Psychoneuroendocrinology 99 (2019) 154–165

Contents lists available at ScienceDirect

Psychoneuroendocrinology

journal homepage: www.elsevier.com/locate/psyneuen

The corticosteroid prednisolone increases amygdala and insula reactivity to food approach signals in healthy young men

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ARTICLE INFO

Keywords:
Prednisolone
Corticosteroids
Glucocorticoids
Amygdala
Insula
Limbic
Food
Approach
Motor
Prednisolone
fMRI
Neuroimaging

ABSTRACT

Short- and long-term treatment with glucocorticoids is widely used in clinical practice and frequently induces features of iatrogenic Cushing syndrome, such as abdominally centered weight gain. Despite decades of glucocorticoids usage, the mechanisms underlying these side effects are still only partly understood. One possibility is that glucocorticoids impact subcortical (hypothalamus, amygdala, insula) and cortical (orbitofrontal and cingulate cortex) brain regions involved in appetite regulation and reward processing. In the present study, we used functional magnetic resonance imaging (fMRI) to study the acute effects of a prednisolone infusion on reactivity of brain reward systems to food stimuli. Twenty healthy normal-weight men were tested in a randomized, double-blind, cross-over study. After an overnight fast and infusion of either 250 mg prednisolone or placebo (always administered between 8 and 9 A M), fMRI scans were taken while presenting food and object pictures in a Go/NoGo (GNG) task. At home, participants were asked to register what they had eaten. On the following morning they came back to the lab and had a supervised *ad libitum* breakfast at a standardized buffet. Food-Go in contrast to Object-Go pictures yielded increased blood oxygen level dependent (BOLD) activity in hippocampus, amygdala, orbitofrontal cortex, insula and anterior cingulate cortex. Prednisolone increased activation in the bilateral amygdala and right insula for approach-associated food pictures. The buffet test did not reveal significant differences in calorie consumption or preferences of different macronutrients. However, prednisolone-induced insula reactivity to Food-Go images was associated with greater caloric intake, both at home and in the standardized buffet. In sum, we observed a specific effect of prednisolone on the BOLD response of the amygdala and insula to approach-associated food stimuli. As these brain areas have previously been implicated in hedonic eating, the present pattern of results may reflect an increased anticipated reward value of food modulated by glucocorticoids. These effects might potentially drive increased food intake and weight gain under prolonged glucocorticoid treatment.

1. Introduction

Short and long-term treatment with corticosteroids is extensively used in clinical contexts. Their chronic application not only elicits the well-documented positive responses on therapeutic targets but frequently induces features of iatrogenic Cushing syndrome. One of these features is abdominally centered weight gain accompanied by symptoms of metabolic syndrome like hypertension and insulin resistance. These unwanted effects vary depending on the dose and on the individual's sensitivity to glucocorticoids. This pattern is exemplified by a study on long-term side effects of prednisolone in patients with rheumatoid arthritis (Wassenberg et al., 2005). Symptoms and signs of Cushing syndrome varied considerably between individuals, but were observed in particularly sensitive patients already at a daily dose as low as 5 mg. Among these unwanted effects, the development of visceral obesity is of special importance and contributes to features of the metabolic syndrome. Abdominal weight gain has as well been described in patients treated with glucocorticoids for several diseases. The effect is occasionally therapeutically used in cancer patients who suffered from cancer-associated loss of appetite and cachexia. A similar orexigenic effect of glucocorticoids has also been demonstrated in healthy participants. For instance, in short-term clinical studies in healthy individuals, Tataranni et al. indicated an increased food intake and higher weight gain following therapy with dexamethasone compared to placebo (Tataranni et al., 1996). Similarly, low dose corticotropin-releasing hormone-test in healthy participants led to enhanced appetite

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https://doi.org/10.1016/j.psyneuen.2018.09.007
Received 20 November 2017; Received in revised form 6 September 2018; Accepted 7 September 2018

relative to placebo. Peak cortisol levels directly correlated with caloric intake of these subjects (George et al., 2010).

The mechanisms underlying these effects of glucocorticoids are still only partially understood. Animal studies suggest that some of these effects are directly mediated via hypothalamic centers which have been shown to play a central role in the regulation of energy balance and food intake. They serve as targets for peripheral cues modulating food intake and energy homeostasis, such as the food-regulating hormones leptin, insulin, ghrelin, adiponectin and/or glucagon-like peptide-1 (GLP-1; Morton et al., 2014). In addition, glucocorticoids are thought to modulate not only hunger and energy homeostasis, but also hedonic eating, i.e. the response to palatable food regardless of energetic imbalances. To gain insight into this regulation, a study in humans tested whether glucocorticoids could influence the startle eye blink response while viewing food pictures (Ferreira de Sá et al., 2014). The startle eye blink is measured as the contraction of ocular musculature in response to sudden, intense sound bursts, and the magnitude of this reaction is modulated by the motivational value of visual stimuli presented before or during the tone. In the context of food processing, the startle reflex is potentiated in response to food relative to non-food pictures when subjects are in a food-deprived state, and this effect correlates with increased hunger ratings (Ferreira et al., 2013). Ferreira de Sá et al. showed an enhancement of the startle response after application of prednisolone in contrast to placebo when volunteers were exposed to pictures of high-glycemic food (Ferreira de Sá et al., 2014). No such drug-dependent difference was seen during the presentation of low-glycemic or neutral food pictures. Comparably, Epel et al. reported enhanced preference for sweet food in participants with stress-induced increases of cortisol levels (Epel et al., 2001). These data point towards a specific effect of glucocorticoids on the anticipation and processing of high-glycemic food. Retrospective data from patients with endogenous glucocorticoid excess due to Cushing's disease support this finding as craving for sweet and savory food was significantly reduced after successful therapy (Geer et al., 2016). Currently, it is unclear which pathways are involved in this regulation, and the brain centers mediating glucocorticoid effects on hedonic eating are elusive. In contrast, numerous studies have demonstrated that brain areas related to the reward system are activated by food cues. This includes the amygdala, hippocampus, striatum, insula, anterior cingulate cortex and orbitofrontal cortex (Schur et al., 2009). Previous imaging studies have already shown that hormones regulating food intake are potent modulators of activity in this brain areas, including ghrelin (Malik et al., 2008), GLP-1 (van Bloemendaal et al., 2015) and insulin (Wallner-Liebmann et al., 2010). While comparable studies for glucocorticoids are missing, Montoya et. al. investigated food-unrelated reward processing using an incentive monetary delay task (Montoya et al., 2014). They observed attenuated activity in the striatum and the amygdala after oral administration of hydrocortisone in contrast to placebo. Kinner et. al. used a similar task but could confirm this result only for male participants while female participants showed increased activity in reward related brain areas after application of hydrocortisone in contrast to placebo (Kinner et al., 2016).

Nevertheless, in these studies, glucocorticoids were administered one hour before scanning, thus presumably tapping into their fast, non-genomic effects. These non-genomic effects were also demonstrated by Strelzyk et al. who reported a decrease of global brain activity in a resting state EEG analysis within 20 min after cortisol administration, suggesting a global desensitization of the brain. Another experiment revealed decreased perfusion of the bilateral thalamus within the first 10 min after cortisol infusion (Strelzyk et al., 2012). In contrast, less is known regarding the slow, genomic effects of glucocorticoids, which are thought to be responsible for most of its clinical repercussions (Kadmiel and Cidlowski, 2013). Some evidence suggests that these slower effects actually result in *increased* neural reactivity to salient stimuli (Henckens et al., 2010). Moreover, although prednisolone and other synthetic glucocorticoids are chemcially comparable to natural glucocorticoids, their pharmacokinetic and pharmacodynamic properties differ. For instance, prednisolone has a higher glucocorticoid relative to mineralocorticoid receptor affinity. Hence, it is clinically relevant to know to which extent natural and synthetic glucocorticoids have comparable effects on the neural processing of aliments.

