Cover Sheet

Title: Enhanced food-related responses in the ventral medial prefrontal cortex in orexin-deficient narcolepsy patients

Running head: Food-related vmPFC responses in narcolepsy patients

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Abstract

Narcolepsy Type 1 is a chronic sleep disorder caused by a deficiency of the hypothalamic neuropeptide orexin (hypocretin). In addition to sleep regulation, orexin signaling is important for motivational processes. Weight gain and obesity are common in narcolepsy. We recently showed that food-specific satiety had reduced effects on food choices and caloric intake in narcolepsy patients, suggesting an important functional role for orexin in human food-related motivation. However, the neurocognitive processes associated with food-related motivation and overeating in orexin-deficient patients are unknown. We explored the neural correlates of attention to food in narcolepsy type 1 patients (n=23), healthy BMI-matched controls (n=20), and idiopathic hypersomnia patients (n=15); the latter serving as a control group with excessive daytime sleepiness but normal orexin levels.

Attentional bias to food words was measured with a Food Stroop task during fMRI. Relative to healthy controls and idiopathic hypersomnia patients, narcolepsy patients showed enhanced ventral medial prefrontal cortex (vmPFC) responses when color-naming food versus neutral words. Narcolepsy patients relative to healthy controls also displayed stronger vmPFC-motor cortex connectivity. In addition, the vmPFC responses for food versus neutral words were predictive of spontaneous snack intake after scanning, which was greater in narcolepsy patients than in healthy controls and idiopathic hypersomnia patients. Our results show that orexin deficiency is associated with enhanced vmPFC responses during food-driven attention, predicting increases in food intake.

Introduction

Narcolepsy Type 1 (NT1) is a disabling sleep disorder, primarily characterized by excessive daytime sleepiness and emotionally triggered episodes of muscle weakness called cataplexy. The disorder is caused by a loss of orexin (hypocretin)–producing neurons located in the lateral hypothalamus. Orexin mediates behavior under situations of high motivational relevance, through excitatory influences on the histaminergic, monoaminergic, and cholinergic system (1). Interestingly, the incidence of obesity is twice as high in narcolepsy compared with the normal population (2–4). We recently showed that food-specific satiety had reduced effects on food choices and caloric intake in narcolepsy patients, suggesting an important functional role for orexin in human food-related motivation (5). However, the neurocognitive processes associated with food-related motivation and overeating in orexin-deficient patients are unknown.

Enhanced attention towards food over non-food information (i.e. attentional bias) has been proposed to contribute to the development and/or maintenance of obesity (e.g. for a review see[6]). Functional MRI studies revealed that food cues relative to neutral cues can elicit enhanced activation of the reward regions in the mesolimbic dopamine pathway in overweight relative to healthy weight individuals (7–9), including the ventral medial prefrontal cortex (vmPFC), striatum, insula and amygdala, which might drive excessive attention towards food cues. Detecting food rapidly and maintaining attention on food could increase the likelihood of overeating and, in the long term, obesity (10–12). In addition, loss of executive control during food-related distraction has been related to obesity (13). Although obesity is a common symptom in narcolepsy and orexin neurons interact with the mesolimbic dopamine system (14–16), it is unclear

whether narcolepsy patients show abnormal attentional bias toward food cues, and what neurocognitive mechanism would underlie this effect.

To investigate the effect of orexin deficiency on attentional bias for food, we used a Food Stroop task (i.e. measuring reaction times toward food words and neutral words) (13, 17) during fMRI in narcolepsy patients compared with healthy BMI-matched controls. To control for possible decreased alertness and medication-withdrawal (patients were at least 1 week off medication), we also included a control group of patients with idiopathic hypersomnia, without orexin deficiency. Since spontaneous snack intake was already shown to be increased in narcolepsy versus controls in a largely overlapping sample (5), we investigated whether brain responses on the Food Stroop would relate to this snack intake. Additionally, we applied a Classic Stroop task (i.e. measuring response conflict) to assess general executive control abilities and evaluated the relative contribution of the neural findings on the Classic Stroop and Food Stroop tasks to spontaneous snack intake.

Methods and Materials

Participants

Sixty right-handed participants were included in the experiment (20 healthy controls, 23 narcolepsy type 1 (NT1) patients and 15 idiopathic hypersomnia (IH) patients). See Supplemental data S1 for details on subject recruitment and inclusion and exclusion criteria.

