Brain activations show association with subsequent endocrine responses to oral glucose challenge in a satiation-level dependent manner

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ABSTRACT
Aims: The communication between brain and peripheral homeostatic systems is a central element of ingestive control. We set out to explore which parts of the brain have strong functional connections to peripheral signalling molecules in a physiological context. It was hypothesised that associations can be found between endocrine response to glucose ingestion and preceding brain activity in dependence of the nutritional status of the body.

Materials and methods: Young, healthy male participants underwent both a 38 h fasting and a control condition with standardized meals. On the second day of the experiment, participants underwent fMRI scanning followed by ingestion of glucose solution in both conditions. Subsequent endocrine responses relevant to energy metabolism were assessed. Associations between preceding brain activation and endocrine responses were examined.

Results: In both fasting and non-fasting conditions, brain activity was associated with subsequent endocrine responses after glucose administration, but relevant brain areas differed substantially between the conditions. In the fasting condition relations between the caudate nucleus and the orbitofrontal regions with insulin and C-peptide were prevailing, whereas in the non-fasting condition associations between various brain regions and adiponectin and cortisol were the predominant significant outcome.

Conclusion: Connections between endocrine response following a glucose challenge and prior brain activity suggests that the brain is playing an active role in the networks regulating food intake and associated endocrine signals. Further studies are needed to demonstrate causation.

The type and amount of food individuals consume is influenced by the activity of dedicated centres in the central nervous system (CNS). These are in turn influenced by and act through endocrine signalling pathways; as well as the general metabolic situation and energy status of the individual [1–5]. Energy intake relies on the hypothalamic homeostatic systems [6,7] as well as a more extended system involving other cortical and subcortical structures which integrate reward-related processes [8, 9]. The brain thus plays a central regulatory role in food intake control and in mental and metabolic conditions in which ingestive control is dysregulated.

The link between activity in different brain regions and endocrine responses during and after food intake has been minimally explored, although it is known that brain activity is responsive to peripheral signalling. A number of previous studies have successfully explored the effects of administration of endocrine substances such as leptin, adiponectin, insulin, glucose, GLP-1, ghrelin and peptide YY [1,5,10–18]. These studies helped to establish a causal relationship between the administered hormone and brain activity. However, studies that artificially administer biologically active substances might be criticized as the dosages may exceed those physiological levels. Furthermore simplistic linear approaches investigating isolated effects of endocrine messenger substances might not correspond to complex, physiological realities of...
endocrine-neural crosstalk [9].

In the current study we therefore investigated brain activation in relation to physiological changes in subsequent endocrine responses. An understanding of endocrine responses to ingestion of high-energy foods, in this experiment glucose, is of vital importance to understanding the physiology behind food intake, and by extension the pathophysiology behind a wide variety of mental and metabolic conditions associated with dysregulated food intake. Glucose is of particular importance as it is the primary energy source of the brain and has been found to alter fMRI signalling in different cortical regions [1–4]. To be able to study the response on glucose ingestion as a central factor in energy metabolism we focussed this analysis on hormones with strong links to glucose metabolism (insulin, C-peptide, cortisol, ACTH). Because of the central importance of adipokines in discoveries of brain-endocrine crosslinks [3], and its unique role in glucose metabolism [19], adiponectin was also added to the analysis.

A recent study by Opstal et al. showed evidence that glucose ingestion is associated with decreased BOLD activity in insula, thalamus, anterior cingulate gyrus, orbitofrontal cortex, amygdala, hippocampus and occipital cortex [20]. The authors suggested at the same time that brain activity modulating effects may be conveyed by insulin levels. However, no quantification of individual associations between brain activation and endocrine levels were provided. Similarly, studies have found activity attenuating effects of insulin administration in occipital, prefrontal cortical regions, the hypothalamus, while a responsiveness to insulin was also identified by some studies for striatal regions, the insula cortex and the cingulate cortices [21]. Individual associations are typically not reported in relevant studies, with some exceptions such as Heni et al. reporting significant negative associations between insulin increases in insulin and brain responses after glucose ingestions in the prefrontal and parietal cortex (inferior frontal gyrus, middle frontal gyrus, cingulate gyrus and inferior parietal gyrus). If associations with hormone levels after glucose administration also exist with brain activity measured prior to glucose administration and if these effects differ generally in their direction has not been sufficiently investigated. Furthermore, if these effects are similar in fasted and non-fasted individuals, or if they are strengthened in fasted individuals or essentially different has not been elucidated in controlled experiments. It has been shown previously that restrictive diets have a significant effect on cerebral activity [22]. Such effects have since then been shown for resting state imaging [10,23,24] and food image stimulated whole brain activation patterns [25,26]. The latter typically result in increased activation of insular and orbitofrontal cortices [27].