In the present study, we aimed to characterize the effects of the glucocorticoid prednisolone on eating behavior and the neural response to food stimuli. To that end, we used a Go/NoGo paradigm in which food cues served either as approach or avoidance signals, since brain activation in simple passive viewing tasks might be confounded by participants' own attitudes towards food (Smeets et al., 2013). Furthermore, such a paradigm permits to link neural responses to food with impulsivity, a key factor in the voluntary control of eating behavior (Veling et al., 2017). We hypothesized that the application of prednisolone would lead to an increased activity of reward-related brain areas when stimulated by food approach cues. We also expected that prednisolone would induce stronger approach behavior to food signals in the task and an increased food intake within 24 h after the administration. In addition, we expected prednisolone effects to be generally stronger for sweet relative to savory food, as has been observed in previous studies (Ferreira de Sá et al., 2014). Finally, we also tested whether prednisolone had general effects on motor execution and inhibition in an exploratory fashion, given that previous studies suggest that glucocorticoids can impact executive function (Schlosser et al., 2013; Shi et al., 2018).

2. Material and methods

2.1. Participants

Twenty-two healthy young male volunteers were recruited for the study, but two participants had to be excluded from further analyses due to scanning artefacts caused by excessive head movements (i.e. above 3 mm in any direction). This left a final sample of 20 subjects. We restricted the study to males to avoid any sex-steroid dependent interaction. Participants were homogeneous regarding age (mean 24.6 years, range 20–33), body-mass index (BMI; mean 22.9 kg/m^2, range 18.6–25.5 kg/m^2), self-reported handedness (all right handed), and fluent in German. We measured glycated hemoglobin (HbA1C) to ensure that participants did not have diabetes or insulin resistance, since insulin is known to modulate neuronal response to food cues (Wallner-Liebmann et al., 2010). All participants had HbA1C parameters within the normal range (mean 5.3%, range 4.6–5.6%). This study was approved by the University of Lübeck Ethics Committee and was performed in accordance with the declaration of Helsinki. Written informed consent was obtained from all participants, who were compensated for participation.

2.2. Procedure

The study was conducted as a double-blinded, placebo controlled cross-over trial. All participants were tested two times with a minimum of four weeks between recordings. They received an infusion of 100 ml saline containing 250 mg prednisolone (Pred) or saline alone (Plac) in random, counterbalanced order. Infusions were prepared by an independent medical professional not directly involved in the measurements. Participants were tested in the morning between 8 a.m. and 9 a.m. following an overnight fast. We first infused the medication within 10 min and subsequently the participants received a standardized cheese sandwich. Following this small breakfast snack, the volunteers filled in a 10 cm visual analogue scale (VAS) of 8 items (active, passive, calm, restless, awake, sleepy, dizzy and sick). After a fixed four hour waiting period, participants were transferred to the scanner room, where they underwent a standardized pre-scan questionnaire and repeated the initial visual analogue scale. This four hour interval is sufficient for central effects of prednisolone to take place, as previously

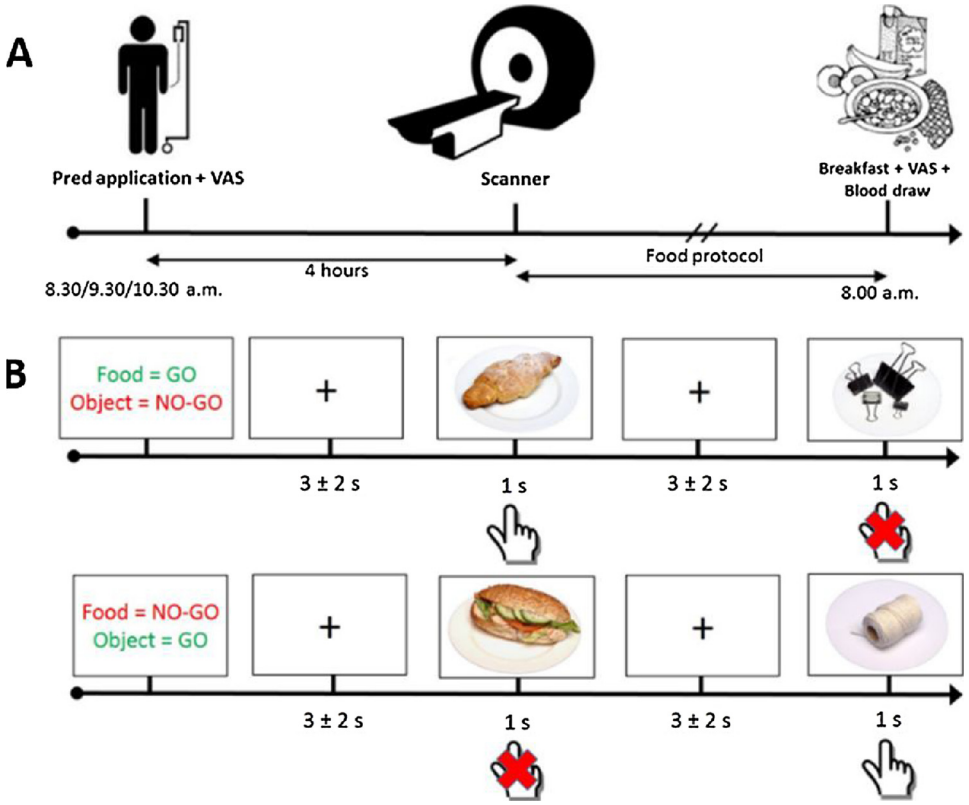

Fig. 1. A: Schematic overview of the study design. Participants arrived in the morning and were staggered in intervals of one hour. **B**: Schematic overview of the fMRI paradigm.

suggested (Czock et al., 2005). During the waiting period, all participants remained in a quiet room. They were asked to refrain from physical activity and were only allowed to drink water. After the fMRI scan (see below), we handed out a food protocol in which participants had to record their food intake up to the next morning. All volunteers were instructed to stop eating at 10 p.m. and not to drink alcohol until the next morning. The following day, participants were tested under fasting conditions at 8 a.m. After a blood sample was drawn, they were provided a standardized breakfast buffet. This allowed us to exactly quantify food intake by weighing the initially offered and the leftover food. For a schematic overview of the procedure, see Fig. 1A.

2.3. Cortisol

Cortisol estimation was performed using a competitive chemiluminescent immunoassay on an ADVIA Centaur XPi 2000 (Siemens Health Care Systems, Germany). The analytical range was 5.5–2069 nmol/l. Interassay coefficients of variation were 4.98% at high levels, 4.44% at median levels and 6.58% at low levels.

2.4. fMRI paradigm

We conducted a Go/NoGo (GNG) task to assess impulsive behavior in response to palatable food cues (Teslovich et al., 2014). We used each 50 food (25 sweet, 25 savory) and 50 object pictures, which were taken on the same plate and under equal light conditions and angle (Brooks et al., 2011). Each picture was presented for one second with a variable inter-stimulus interval from one to three seconds. In alternating blocks, participants had to press a response button when either food pictures were presented (Food-Go, Object-NoGo) or when object pictures were presented (Object-Go, Food-NoGo). NoGo trials were presented in 20% of all trials. The blocks were switched after half of each run and the order of blocks was balanced across runs. Participants underwent four runs in each fMRI scan for a total of 400 trials. A schematic illustration of the fMRI paradigm is presented in Fig. 1B.