All patients were diagnosed according to the International Classification of Sleep Disorders – Third Edition (ICSD-3). All had clear-cut cataplexy as well as a low mean sleep latency (< 8 minutes) measured with the Multiple Sleep Latency Test (MSLT) and at least 2 sleep onset REM periods (SOREMPs) during MLST naps and the previous night's diagnostic sleep study. In 13 patients, orexin cerebrospinal fluid levels were known and shown to be equal or lower than 110 pg/ml.

Patients with idiopathic hypersomnia all had clear excessive daytime sleepiness, a mean sleep latency at the MSLT of 8 minutes or less, and the symptoms were not explained by another sleep disorder.

All participants were recruited on a voluntary basis and gave written informed consent before the start of the study. The study was approved by the Ethical Committee of the Radboud university medical center (CMO Arnhem-Nijmegen) and reported in the acknowledged Dutch Trial register (www.trialregister.nl: TC=4508). See Supplemental data S2 for details on Study procedure.

Food Stroop task and Classic Stroop task

Subjects were instructed in both tasks before going into the scanner and were further familiarized with the task by practicing the color-button contingency and performing 10 practice trials with feedback (correct/incorrect) in the scanner. For task details see Fig. 1A. In short, subjects had to indicate the color of the word presented on the screen pressing the button reflecting that color as fast and accurately as possible. In the Food Stroop task, subjects were presented with food words and neutral words, whereas in the Classic Stroop task, subjects were presented with congruent color words (e.g. the word

"GREEN" printed in green) or incongruent color words (e.g. the word "GREEN" printed in red). The tasks were programmed in Presentation software (Neurobehavioral Systems Inc. htpps://www.neurobs.com). All task stimuli were presented with a digital projector on a screen at the back end of the MRI scanner bore, which was visible via a mirror mounted on the head coil. Responses were made using an MRI-compatible button box. Twenty generally high-calorie, palatable food words were selected from word lists reported in previous studies (17, 18). Food words were matched to twenty neutral words each in terms of word length, number of syllables and frequency of use according to the SUBTLEX-NL norms (19).

The Food Stroop interference score was calculated by subtracting the response time (RT) to neutral words from the RT to food words. Hence a higher interference score indicates more distraction by food words. Similarly, the Classic Stroop interference score was calculated by subtracting the response time (RT) to congruent words from the RT to incongruent words. Thus a higher Classic Stroop interference score indicates less general executive control ability.

Ab-libitum snack intake

After the fMRI session, participants were asked to fill out questionnaires whilst four bowls with a variety of snacks were placed in front of them (see (5) for the results in a largely overlapping, but larger sample). The four bowls contained: crisps, raisins, wine gums and cocktail nuts. They were told that they could eat the snacks if they felt like it. Unbeknownst to participants, we calculated the amount of kilocalories (kcal) consumed

by weighting the bowl before and after, and by multiplying the amount of grams consumed by the amount of kcal/gram of that particular snack.

Behavioral Data Analysis

The mean latencies of the correct responses to the words and the number of correct responses in the tasks were analyzed with SPSS. We excluded trials with a RT < 200 msec.

Two narcolepsy patients (scoring 0% and 5% accuracy) and two IH patients (scoring both 10% accuracy) scored <= 10% on accuracy on the incongruent trials in the Classic Stroop task, resulting in too small number of trials to include in the fMRI analyses. These patients were therefore excluded from the Classic Stroop analyses (remaining NT1 group of n = 21 and IH group of n = 13), though they were included in the Food Stroop analyses. Behavioral group analyses including these outliers indicated no qualitatively different results on the Classic Stroop task compared with excluding these outliers.

Response times were reciprocal-transformed (The reciprocal, x to 1/x, is a strong transformation which can be used on highly skewed data (20)) to assure that all assumptions of parametric data were met. All behavioral outcome measures were tested for and met homogeneity of variance. Repeated measurement ANOVAs were used for the two Stroop tasks separately, to test the main effect of Condition (Food Stroop: food, neutral; Classic Stroop: incongruent, congruent), Group (NT1, healthy controls, IH), and Group * Condition interaction effects.