It is known that the brain networks regulating both hunger and satiety interact with cortical and subcortical brain systems, such as those involved in reward processing and attention [3,12]. Some brain areas, including the hippocampus, ventromedial prefrontal cortex, amygdala, parahippocampal gyrus and fusiform gyrus are also known to be influenced by the presentation of visual food cues [28,29]. Furthermore, the insula appears to respond to food-related visual cues and this response is modulated by the level of satiety [26,27]. Basal ganglia such as the striatum have also been found to interact with endocrine signalling pathways [3]. Based on these previous results and a literature review of fMRI studies addressing food intake and fasting [30–35], the current study followed a regions of interest (ROIs) approach, investigating changes of activity in the amygdala, caudate nucleus, insula (3 different regions), nucleus accumbens (NAcc), orbitofrontal cortex (OFC, 2 different regions), pallidum and the putamen.

In a previous companion study [4,36] we demonstrated that endocrine responses in different levels of satiety were associated with subsequent brain activity. In this previous study, associations were shown for blood glucose levels in the non-fasting condition and subsequent activation patterns in orbitofrontal regions. In the fasting condition associations between adiponectin and subsequent activation in the caudate nucleus and associations between insulin and C-peptide levels and orbitofrontal regions were found [4]. The present study rather explores the possibility of associations between brain activity obtained prior to a glucose challenge and the endocrine responses following this challenge in fasting and non-fasting states (see Fig. 1). Several theories have addressed the interplay between brain and endocrine system and have placed the brain in a central regulatory position controlling food intake by modulating peripheral endocrine signals [37,38]. As an example, for such central-to-peripheral control, a study by Heni et al. [39] found that transnasally administered insulin not only modulated activity in specific brain areas, e.g. the hypothalamus, but also regulated peripheral insulin sensitivity in a time-dependent fashion.

For this study, it was hypothesised that there are significant associations between endocrine markers and central regions of interest both selectively chosen based on previous studies. These associations have predominantly been shown as non-quantitative effects after a certain intervention. This experiment investigated associations of the linear combinations of endocrine responses to oral glucose with the prior brain activity.

1. Methods

1.1. Participants

All 24 participants were healthy males with normal body weight and no known metabolic disease (mean age [SD] 24.3 [1.3] years; mean BMI [SD] 23.4 [1.4] kg/m²) and eugonadal. The participants underwent a physical examination and a medical history prior to acceptance into the study. Exclusion criteria included self-reported chronic or acute medical illness, use of regular medications, use of recreational drugs, abnormal sleep-wake cycles (shift worker), engagement in high performance sport (>12 h/week), specific diets (vegan, vegetarian etc.) or abnormal eating behaviour, cigarette smoking or more than 5 standard alcoholic drinks per week (>50g alcohol/week). Participants were asked not to engage in vigorous exercise or drink alcohol 24 h prior to the study and not to drink alcohol excessively and sleep in a regular rhythm in general during participation in the study. All subjects provided written informed consent. The study abided by the declaration of Helsinki and was approved by the Ethics Committee of the University of Lübeck.

The sample size was determined from prior pilot studies as well as previous research comparing metabolic states and brain activity [1,4,34,36]. One participant had to be removed from the study due to movement artefacts on the fMRI imaging.

1.2. Experimental setting

All participants underwent two conditions which were separated by seven days: a fasting condition (no caloric intake for 38 h) and a non-fasting condition involving standardised meals at set times consisting of certain ratios of protein (P), fat (F) and carbohydrate (C). The participants were randomised into whether they initiated with the fasting or non-fasting condition. The sample size was determined from prior pilot studies as well as previous research comparing metabolic states and brain activity [1,4,34,36]. One participant had to be removed from the study due to movement artefacts on the fMRI imaging.
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.

1.7. Statistics and fMRI analysis

Matlab R2015b, SPSS 22, Python 3 and R 0.99.902 were used for data analysis. A multivariate multiple regression analysis was performed to investigate associations between percent signal change of the 10 bilateral ROIs (dependent variables) and the serum hormonal area under the curves (AUC, independent variables). AUC values were used to represent the level of activity of individual hormones across the condition given the high level of standardisation in food intake and experiment timing. Hormone data have been described previously in detail [4], the data was made available in a separate publication [4,36].

fMRI data was analysed using SPM 8 (Wellcome Trust Centre for Neuroimaging, UCL, UK). Preprocessing of the functional data included slice time correction with Fourier phase shift interpolation, 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 [4]. Functional images were spatially normalized to MNI space by applying the normalization parameters of the structural DARTEL normalization procedure to the functional data. Finally, functional data was smoothed with an 8 mm full width at half maximum (FWHM) Gaussian kernel and then analysed in a comparative fasting N control paradigm. A general linear model was used for the two conditions with the SPM 8 canonical hemodynamic response function, restricted maximum likelihood and an additional regressors for movement artefacts. Percent signal change values were calculated with the function Rfxplot for SPM8 with Matlab 2015b [42].