2.5. MRI image acquisition

We used a 3 T Philips Ingenia 3.0 T Scanner with a 32-channel head coil. Anatomical scans were composed of 180 sagittal slices (TR = 7.7, TE = 3.5, FOV = 240, matrix = 240 x 240 mm, flip angle = 8°, voxel size = 1 mm isotropic). A T2*-weighted gradient echo-planar sequence for blood-oxygen level dependent (BOLD) imaging was used to obtain the functional volumes. Each scan comprised 38 slices acquired in interleaved order (TR = 2 s; TE = 30 ms; FOV = 192, matrix = 64 × 64; flip angle = 80°; voxel size = 3 mm isotropic). We acquired four consecutive runs of 220 volumes each.

2.6. Behavioral data analyses

SPSS (IBM, Version 22) was used for the analysis of food intake (buffet test and food protocols) and behavioral performance in the scanner (reaction times in Go trials and error rates). For food intake, we calculated the mean amount of carbohydrates, protein, fat (in grams), and total calorie consumption (in kcal) for each condition and compared prednisolone against placebo with paired t-tests. Regarding behavioral data in the scanner, we performed a repeated measure analysis of variance (rmANOVA) on mean reaction times in Go trials and mean commission error rates in NoGo trials with factors stimulus type (food vs object), condition (prednisolone vs placebo), and run (scanner runs 1–4). Omission errors were not analyzed because they are very infrequent and tend to reflect inattention rather than impulse control (Bezdjian et al., 2009). Significance was set to $p < 0.05$.

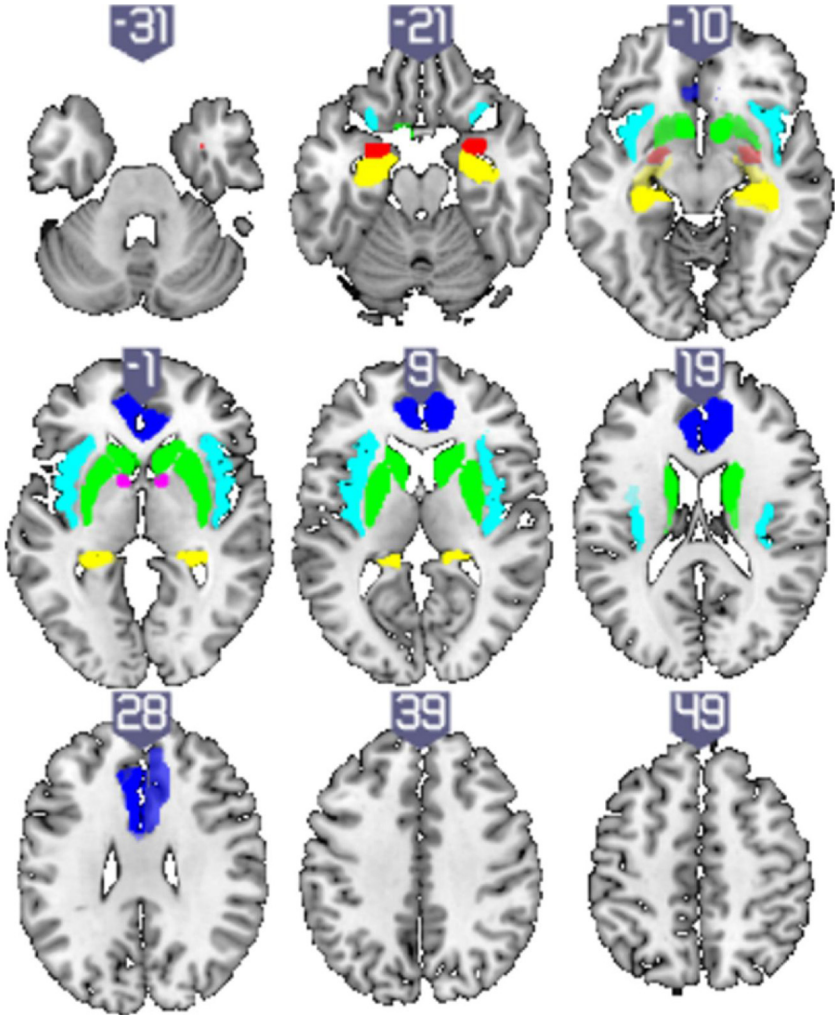

Fig. 2. A priori regions of interest (ROIs): anterior cingulate cortex (ACC; blue), striatum (green); insula (cyan), hippocampus (yellow), nucleus accumbens (violet); amygdala (red). The orbitofrontal cortex (OFC) ROI was defined based on meta-analytic coordinates and is not shown (see Methods) (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

2.7. fMRI data analyses

Functional images were analyzed with Statistical parametric mapping 12 (SPM12, Wellcome Department of Imaging Neuroscience, University College London, London UK). The origin of each volume was set to the anterior commissure so the y-axis crossed the posterior commissure. Volumes were slice-time corrected to the middle slice, realigned to the first functional scan, co-registered between mean functional and anatomical images, normalized to the native voxel size in Montreal Neurological Institute (MNI) space and smoothed with a 8 mm half width at half maximum (FWHM) Gaussian kernel.

For the first level analysis, we defined 5 regressors time-locked to the presentation of each stimulus: Sweet-Go, Savory-Go, Food NoGo, Object-Go, Object-NoGo. Given that the NoGo condition comprised fewer trials (20%), and that the exact Food-NoGo stimuli differed across participants, we did not differentiate between sweet and savory NoGo stimuli. Regressors were convolved with the canonical hemodynamic response function, corrected for serial correlations using SPM's auto-regressive model, and high-pass filtered at 1/128 Hz. Movement parameters derived from realignment were also included as regressors. We specified contrasts for each regressor against baseline to be used in second level analyses, plus a compound Food-Go contrast (Sweet-Go + Savory-Go). For second level analysis, we defined a priori regions of interests (ROI) implicated in food-related reward processing, namely amygdala, anterior cingulate cortex (ACC), insula, orbitofrontal cortex (OFC), hippocampus and striatum (including nucleus accumbens, caudate nucleus, putamen and pallidum). This selection was based on the results of previous studies which investigated the effects of food cues on brain activation in fMRI (Jastreboff et al., 2013; Killgore et al., 2003; St-Onge et al., 2012; Wallner-Liebmann et al., 2010). All these brain areas were found to be activated by food cues in contrast to neutral stimuli. For the amygdala, the insula, the hippocampus, the ACC, the caudate nucleus, the putamen and the pallidum we created the ROI's based on automated anatomical labeling (Tzourio-Mazoyer et al., 2002) using the Wake Forest University Pickatlas (Maldjian et al., 2003). Due to the large size of the atlas' anatomical OFC ROI, we created a sphere with a radius of 10 mm centered at X= -25, Y = 31, Z= -17 (MNI space) corresponding to the peak activation for food cues across 14 studies in an Activation Likelihood Estimation (ALE) meta-analysis (Tang et al., 2012). The nucleus accumbens ROI was created according to the coordinates provided in a combined anatomical-radiologic localization study (Mavridis et al., 2011). Our ROIs are illustrated in Fig. 2.