Functional Imaging

Whole-brain imaging was performed on a 3 Tesla Siemens MR scanner located at the Donders Centre for Cognitive Neuroimaging, Nijmegen, The Netherlands. BOLD-sensitive functional images were acquired using a gradient-echo planar multi-echo scanning sequence (TR: 2070 ms; TEs for 4 echoes: 9 ms, 19.25 ms, 29.5 ms and 39.75 ms). We used a multi-echo EPI sequence to reduce image distortion and increase BOLD sensitivity in regions which are typically affected by strong susceptibility artifacts, such as the ventral striatum and vmPFC (21). One volume consisted of 34 axial slices (voxel size: 3.5 x 3.5 x 3.0 mm^3, field of view: 224 mm, flip angle: 90°). After acquisition of the functional images, a high-resolution anatomical scan (T1-weighted MP-RAGE, TR: 2300 ms, TE: 3.03 ms, 8° flip-angle, 192 sagittal slices, slice-matrix size: 256x256, voxel size: 1x1x1 mm^3) was obtained. Total duration of MRI sessions was 45-60 minutes.

The fMRI data were pre-processed using SPM8 (www.fil.ion.ucl.ac.uk/spm), as described in detail in the Supplemental data section S3.

FMRI Data Analysis

Statistical Model

Statistical analyses were performed according a general linear model (GLM) as implemented in SPM8. At the first level, subject-specific data were analyzed using a fixed effects model which contained 2 regressors of interest with the correct trials on food trials and those on neutral trials of the Food Stroop task and 2 regressors with the correct trials on incongruent trials and those on congruent trials of the Classic Stroop

task. All onsets were modeled using a stick function and convolved with the canonical hemodynamic response function. We also included regressors of non-interest: one for incorrect trials, one for missed trials, as well as six movement parameters - resulting from the realignment procedure - and their six time derivatives to account for head movement, and finally the average 'out of brain' signal, derived from the segmented anatomical scan. High pass filtering (128 seconds) was applied to the time series of the functional images to remove low-frequency drifts and correction for serial correlations was done using an autoregressive AR(1) model.

At the second level, we investigated whole-brain main effect of the tasks and group effects in a random effects analysis. Group differences in brain responses on the Food Stroop (food – neutral) and on the Classic Stroop (incongruent – congruent) contrast were tested with an independent two-sample t-test; the main effects of the tasks were tested with a one-sample t-test. In all second level analyses, we added as covariate of non-interest a summary motion score for every subject, which was calculated as the sum of the root-mean-square value of the subject's frame wise-displacement parameters (x, y, z in mm & pitch, roll, and yaw in degrees (22). We tested for correlations between whole-brain responses to food vs neutral words and spontaneous snack intake across groups as well as BMI across groups. Additionally, we assessed the relative contribution of the neural findings (by extracting beta's from the relevant clusters) on the Food Stroop and Classic Stroop tasks to spontaneous snack intake across all groups by using them as predictors in a multiple regression model in SPSS. We used an uncorrected $p<0.001$ intensity threshold and only report significant responses at cluster level $p < 0.05$, FWE-corrected.

Generalized Psycho-Physiological Interaction (gPPI) Analysis

To test functional connectivity differences between groups during color-naming of food versus neutral words, we conducted a generalized psychophysiological interaction analysis (23). As a seed for the gPPI analyses we used the one cluster that was significantly different between the healthy controls and narcolepsy patients (see Results) during the Food Stroop task (i.e. the right ventral medial prefrontal cortex). See Figure 4a for details and the resulting seed.

We used the generalized PPI toolbox (gPPI; http://www.nitrc.org/projects/gppi; McLaren et al., 2012) in SPM8 (Statistical Parametric Mapping, Wellcome Department of Cognitive Neurology, London, UK), given that gPPI has the flexibility to accommodate multiple task conditions in the same connectivity model. To estimate the neural activity producing the physiological effect in the seed region for each subject, the BOLD signal was extracted from this region and deconvolved (24). This was included in the model as a physiological regressor, as were the onset times for each of the task conditions (food, neutral, congruent and incongruent words) as psychological regressors, as well as the physiological regressor multiplied by the psychological regressors (convolved with the HRF), resulting in nine regressors on the first level (i.e., one physiological, four psychological, and four interaction regressors). One PPI contrast was created for each subject: food trials – neutral trials. On the second level, this PPI contrast was analyzed using independent two-sample t-tests comparing healthy controls with narcolepsy patients, healthy controls with IH patients, and narcolepsy patients with IH patients. We used an uncorrected $p<0.001$ intensity threshold and only report significant responses at cluster level $p < 0.05$, FWE-corrected.