2. Results

2.1. Relationship between post-glucose serum parameters and ROI activations before glucose consumption

The multivariate multiple linear regression revealed statistically significant associations between the endocrine responses following oral glucose administration and the preceding brain activity. Detailed results including directionality of the associations can be found in Table 1 and Table 2 and visualised examples of significant associations as plots in Fig. 2 and Fig. 3. In the fasting condition of the present study, associations were found between the orbitofrontal regions and the caudate nuclei with insulin (positive association) and C-peptide (negative).
demonstrated in non-physiological settings i.e. by artifical stimulation, and that these associations differ between fasting and non-fasting conditions. It was hypothesised that brain activity would be increased in the right amygdala, left caudate nucleus, right caudate nucleus, left rostral OFC, right rostral OFC, and left pallidum as a result of glucose consumption. Overall 10 regression equations were fitted for brain regions of each hemisphere. Associations were reported if the likelihood of their existence by chance only was below 5%, if the p-value was below 0.01 associations are labelled as highly significant with **.

### Table 1

| Region of Interest | Endocrine Parameter | β-coefficient | Standard error | T-value | p-value |
|--------------------|---------------------|---------------|----------------|---------|---------|
| right amygdala     | ACTH                | -3.32E-02     | 1.25E-02       | -2.66   | 0.017   |
| left caudate nucleus| insulin             | 2.77E-04      | 1.08E-04       | 2.56    | 0.021   |
| left caudate nucleus| C-peptide           | -6.07E-02     | 2.80E-02       | -2.17   | 0.046   |
| right caudate nucleus| insulin         | 2.92E-04      | 1.04E-04       | 2.80    | 0.013   |
| left caudal OFC    | insulin             | 2.92E-04      | 8.13E-05       | 3.59    | 0.002** |
| left caudal OFC    | C-peptide           | -5.46E-02     | 2.11E-02       | -2.58   | 0.020   |
| left caudal OFC    | insulin             | 3.35E-04      | 9.85E-05       | 3.40    | 0.004** |
| left caudal OFC    | C-peptide           | -5.63E-02     | 2.56E-02       | -2.20   | 0.043   |
| left rostral OFC   | insulin             | 1.73E-04      | 7.55E-05       | 2.29    | 0.036   |
| right rostral OFC  | insulin             | 2.01E-04      | 8.84E-05       | 2.28    | 0.037   |
| left pallidum      | ACTH                | -2.56E-02     | 1.17E-02       | -2.19   | 0.044   |

Additionally, the activity in the right amygdala and the left pallidum was found to be associated with ACTH (negative). In the non-fasting condition, cortisol levels were significantly associated with an activity in the caudate nucleus, insula, nucleus accumbens, orbitofrontal regions, pallidum and putamen (positive). Adiponectin was associated with preceding activity in the insula, pallidum and putamen (positive). Prior activity within the right pallidum and putamen was associated with ACTH levels (negative), and left caudal nucleus activity with C-peptide levels (positive). Results from ratings of images during the fMRI measurements have been reported previously [4,25].

### 3. Discussion

In both conditions, fasting and non-fasting, activations of relevant brain regions obtained prior to glucose administration were found to be significantly associated with endocrine responses after glucose consumption. This underlines the close link between peripheral endocrine signalling and central activity and supports the hypothesis of this study that there are observable associations between the measured hormones and brain centres.

The present study followed a different approach compared to Heni et al. [39] in that the spontaneous brain activity in fasting and non-fasting states was measured and used to predict endocrine responses, i.e. insulin, C-peptide, cortisol, adrenocorticotropic hormone (ACTH), serum glucose and adiponectin, to a subsequent glucose challenge in the aforementioned ROIs. It was hypothesised that brain activity would be reliably related to endocrine response following the glucose ingestion and that these associations differ between fasting and non-fasting conditions.

In the fasting condition, orbitofrontal regions and the caudate nucleus were predominantly associated with insulin and C-peptide. The link between insulin and activity of similar brain regions has previously been demonstrated in non-physiological settings i.e. by artificial administration of the hormone [11,43]. These studies have found that exposing the CNS directly to insulin modulates brain activity. Another study suggested that this exposition of the brain to peripheral signalling substances might also affect peripheral hormone release [39]. In this particular study by Heni et al., only insulin was nasally administered, and C-peptide and insulin measured peripherally. Direct effect of nasally absorbed insulin into the blood circulation could therefore be differentiated from other pathways, including a potential centrally modulating effect of insulin on the peripheral production of C-peptide. Following this interpretation of existing data, peripheral hormones might influence brain activity in various sites, which in turn could have a modulating effect on peripheral release of such signalling substances. Potential associations of CNS activity and insulin release may in turn influence glucose tolerance, underscoring the potential clinical significance of these findings. Previous findings indicating an association between insulin administration and central activity [21] are supported by these findings. Interestingly, brain activation measured prior to glucose administration showed a positive association with the corresponding significant brain centres, while C-peptide showed a negative correlation. While our study was not designed and is not powered sufficiently to explore these effects in more...
detail and perform interaction analysis, this may be an interesting focus for future research.