We conducted four separate factorial analyses at the second level. In all cases, we included the factor subject in order to account for paired measurements, and contrasts were defined as t-tests. First, we defined the factors Food vs Object and Go vs NoGo and inspected for general motor effects of the task by comparing Go vs NoGo trials. Second, we examined whether prednisolone could modulate these motor effects by testing the interaction between factors prednisolone vs placebo and Go vs NoGo. Third, we tested the main effects of food approach signals

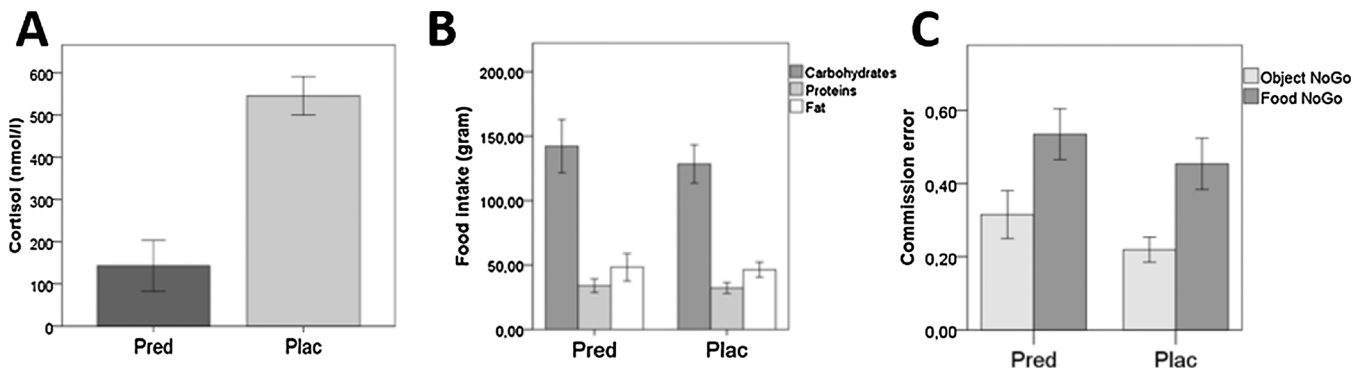

Fig. 3. A: Serum cortisol levels collected the following morning after pred/plac application (mean ± SEM). Endogenous cortisol was suppressed in the prednisolone condition ($t = 13.88$, $p < 0.001$). **B**: Food intake from breakfast buffet, separately for major macronutrients (mean ± 95%CI). There were no significant differences between conditions in food intake (see Section 3.2). **C**: Commission errors in the Go/NoGo task (mean ± SEM). Participants committed more commission errors in the pred relative to the placebo condition ($F = 24.73$, $p < 0.001$) and in the Food-NoGo relative to the Object-NoGo condition ($F = 7.57$, $p = 0.012$) (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

(Food-Go vs Object-Go) and prednisolone vs placebo as well as their interaction. Fourth, we explored whether prednisolone influences the neural response to sweet relative to savory food with factors prednisolone vs placebo and sweet-go vs savory-go. For whole-brain comparisons, significance level was set at $p < 0.05$ FWE (family-wise error) at the voxel level with a cluster-defining value of $k > 10$. For the ROI analysis, we used the small volume correction (SVC) in SPM with a significance level set to $p < 0.05$ FWE corrected on a cluster-defining threshold of $p < 0.01$ and $k > 10$. ROI analyses were only applied in models 3 and 4, i.e. those that tested the effect of prednisolone on food approach signals and for which we had a priori hypotheses.

Finally, we inspected for associations between prednisolone-related neural reactivity to food approach cues and behavioral parameters in the task as well as food intake. We first extracted mean parameter estimates within each cluster surviving SVC in the critical Pred > Plac x Food-Go > Object-Go contrast using Marsbar (http://marsbar.sourceforge.net/). Thus, we obtained the individual beta-values for all four conditions versus baseline (Pred-Food-Go, Pred-Object-Go, Plac-Food-Go, Plac-Object-Go) and subtracted the values of the Plac-Food-Go from the Pred-Food-Go condition. This contrast allowed us to test how prednisolone modulates brain responses to food pictures specifically. Then, we examined whether these values were associated with mean reaction times, error rates and food intake in the prednisolone condition using Pearson correlation coefficients, which were deemed significant at $p < .05$. In the event of a significant correlation, we ran repeated-measures mediation analysis using the MEMORE macro for SPSS (Montoya and Hayes, 2017). This allowed us to formally test whether prednisolone effects on behavior were statistically dependent on brain activity. Indirect mediation effects were considered significant if the bootstrapped 95% bias-corrected accelerated confidence intervals (95% BCa CI) obtained with 5000 resamples did not include zero.

3. Results

3.1. Morning cortisol and subjective state

The prednisolone infusion significantly suppressed endogenous cortisol serum levels measured in the following morning (143.4 ± 30 nmol/L [mean ± standard error]) as compared to placebo (546.4 ± 22.8 nmo/L; $t_{18} = 13.88$, $p < .001$; Fig. 3A).

Prednisolone did not influence participants' rating of their subjective state in the VAS (all $p > .147$).

3.2. Food intake

We did not observe any significant differences in caloric intake or intake of different macronutrients between prednisolone and placebo for the breakfast buffet (calories: 1155.15 vs 1072.85 kcal, $t_{18} = 1.00$, $p = .330$; carbohydrates: 142.22 vs. 128.43 g, $t_{18} = 1.44$, $p = .165$; protein 33.94 vs 32.17 g, $t_{18} = 0.64$, $p = .525$; fat: 48.33 vs 46.38 g, $t_{18} = 0.39$, $p = .701$; prednisolone vs. placebo respectively, Fig. 3B). The food diary also revealed no significant differences in caloric and macronutrient intake, but we observed a non-significant trend towards reduced caloric and carbohydrate intake in the prednisolone condition (calories: 1314.46 vs 1627.85 kcal, $t_{18} = 1.91$, $p = 0.073$; carbohydrates: 148.20 vs. 183.22 g, $t_{18} = 1.77$, $p = 0.093$; protein: 56.77 vs 68.86 g, $t_{18} = 1.18$, $p = 0.253$; fat: 52.61 vs 69.48 g, $t_{18} = 1.62$, $p = 0.121$; prednisolone vs placebo respectively, Fig. 3B).

3.3. Go/NoGo task: behavioral results

Response times in Go trials decreased with time ($F_{3,57} = 3.60$, $p = .018$; Run 1: 575 ± 6.6 ms, Run 4: 557 ± 6.5 ms). There were no other significant effects on reaction times (all $p > .135$). Participants made commission errors (i.e. "false alarms") on 9.5 ± 0.6% of all NoGo trials.

The number of commission errors in NoGo trials was significantly higher for food than for object pictures ($F_{1, 19} = 24.73$, $p < .001$; Food: 12.3 ± 0.8% vs Object: 6.7 ± 0.7%; Fig. 3C). Participants made overall more commission errors after prednisolone administration ($F_{1, 19} = 7.57$, $p = 0.012$; pred: 10.6 ± 0.9% vs placebo: 8.4 ± 0.6%; Fig. 3C). There were no interactions between stimulus type and treatment ($p = .761$), nor between run and other factors (all $p > .312$). Reaction times and commission errors did not differ between sweet and savory food pictures ($p = .315$), nor was there an interaction between this factor and prednisolone ($p = .352$).

3.4. Go/NoGo task: fMRI results

To verify that the paradigm yielded generally valid neural effects, we first compared the main task conditions Go and NoGo. Go- in contrast to NoGo-trials revealed strong activity in the contralateral sensorimotor cortex (left postcentral and precentral gyrus). The NoGo-condition in contrast to the Go-condition activated the bilateral supplementary motor cortex, bilateral anterior insula, bilateral supramarginal gyrus and bilateral middle frontal gyrus. For complete results see Table 1.

We subsequently inspected whether the motor effects above reported could be modulated by prednisolone. One cluster in the postcentral gyrus showed enhanced activity in NoGo relative to Go trials in the prednisolone condition compared to placebo (Table 1).

Next, we analyzed effects of food-related stimuli. In the right

Table 1
Summary of brain activation in each contrast.