Results

Participants

Table 1 summarizes the demographic and clinical characteristics of the participants who were included in the data analysis. Narcolepsy patients and healthy controls were well matched on gender, age, BMI and education level. Patient groups did not differ in medication type used, daytime sleepiness, and were –as expected- significantly sleepier than the healthy controls. As expected, there was significant difference between narcolepsy and IH patients on the quality of sleep, with narcolepsy patients reporting a lower quality of sleep. Working memory capacity, as measured with the digit span, did not differ between the groups.

Ad libitum food intake

Narcolepsy patients spontaneously consumed significantly more calories (mean: 324.71 SD: 272.20) during the ad-libitum snack intake than healthy controls (mean: 114.29 SD: 150.46; $F(1,42)=11.108$ $p=0.002$) and IH patients (mean: 80.85 SD: 126.56; $F(1,37)=12.086$, $p=0.001$), but there was no difference between healthy controls and IH patients ($F(1,34)=0.483$, $p=0.492$).

Behavioral performance on the Food Stroop task

Participants did not respond faster to food words than to neutral words (main effect of Condition: F(1,55)=0.166, p=0.690). We did not see a main effect of Group: (F(2,55)= 2.339, p=0.106), and no significant Condition * Group effect on RTs (F(2,55)= 1.520, p=0.228) (Table 2; Figure 2).

For Food Stroop accuracy, we observed no main effect of Condition (F(1,55)=0.019, p=0.889), no main effect of Group (F(2,55)=0.119, p=0.888), and no significant Condition * Group effect (F(2,55)=0.627, p=0.538).

Food Stroop fMRI results

The main task effect of the contrast food words minus neutral words across groups yielded no significant brain responses when applying the pFWE<.05 cluster corrected threshold. Using an uncorrected threshold (p<.001), responses were found in the right inferior frontal cortex (Brodmann area 48; x,y,z: 42, 30, 16, t=4.32, k=45, $p_{cluster\_uncorrected}$=0.006), left inferior orbitofrontal cortex (Brodmann area 11; x,y,z: -30, 34,-14, t=4.10, k=40, $p_{cluster\_uncorrected}$ =0.009; Figure 3a) and in the left hippocampus (Brodmann area 20 x,y,z: -30, -20, -18, t=4.56, k=21, $p_{cluster\_uncorrected}$ =0.047). Importantly, on a corrected threshold, narcolepsy patients displayed increased responses for food versus neutral words in a region of the reward circuitry, i.e. the ventral medial prefrontal cortex (vmPFC/Brodmann area 25; x,y,z: 6, 10,-14, t=4.45, k=87, $p_{cluster\text{-}FWE}$=0.011; Figure 4b) compared with healthy controls. This vmPFC region (vmPFC/Brodmann area 25; x,y,z: 8, 14, -12, t=5.07, k=149, $p_{cluster\text{-}FWE}$<0.001) and the left superior temporal lobe (Brodmann area 48; x,y,z: -44, -12, -08, t=5.36, k=248, $p_{cluster\text{-}FWE}$<0.001) were also more active in narcolepsy patients compared with IH patients.

There were no differences in brain responses between healthy controls and IH patients. We did not observe significant correlations with BMI scores nor snack intake, within or across groups.

Functional connectivity with the vmPFC seed during the Food Stroop task

We found stronger functional connectivity for narcolepsy patients relative to healthy controls between the vmPFC seed and the right premotor cortex during the Food Stroop task (food – neutral trials) (Brodmann area 6; x,y,z: 46, 8, 42, t=4.48, k=70, $p_{cluster\text{-}FWE}$=0.032; Figure 4b). There were no significant between-group differences in functional connectivity with the vmPFC when comparing narcolepsy patients with IH patients, or IH patients with healthy controls.