In the non-fasting condition, associations were found for the activation of a wide variety of the selected brain regions with adiponectin and cortisol. This pattern of associations differs substantially from the pattern we measured in the fasting condition. This difference in patterns of associations between the nutritional statuses may indicate a dependency of these effects on the energy status of the body. The hormones involved in these associations are insufficiently investigated regarding their role in brain activation in the context of food intake. The distinctly different pattern of hormones and brain centres involved in these associations may be considered as hypothesis generating work: Brain networks regulating hunger and salience and the peripheral endocrine signals they are majorly influenced by during hunger may differ substantially. This supports our hypothesis that the interacting networks we found in this study are profoundly different for a fasting and non-fasting status.

While the associations found in this present study cannot assumed to have a causative role of the brain activations in the modulation of post-glucose endocrine responses, they underscore the close link between both systems. Our findings are in line with theories highlighting the brain as a central coordinator in energy metabolism [37,38,49].

Another limitation of this study is the lack of non-food related control images, which would have allowed to contrast the brain activation with food related activation. While ROIs where specifically chosen because they are associated with food reward processing and perception in the literature, this lack of control means activation of brain centres may be driven in parts by unspecific responses to displayed images. Another limitation is that exclusion criteria were only checked with a medical examination and history. Handedness was not taken into account in this analysis. Furthermore, since we are reporting associations with a p-value of less than 0.05 the possibility of false-positive and false-negative results needs to be taken into account when interpreting these results. This study only looked at young healthy man, which results in limited potential to extrapolate the results on the general population. Future studies are needed to validate these results in female subjects, populations of different age groups and diseased populations such as those with diabetes type 2, obesity, varying psychological states like depression, anxiety, addiction and eating disorders.

Fig. 2. Scatterplots showing the association of insulin post glucose consumption and the caudate nucleus and OFC bilaterally in the fasting condition prior to glucose consumption. The percent signal change is depicted in relation to the AUC of cortisol and a line of best fit is added (least squares method) for visualizing individual results of the regression analysis.
Fig. 3. Scatterplots showing the association of cortisol post glucose consumption and the OFC and insula bilaterally in the control condition prior to glucose consumption. The percent signal change is depicted in relation to the AUC of cortisol and a line of best fit is added (least squares method) for visualizing individual results of the regression analysis.
Further research is needed to identify links between CNS and peripheral signalling substances involved in food intake control and glucose metabolism. Evidence demonstrating activity of glucose metabolism regulating hormones and adiponectin such as Heni et al. [39] in the context of recent research showing functional activity of corresponding receptors in the brain [46, 47] may indicate a direct modulating effect of such hormones on central centres. In the context of this study, this may indicate that the general endocrine “climate” influences higher central nervous activities which may in turn have a direct influence on hunger, mood and emotional control.

As pointed out above, these correlational models infer no causation or clear directionality of the results. We therefore propose to replicate the current findings and to employ Structural equation modelling (SEM) that allows to reveal causal relationships between different variables. A recent example of the application of SEM to the interaction of brain responses and hormones has examined to interplay of cortisol and hippocampal-extrastriate functional connectivity during visuospatial retrieval [48]. This study investigated associations of peripheral glucose metabolism regulating hormones and adiponectin after administration of oral glucose and fMRI activation previous to glucose loading. The discussed open questions notwithstanding, a reciprocal relationship between peripheral endocrine signals and CNS activity under physiological conditions is strongly suggested by the current set of data. This supports similar results derived of experiments administering hormones. Furthermore, this study indicates that functionally networks between brain regions and endocrine signalling substances involved in food intake control may differ substantially between hunger and satiated conditions. This results require replication and further exploration by future studies, looking into causal links and participants with different demographic backgrounds.

**Statement of ethics**

All subjects provided written informed consent. The study abided by the declaration of Helsinki and was approved by the Ethics Committee of the University of Lübeck (reference: 13–108).

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**Author Contributions**

Janis Marc Nolde; Conceptualization, Data curation, Formal analysis, Investigation, Visualization, Writing – original draft, Writing – review & editing

Sophia G Connor; Formal analysis, Writing – original draft, Writing – review & editing

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**Declaration of competing interest**

Declarations of interest: none.

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