Contrast / Brain region	k	T	X	Y	Z
NoGo > Go[a]					
Anterior Insula R	1270	10.16	33	23	−1
Middle frontal gyrus R		8.61	36	41	29
Inferior frontal gyrus R		8.57	42	20	5
SMA R + L	450	9.64	6	14	53
Middle frontal gyrus R		7.31	18	5	65
Supramarginal gyrus R	611	8.36	60	−46	29
Inferior parital lobe R		6.93	45	−46	50
Middle temporal gyrus R		6.63	60	−46	5
Precuneus R	168	7.21	9	−67	44
Anterior Insula L	120	6.97	−33	23	−4
Inferior parietal lobe L	63	6.67	−33	−55	44
Middle frontal gyrus L	129	6.00	−33	35	29
Middle frontal gyrus L		5.63	−36	47	20
Supramarginal gyrus L	30	5.78	−60	−49	29
Precentral gyrus L	21	5.51	−39	−1	41
Go > NoGo[a]					
Postcentral gyrus L	530	11.56	−54	−22	50
Precentral gyrus L		10.52	−33	−25	59
Precentral gyrus L		10.23	−42	−16	59
Cerebellum R	96	8.67	21	−55	−22
Rolandic operculum L	140	7.56	−48	−22	20
Hippocampus R	71	7.54	39	−19	−16
Anterior Insula L	42	7.33	−39	−4	14
Caudate R	19	6.07	21	−1	26
Medial frontal cortex L	19	5.20	−6	62	−4
Medial frontal cortex L		5.03	−3	53	−10
Pred > Plac x NoGo > Go[a]					
Postcentral gyrus R	67	5.79	54	−22	38
		5.47	54	−16	29
Food-Go > Object-Go					
Occipital lobe[a]	131	7.12	6	−82	−4
Hippocampus L[b]	57	3.72	−27	−37	−1
Hippocampus R[b]	104	4.32	27	−31	−4
Amygdala R[b]	17	3.27	24	5	−19
Insula R[b]	46	3.77	39	−1	2
Orbitofrontal cortex L[b]	7	2.97	−27	38	−10
Pred > Plac					
Amygdala L[b]	5	2.85	−27	2	−16
Plac > Pred					
Putamen[b]	13	3.68	15	11	−10
Pred > Plac x Food-Go > Object-Go					
Insula R[b]	25	4.10	33	11	14
Amygdala L[b]	25	3.63	−21	−4	−19
Amygdala R[b]	16	3.11	33	−1	−25
Pred > Plac x Sweet-Go > Object-Go					
Insula R[b]	20	4.12	33	11	14
Amygdala L[b]	23	3.89	−21	−4	−19
Hippocampus L[b]	21	3.36	−21	−4	−22
Putamen R[b]	12	3.36	27	8	14
Pred > Plac x Savory-go > Object-Go					
Insula R[b]	26	3.73	33	11	14
Amygdala L[b]	16	3.03	−21	−4	−19
Amygdala R[b]	15	3.43	33	−1	−25
Hippocampus R[b]	10	3.56	33	−4	−25

Coordinates presented in MNI space. T: t-values. K: cluster size in voxels. ACC: anterior cingulate cortex. SMA: supplementary motor area. [a] Whole-brain voxel-level corrected, FWE < .05, k = 10 [b] Small volume corrected, FWE < 0.05.

amygdala, the right insula, bilateral hippocampus and the left orbitofrontal cortex, neural activity was higher for Food-Go relative to Object-Go stimuli. Whole-brain analyses revealed additional strong effects in the bilateral occipital lobe (Table 1 and Fig. 4).

When examining the main effects of prednisolone in contrast to placebo, ROI analyses revealed increased activation in the left amygdala. The activity of the right putamen was decreased in the prednisolone as compared with the placebo condition (Table 1). An uncorrected whole brain analysis (p < .001, k > 10) suggested an additional decreased activation of the bilateral thalamus (left: t = 3.22, X = -9, Y = -16, k = 24; right: k = 15, t = 3.51, X = 9, Y = -16, Z = 17, k = 15) but this effect did not survive correction for multiple testing.

Most relevant to our research goals, ROI analyses of the interaction between Food-Go stimuli and prednisolone revealed significant activations in the right insula and the bilateral amygdala (Fig. 5). The comparison of activity in these brain areas between sweet and savory food pictures did not show any significant differences (p > 0.171 for all). When restricting the analysis on the interaction of sweet > object and prednisolone > plac, the activation of the right amygdala became insignificant but there was an additional significant activation in the head of the left hippocampus. The reverse contrast (savory > object in interaction with factor prednisolone vs. plac) revealed an additional activation in the head of the right hippocampus. For all activations see Table 1.

Regarding brain-behavior relationships, we found a significant correlation between the strength of the activity in the left amygdala (Pred-Food-Go minus Plac-Food-Go) and reaction time to food approach cues in the prednisolone condition (r = .555, p = .011; Fig. 6A). There was, however, no mediation effect (95% BCa CI B= [-11.39, 1.29]). Furthermore, left amygdala reactivity correlated negatively with the commission error rate for Food-NoGo in the prednisolone condition (r =.467, p = .038; Fig. 6B). This mediation effect was significant (95% BCa CI B= [-0.069, -0.006]), indicating that prednisolone was associated with lower commission errors in response to food stimuli in subjects with high amygdala reactivity to food stimuli. Reactivity of right amygdala and right insula was not associated with behavior in the Go/NoGo task (all p > .179).

We observed additional significant correlations between the neural response of the right insula (Pred-Food-Go minus Plac-Food-Go) and food intake. Critically, the amount of caloric intake from the breakfast buffet (prednisolone: r = .468, p = .037, Fig. 6C) as well as from the food diaries (r = .607, p = .005, Fig. 6D) was associated with insula reactivity. Nevertheless, we observed no mediation effects of prednisolone on calorie consumption via insula reactivity for either the breakfast buffet (95% BCa CI B= [-49.03, 101.73]) or the food diaries (95% BCa CI B= [-85.43, 124.36]). Regarding macronutrients, we found a significant correlation between neural response of the right insula and protein intake in the breakfast buffet for the prednisolone condition (r = .735, p < .001). There was however no indirect effect of prednisolone on protein consumption (95% BCa CI B= [-1.33, 4.08]). For fat and carbohydrates we only found a non-significant trend towards a positive correlation (fat r = .384, p = .094; carbohydrates r = .385, p = .094). Analysis of the food diaries revealed a positive correlation between carbohydrate intake and activity of the right insula in the prednisolone condition (r = .458, p = .042), though there was no indirect effect (95% BCa CI B= [-5.18, 20.98]). For fat intake we found only a trend towards a positive correlation (r = .444, p = .057), and no association for protein intake (r = .361, p = .129).

4. Discussion

We investigated the effects of a single intravenous application of prednisolone on the neural response to food stimuli in a randomized, double-blind, placebo controlled fMRI study. We also assessed food intake with direct measurement of food consumption as well as preferences in a buffet test 24 h after the prednisolone infusion. Although prednisolone did not increase food intake, it did suppress endogenous cortisol and altered behavioral and neural responses to food cues. Crucially, prednisolone heightened brain reactivity to approach-related food pictures in the insula and the amygdalae. Moreover, prednisolone-induced activity in these areas was associated with task performance and food intake. Our results elucidate the neural pathways through which exogenous glucocorticoids might increase the salience of food cues and thereby contribute to altered eating behavior and weight gain in the long run.