Behavioral performance on the Classic Stroop task

To check whether any observed differences in the Food Stroop task or in snack intake could be due to general executive control deficits(25), we employed the Classic Stroop task. As expected, participants were faster on the congruent trials than on the incongruent trials (main Condition: $F(1,51)=200.986$, $p<0.001$). We did not see a main effect of Group ($F(2,51)=1.165$, $p=0.320$), and no significant Condition * Group effect on RTs ($F(2,51)=0.050$, $p=0.952$) (Table 2). Participants were also more accurate on the congruent versus the incongruent trials (main Condition: $F(1,51)=32.427$, $p<0.001$). We did not see group differences across trials (main Group: $F(2,51)=0.999$, $p=0.375$) or as a function of congruency (Condition * Group: $F(2,51)=0.255$, $p=0.776$) (Table 2).

Classic Stroop fMRI results

The main task effect of the contrast incongruent words minus congruent words across groups resulted in significant clusters (Figure 5a) in the bilateral inferior frontal cortex (right x,y,z: 40, 26, 22, t=5.89, k=773, $p_{cluster\text{-}FWE}$<0.001; left x,y,z: -36, 24, 20, t=5.02, k=725, $p_{cluster\text{-}FWE}$<0.001), supplementary motor cortex (x,y,z: -6, 14, 54, t=4.87, k=201, $p_{cluster\text{-}FWE}$<0.001), right superior frontal cortex (x,y,z: 26, 12, 60, t=4.82, k=233, $p_{cluster\text{-}FWE}$<0.001) and left middle frontal cortex (x,y,z: -26, -10, 52, t=4.75, k=85, $p_{cluster\text{-}FWE}$=0.014). Compared with healthy controls, narcolepsy patients displayed lower responses for incongruent words minus congruent words in the left dorsal medial prefrontal cortex (dmPFC) (superior frontal gyrus/ Brodmann area 32; x,y,z: -18, 38, 34, t=5.73, k=191, $p_{cluster\text{-}FWE}$<0.001: Figure 5b). There were no differences in brain responses between narcolepsy patients and IH patients. Compared with healthy controls, IH patients displayed a decreased response in the posterior cingulate cortex (x,y,z: -4, -42, 20, t=4.78, k=80, $p_{cluster\text{-}FWE}$=0.010).

Relative contribution of neural Stroop responses in predicting food intake

To assess the relative contribution of the responses in the vmPFC responses during the Food Stroop task and in the dmPFC during the Classic Stroop task to spontaneous snack intake, we performed a multiple regression analysis across participants. A significant regression model was found (F(2,57) = 4.351, p=0.018), with R^2 of .137. Only the vmPFC responses elicited on the Food Stroop task were a significant positive predictor of spontaneous snack intake (beta = .353, t=2.79, p =0.007; Figure 6), whereas the dmPFC

responses on the Classic Stroop task were not significantly correlated to spontaneous snack intake (beta = 0.076, t=0.604, p =0.549). Thus, food reward-related vmPFC responses on the Food Stroop task, which were increased in narcolepsy patients versus healthy controls and IH patients, have a relatively larger contribution to spontaneous snack intake than the executive functioning-related dmPFC cortex responses, which were decreased in narcolepsy patients versus healthy controls. Brain responses in the vmPFC and dmPFC did not significantly predict BMI scores.

Discussion

In this study we aimed to elucidate the role of orexin in neurocognitive mechanisms underlying food attentional bias by investigating orexin-deficient narcolepsy patients. Narcolepsy patients showed increased activation of the vmPFC when responding to food words relative to neutral words, compared with healthy controls as well as with IH patients (who are comparably sleepy and medicated, but have normal orexin levels). In addition, narcolepsy patients relative to healthy controls displayed higher vmPFC connectivity with the motor cortex when responding to food words relative to neutral words.

The vmPFC is part of the fronto-striatal reward circuitry and is often found to show enhanced activity when people are cued with high caloric food cues (e.g. pictures or words) versus low caloric food cues (6, 7, 9, 26, 27). Indeed, enhanced reactivity to food cues has been shown to predict future weight gain in healthy weight individuals (10, 11). For example, Stice and colleagues (12) found that elevated vmPFC/orbitofrontal cortex responses to cues signaling impending milkshake receipt predicted future body

fat gain over 3-years follow-up in healthy weight adolescents. The current finding of enhanced vmPFC responses in response to rewarding food (versus neutral) words and the enhanced functional connectivity between vmPFC and motor cortex in narcolepsy patients, suggests that narcolepsy patients have enhanced reward-driven invigoration in response to food words which could underlie their weight gain over time. This is further substantiated by our findings that the vmPFC responses to food (versus neutral) words were a positive and unique predictor (relative to dmPFC responses for incongruent versus congruent words) of spontaneous snack intake after scanning.

