin Res Rev 2017;11:S1041–3. https://doi.org/10.1016/j.dsx.2017.07.037.
[81] Segal KR, Landt M, Klein S. Relationship between insulin sensitivity and plasma leptin concentration in lean and obese men 1996;45(July):6–9.