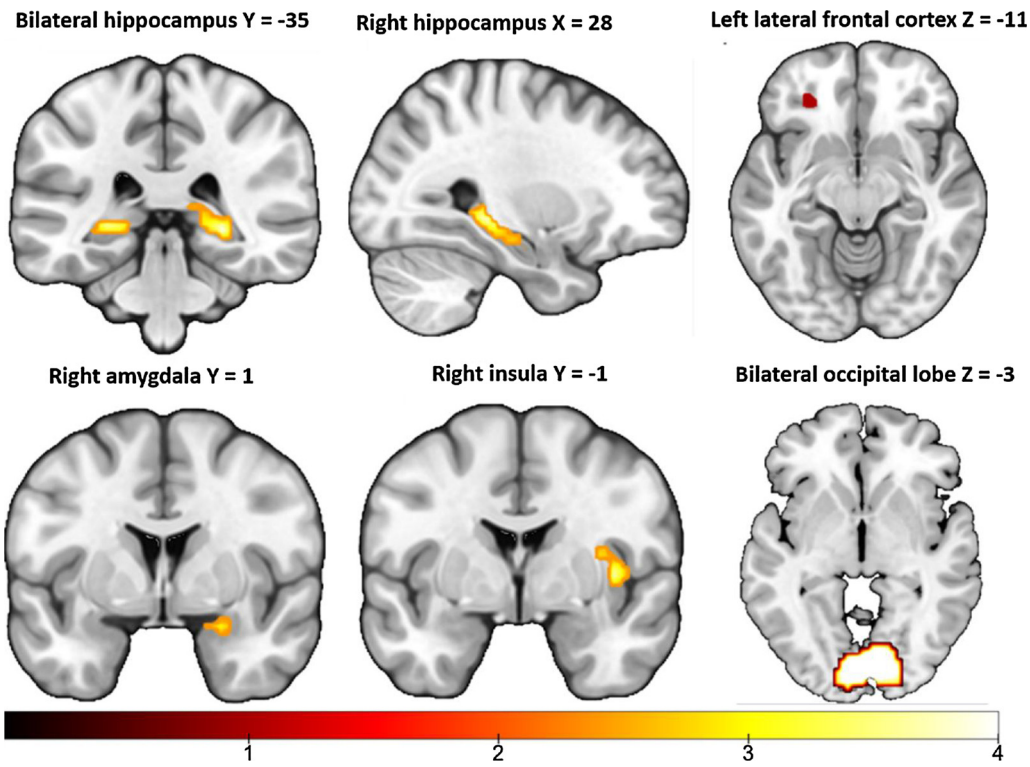

Fig. 4. Main effects of food > object. Activation maps are thresholded at FWE < 0.05 after applying small volume correction on cluster defining threshold of $p < 0.01$ and $k > 10$. Activation map of the occipital lobe is thresholded at FWE < 0.05 for whole brain analysis. Color coding corresponds to the estimated t-values (scaled at a maximum of t = 4 for comparison between regions) (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

4.1. Endocrine and task results

Behavioral data indicated that participants remained attentive throughout the task with decreasing reaction times over time and overall low error rates. When comparing food and non-food cues, we observed more impulsive behavior in response to food cues reflected in an increased commission error rate. This is consistent with a previous study on an increased false alarm rate for food items in the NoGo condition (Teslovich et al., 2014). Importantly, prednisolone generally increased commission errors regardless of stimulus type. This is in contrast with studies showing that a rise in cortisol facilitates response inhibition (Schlosser et al., 2013; Shi et al., 2018). Thus, while increases in circulating cortisol might improve attentiveness, synthetic glucocorticoids might have an opposite, detrimental effect on executive function. Although we did not observe the hypothesized interaction between prednisolone and stimulus type, this result suggests that exogenous glucocorticoids could cause a general increase of impulsive behavior.

4.2. Effects of prednisolone administration on food intake

Regarding food intake, we did not find significant effects of prednisolone on food consumption in the following 24 h. The differentiation with regard to macronutrients (carbohydrates, fat, protein) as well as a selective analysis of sweet components showed no significant effects of prednisolone either. As the food diaries even revealed a non-significant trend towards a decreased food intake in the prednisolone condition, our results are in contrast to data of Tataranni et. al., who reported a considerable increase in food intake following treatment with methylprednisolone (Tataranni et al., 1996). These differences may be explained by the timing and dosage of prednisolone exposure in the two studies. In our study, a single prednisolone infusion was given which may not be sufficient to induce changes in food intake. In contrast, Tataranni and colleagues gave prednisolone over a period of 4 days, which may be necessary to alter eating behavior. Note, however, that we only observed the trend in the food diaries, which are known to be rather inaccurate (Cook et al., 2000), but not in the buffet test, in which we could directly measure participant's food intake.

4.3. General task effects on neural activity

Comparing NoGo and Go trials (across food and object images) revealed a typical activity pattern in brain regions relevant for response inhibition, such as the anterior insula, the supplementary motor area, and the dorsolateral prefrontal cortex (Criaud and Boulinguez, 2013). Motor execution in Go-trials, on the other hand, yielded activity in the sensorimotor cortex, cerebellum, and dorsal caudate.

Results for the contrast of food and object stimuli are also in line with previous research using similar paradigms. Food stimuli in contrast to non-food items yielded increased activity bilaterally in the hippocampus, right amygdala, orbitofrontal cortex, right insula and anterior cingulate cortex (ACC). These results confirm previous studies about the role of such brain centers in the regulation of eating behavior (Jastreboff et al., 2013; Killgore et al., 2003; Wallner-Liebmann et al., 2010). Enhanced activation in response to food cues has been observed in these brain areas in different conditions such as obesity (Jastreboff et al., 2013), sleep restriction (St-Onge et al., 2012) and when fasting compared to satiety (Porubská et al., 2006). As part of the food reward system, activity of the amygdala has been found to correlate with the anticipated reward value of food cues (Gottfried et al., 2003). Also the hippocampus seems to be important in appetite regulation as animal data demonstrate hyperphagia upon its damage (Forloni et al., 1986) and human studies suggested a correlation between self-report scores for food-craving and hippocampal activation (Jastreboff et al., 2013). Hippocampal activation may reflect an assessment of the reward value of food items which triggers reward seeking behavior (Pelchat et al., 2004). Summarizing general task effects, our results speak for the validity of the paradigm to investigate the brain systems implicated in motor impulsivity and in food reward processing.

4.4. Motor and task-independent effects of prednisolone

Unexpectedly, prednisolone strongly potentiated postcentral gyrus activity during motor inhibition. This result is relevant because subjects