Enhanced responses to food cues have been associated with increased dopamine release in reward-related brain areas (28, 29). Similarly, animal studies have demonstrated that, in response to salient events, orexin projections enhance dopamine firing rates in reward-related areas, including the vmPFC, nucleus accumbens and the dopaminergic ventral tegmental area (VTA) (16, 30). Since narcolepsy is characterized with orexin deficiency, a *decrease* (via lower VTA activity) instead of an increase in activity of reward-related brain areas might have been expected. Indeed, in a study with monetary reward cues, narcolepsy patients relative to healthy controls, lacked VTA and vmPFC activity when prompted with high versus low incentive monetary cues(31). Presently, we only observed enhanced vmPFC responses and connectivity for (food) reward-related stimuli and no accompanying diminished responses in other reward regions. How orexin deficiency in narcolepsy patients exactly relates to enhanced vmPFC activity in response to food stimuli requires further study.

On the general executive control task, e.g. Classic Stroop, narcolepsy patients displayed lower responses in dmPFC for incongruent colored words versus congruent colored words than healthy controls (but not versus IH). The dmPFC is part of the executive

control network and is sensitive to the degree of response conflict (32–34). Behaviorally, there were no significant group differences on the Stroop interference effect, which is in line with previous cognitive studies assessing executive functioning in narcolepsy (35, 36). Similar to narcolepsy patients, IH patients showed normal Stroop behavior but displayed lower responses in the middle cingulate cortex relative to healthy controls, which is also part of the executive control network. Hence, general sleepiness in both patient groups might be related to diminished responses in these executive control/attention regions, as shown before during sleep deprivation (37–39). It is less likely that diminished executive control responses in dorsal frontal regions in NT1 lead to overeating, as we currently did not find a relation with snack intake.

One caveat of this study is the absence of expected Food Stroop main effects, in both behavioral and fMRI responses. A previous fMRI study used the same Food Stroop task to measure attentional bias to food words relative to neutral words in healthy controls (n=76, 85% women, BMI: 19-35) (13). They reported activation patterns in frontal-parietal areas (including the inferior frontal cortex, inferior orbitofrontal cortex and middle temporal cortex) and slower reaction times (i.e. indicating interference of food words) when healthy controls responded to food relative to neutral words. On a lower statistical threshold ($p<0.001$ uncorrected), we indeed find similar brain areas for the food vs neutral contrast as reported in Janssen et al. (13). The decrease in power might be due to the fact that our participants were less weight concerned than the subjects of Janssen et al (13), who all signed up for an intervention study to change eating habits. Indeed, individuals who are preoccupied with a healthy weight also show increased behavioral food attentional bias (40, 41). Moreover, our study included both patients and healthy volunteers, with the healthy controls showing - if anything - RT interference

by the food words (as in Janssen et al. (13)), whereas the patients demonstrated - if anything - RT facilitation by food words (see Fig 2). Although these opposite behavioral effects in patients versus controls did not reach significance, they could have resulted in the absence of main task effects. Importantly, our study was able to pick up enhanced vmPFC responses in narcolepsy patients relative to healthy controls and IH patients, which was also predictive of spontaneous calorie intake later in the day. One of the strengths of the current study is that we tested narcolepsy and IH patients at least 1 week off their medication, reducing the effects of, amongst others, psychostimulants in our findings. Moreover, by including a group of IH patients, we could discern sleep-disorder related issues (like excessive sleepiness and medication withdrawal) from orexin-deficiency effects. Indeed, relative to healthy controls, IH patients responded behaviorally and neurally similar on the Food Stroop task suggesting it is unlikely that excessive sleepiness or medication withdrawal alone would explain our findings in narcolepsy.

Our study is the first to study the neurocognitive mechanisms of food reward processing in orexin-deficient narcolepsy patients. These findings do not only point to an important role for orexin in food-related motivation in humans, but also suggest possible underlying factors of overeating in narcolepsy.

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Author Contributions

RJ.v.H. participated in the design of the experiments, performed the human studies, analyzed and interpreted most data, and wrote the manuscript.

LJ.J. participated in the design of the experiments and helped analyze the data.

P.v.M. recruited patients and helped organize the experiments.