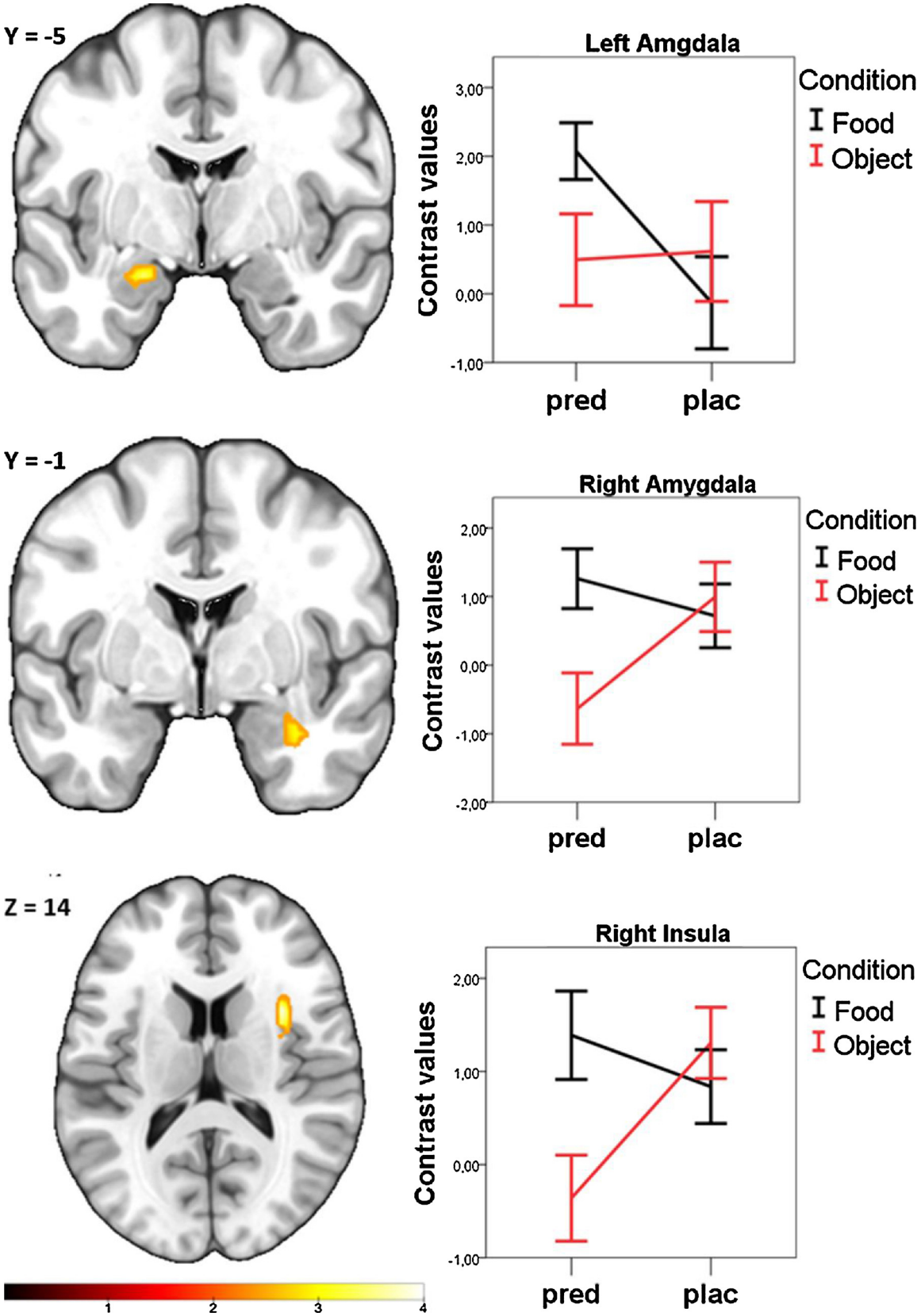

Fig. 5. Interaction between prednisolone (pred) vs. placebo (plac) administration and condition (Food-Go vs. Object-Go). Activation maps are thresholded at FWE < 0.05 after applying small volume correction on a cluster defining threshold of $p < 0.01$ and $k > 10$. Contrast values are mean ± SEM. Color coding corresponds to the estimated beta-values.

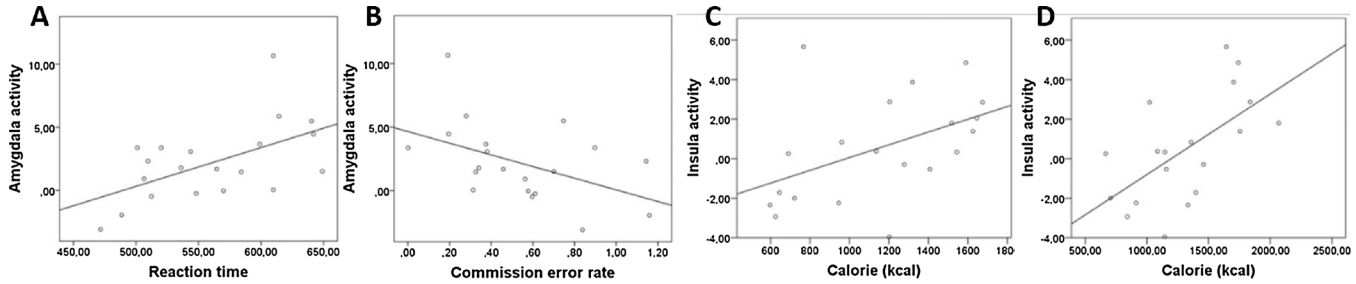

Fig. 6. Correlations between brain activity (pred-Food-Go minus plac-Food-Go) and behavior in the prednisolone condition. **A:** Correlation between amygdala activity and reaction time to Food-Go cues in the prednisolone condition; r = .555, p = .011. **B:** Correlation of amygdala reactivity with commission error rate for Food-NoGo stimuli in the prednisolone condition; r = .467, p = .038. **C:** Correlation of insula activity and caloric intake in the breakfast buffet in the prednisolone condition; r = .468, p = .037. **D** Correlation between insula activity and at-home caloric intake according to food diaries in the prednisolone condition; r = .607, p = .006. Brain activity is expressed in arbitrary contrast values. Reaction time is expressed in milliseconds. Error rate is expressed as a proportion and summed across the four runs.

incurred more commission errors in the prednisolone than in the placebo condition. The cluster was roughly located in the hand area of the primary somatosensory cortex and did not overlap with the typical motor inhibition network observed in the NoGo > Go contrast. Such unusual localization warrants caution interpreting the functional significance of this effect, which might have arisen as a consequence of enhanced motor preparation or inhibitory effort. Irrespective of the task condition, prednisolone had modest effects on activity of the left amygdala and bilateral thalamus, though the latter effect did not survive multiple comparison correction. The activation of the left amygdala can be explained with the strong expression of glucocorticoid receptors in this structure (Wang et al., 2014).

4.5. *Effects of prednisolone administration on neural response to food signals*

Our results provide evidence for a direct effect of prednisolone on the neural response to approach-related food stimuli in the bilateral amygdala and the right insula. These findings demonstrate an impact of prednisolone on brain regions involved in the regulation of food intake, whereas we did not observe glucocorticoid-related effects on hypothalamic centers.

Most relevant to our question is the interaction of prednisolone administration and food stimuli in the bilateral amygdala and the right insula. The amygdala is an important brain area for emotional reactions to external stimuli and critically involved in fear conditioning (LeDoux, 2003). Beyond this classical view, however, the role of the amygdala in positive affect is increasingly recognized (Weymar and Schwabe, 2016). A number of studies have further established the link between amygdala activity and reward-related behavior, and have defined this structure as a part of the food reward system (Janak and Tye, 2015). As described above, in fMRI studies the amygdala becomes activated in response to food stimuli, with an enhanced activation in normal weight subjects during hunger (LaBar et al., 2001) and in obese individuals (Jastreboff et al., 2013). Self-reported hunger scores were previously found to be correlated with activation of the amygdala (Mehta et al., 2012). The calorie amount of presented food items appears to correlate with the activation of the amygdala, suggesting a higher estimated reward value of high calorie foods (Goldstone et al., 2009). In a memory task with food and non-food pictures, Morris and Dolan obtained a positive correlation between amygdala activation and the rate of food recognition in a memory task. This correlation was no longer present when participants were satiated, indicating an involvement of the amygdala in encoding food-related emotional memories (Morris and Dolan, 2001). Thus, the functional significance of the amygdala seems to be in encoding the value of food cues dependent on the context of previous experiences and current motivation to eat.

Although food items as well as prednisolone increased impulsive behavior in the Go/NoGo task, our study shows that participants with high glucocorticoid-induced amygdala reactivity to food approach cues were slower in the Food-Go condition and made less commission errors in the Food-NoGo condition. Thus, we assume that amygdala reactivity goes along with a higher attention for salient food cues under prednisolone, such that participants dwelled longer on food images and were more accurate in identifying them. This is further suggested by the observed mediation effect, whereby prednisolone led to less commission errors for Food-NoGo pictures as a function of amygdala reactivity. This also implies, however, that the increased commission error rate to food cues as well as object pictures in the prednisolone condition cannot be explained by effects on brain areas involved in hedonic eating.

As commented earlier, prednisolone may act on the densely expressed glucocorticoid receptors in the amygdala (Wang et al., 2014). Systemic (Arvaniti et al., 2001) as well as direct administration of glucocorticoids to the amygdala increase mRNA level of corticotropin-releasing factor (CRF) and increase the ingestion of pleasurable food in rats (Dallman et al., 2003). In humans, a similar interaction may be present. A positive correlation between morning cortisol levels and activation of the amygdala after the ingestion of milkshakes has been reported in young obese women. If participants were exposed to additional acute stress, the milkshake-induced amygdala activation was even further increased in comparison to a control condition, but these effects were not detectable with tasteless solutions (Rudenga et al., 2013). This agrees with our data showing that glucocorticoids enhance the response of the amygdala to palatable food cues. It also fits to studies describing glucocorticoids as an essential part of the reward system per se (Piazza and Le Moal, 1997) and linking glucocorticoid effects in the brain with reward-seeking behavior (de Jong and de Kloet, 2004). Our results however contrast with those of Montoya et al., who reported decreased activation of the reward system, including the amygdala and the ventral striatum in an incentive monetary delay task under the effects of 40 mg cortisol (Montoya et al., 2014). The difference between both studies might be caused by the different duration of glucocorticoid action. In the study by Montoya et al., fMRI was performed 50 min after oral cortisol intake, whereas we studied the effects 4 h following intravenous application. Indeed, glucocorticoid administration causes an initial desensitization of limbic regions, but increases amygdala reactivity after a few hours (Henckens et al., 2010).

We also observed enhanced insula reactivity in response to food approach cues. Furthermore, insula activity was associated with enhanced caloric, carbohydrate, and protein intake. The insula receives numerous somatic and visceral afferent signals, and is thought to be important for integrating information from different functional networks (Kurth et al., 2010). Similarly to the amygdala, the insula has been found to show increased activation during hunger states (LaBar et al., 2001) and when presenting high calorie foods in comparison to

low calorie ones (Goldstone et al., 2009). It has been proposed that the insula contributes to linking olfactory and gustatory memory with emotional information in order to assess the value of food items (Small et al., 2001). Indeed, the activity of the insula is positively modulated by appetite ratings (Porubská et al., 2006). In line with these and our results, we speculate that subjects with higher insula reactivity are more susceptible to experience glucocorticoid-induced increases in eating behavior. Another study revealed that insula reactivity to fattening in contrast to non-fattening food cues predicts subsequent fat intake on an ad libitum breakfast buffet (Mehta et al., 2012). In contrast to our results, however, Mehta et al. did not obtain any significant correlations between insula activity and caloric, carbohydrate, or protein intake. It should also be noted that the present mediation analyses on food intake turned out non-significant, presumably because prednisolone did not have a direct impact on eating behavior (Montoya and Hayes, 2017). As suggested elsewhere, glucocorticoids' influence on eating behavior and the brain regions governing it might be strongest upon long-term administration. Prospective, longitudinal studies are needed to verify the latter possibility.

However, the mechanism of glucocorticoid action in the insula remains unclear. A resting-state analysis obtained an increment of regional cerebral blood flow in the insula after administration of insulin but not after oral cortisone (Schilling et al., 2014). In line with this finding, Wallner-Liebmann et al. described a positive correlation between fasting insulin levels and insula reactivity to high-calorie food pictures in both lean and obese participants (Wallner-Liebmann et al., 2010). In contrast, Tataranni et. al. did not report increased insulin levels in healthy participants following methylprednisolone administration (Tataranni et al., 1996). Further combined pharmacological studies are needed in order to ascertain whether the observed increase in insula activity is mediated by glucocorticoid-induced insulin resistance.

Taken together, the increased reactivity in amygdala and insula to food cues after prednisolone administration might be indicative of an increase in the anticipated reward value of food items. Two correlational findings offer further support for this assertion. First, amygdala reactivity predicted enhanced reaction times and lower commission error rates for Food-Go pictures under prednisolone. Second, insula reactivity predicted enhanced caloric consumption in both buffet and food diaries in the prednisolone condition. Thus, glucocorticoids may contribute to enhance food intake and weight gain due to their action on limbic areas. Although prednisolone did not significantly alter mood, the well-established side effects of glucocorticoids on affective tone (Brown, 2009) may play an important additional role in glucocorticoid-induced weight gain. Genetic variation in glucocorticoid-related transcription factors might also account for some interindividual variability in glucocorticoid effects on brain activity, as has been shown, for instance, in the context of depression (Arloth et al., 2015). This remains a promising approach for further studies.

Though we did not observe any prednisolone-induced differences in hypothalamus activity, potential effects of glucocorticoids in this structure should not be neglected. Previous studies showed that glucocorticoids increase orexigenic agouti-related peptide (AGRP) and decrease anorexigenic proopiomelanocortin (POMC) levels in the nucleus arcuatus (Arvaniti et al., 2001). Because the amygdala is connected directly and indirectly with the hypothalamus, an indirect modulation of amygdala activity through effects on the hypothalamus cannot be excluded (Kelley, 2004). Nevertheless, the small size of the hypothalamus and its close position to the surrounding air-filled sinuses complicate the assessment of signal changes in fMRI. Hence, our negative finding should be interpreted with caution.

4.6. Study limitations

A limitation of our study is the small sample size, which may attenuate statistical power. Potentially this is one of the reasons why we did not obtain significant differences in food intake. However, our sample size is very comparable to similar pharmacological fMRI studies (Jastreboff et al., 2013; Wang et al., 2004) with the added advantage of a cross-over design, in which each subject serves as his own control. The combination of a Go/NoGo task and the presentation of food and object images made it possible to investigate the neural response to food cues as well as impulsive behavior in one task. However, such a paradigm might have distracted participants from an in-depth hedonic valuation of the food images. This might partly explain why we only observed prednisolone effects on neural activity at the ROI level. Regarding food intake, it should be kept in mind self-reported food diaries are known to be slightly inaccurate in comparison to more controlled tests (Cook et al., 2000) and that ad-libitum buffets are an inherently artificial situation in which the food has been first selected by the experimenters and not the subjects themselves. These may constitute reasons for our negative results using these measures.

5. Conclusion

In healthy young men, a single administration of prednisolone led to increased reactivity of amygdala and insula to food stimuli and to more impulsive behavior. Given the essential role of these brain regions in the food-processing and reward systems, our results suggest that prednisolone increases the anticipated reward value of food. Prednisolone did not increase food intake within 24 h after intravenous administration, in general or for specific macronutrients. However, subjects with enhanced insula reactivity consumed more calories, carbohydrates, and proteins. Therefore, the observed prednisolone effects on brain activity and impulsivity could be at play during prolonged administration and thereby contribute to glucocorticoid-related alterations in eating behavior.

Role of the funding source

This work was supported by intramural grants of the University of Lübeck to GB and UMK and by the German Science Foundation (Deutsche Forschungsgemeinschaft, DFG) through the TR-CRC 134 project to GB and UMK (project Z2). UMK is supported by the DFG (KR3691/5-1). Funding sources had no role in study design; in the collection, analysis and interpretation of data; in the writing of the report; or in the decision to submit the paper for publication.

Contributors

GS and MBR wrote the protocol, gathered the data and performed the data analyses. GS wrote the first draft of the manuscript. GB, BH, and UMK conceived the study. All authors contributed to and approved the final manuscript.

Conflict of interest

All authors declare that they have no conflicts of interest.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.psyneuen.2018.09.007.

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