GJ.L. recruited patients and help revise the manuscript.

R.C. initiated the study and was involved in the experimental design, data interpretation and in revising the final version.

S.O. initiated the study and was involved in the experimental design and data interpretation. He supervised the project and was involved in revising the final version.

E.A. was involved in the experimental design and data interpretation. She supervised the project and was involved in revising the final version.

Potential Conflicts of Interest

The authors declare no conflict of interest.

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Figure legends

Figure 1 Sample trial of the Food Stroop task. On each trial, participants indicated the color of the word presented on the screen by pressing the button reflecting that color. Participants were presented with food and neutral words.

Figure 2 Reaction times during the Food Stroop task. Values are RT means for the difference between food and neutral words. Bars indicate standard errors of the group mean. Note that statistics were done on reciprocal transformed data (original data shown here); Controls= healthy controls; NT1= Narcolepsy type 1 patients; IH: idiopathic hypersomnia patients. RT= reaction time; ms= milliseconds.

Figure 3 Neural Food Stroop effect. a) Main effect of the contrast of food minus matched neutral words. b) Stronger BOLD response in Narcolepsy type 1 patients versus healthy controls on the food versus neutral words contrast. All statistical parametric maps were overlaid onto a T1-weighted canonical image. Images are shown in neurological convention (left = left). Full brain statistical parametric maps were thresholded at p <0.001 uncorrected (for illustration purposes), encircled regions are significant clusters at pFWE<.05. Color scale indicates T-scores ranging from 3 (red) to 4 (yellow).

Figure 4 a) The right vmPFC seed, defined as the significant cluster from the food – neutral trials contrast indicating more activity in Narcolepsy type 1 patients relative to healthy controls (Figure 3b), combined with the corresponding Automated Anatomical Labeling (AAL) masks. b) Functional connectivity between the vmPFC seed and the right motor cortex was higher in Narcolepsy type 1 patients. All statistical parametric maps were overlaid onto a T1-weighted canonical image. Images are shown in neurological convention (left = left). Full brain statistical parametric maps were thresholded at p

<0.001 uncorrected (for illustration purposes), encircled regions are significant clusters at pFWE<0.05. Color scale indicates T-scores ranging from 3 (red) to 4 (yellow).

Figure 5 a) Main effect across groups on the incongruent versus congruent words contrast in the classic Stroop task. Color scale indicates T-scores ranging from 2 (red) to 5 (yellow). b) Stronger BOLD response in healthy controls versus Narcolepsy Type 1 patients on the incongruent versus congruent words contrast. All statistical parametric maps were overlaid onto a T1-weighted canonical image. Images are shown in neurological convention (left = left). Full brain statistical parametric maps were thresholded at p <0.001 uncorrected (for illustration purposes), encircled regions are significant clusters at pFWE<0.05. Color scale indicates T-scores ranging from 3 (red) to 4 (yellow).

Figure 6 Visual presentation of the relative contribution of the responses in the vmPFC responses during the Food Stroop task to spontaneous snack intake in the healthy controls, Narcolepsy type 1 and idiopathic hypersomnia patients.

Tables

Table 1 Demographic and clinical characteristics.

	Controls (n=20)	**NT1 patients (n=23)**	**IH patients (n=15)**	**STATS** Controls vs NT1:	**STATS** Controls vs IH:	**STATS** NT1 vs IH:
Male/ Female	10/10	12/11	7/8	p=0.887	p=0.845	p=0.740
Age	36.75 (12.14)	33.83 (8.36)	36.20 (12.89)	p=0.358	p=0.898	p=0.494

Total score Digit Span	16.20 (4.10)	15.13 (3.36)	15.47 (2.82)	p=0.353	p=0.566	p=0.751
Education levels:	2.95 (0.95)	2.78 (0.80)	2.86 (0.64)	p=0.538	p=0.246	p=0.790
BMI	25.30 (3.84)	26.70 (3.95)	24.22 (4.72)	p=0.245	p=0.464	p=0.089
Disease duration	-	8.17 (8.29)	6.40 (8.13)	-	-	p=0.520
ESS	14.40 (3.66)	24.13 (4.84)	23.66 (3.48)	p<0.001*	p<0.001*	p=0.751
PSQI	6.40 (3.66)	17.47 (3.11)	14.87 (3.48)	p<0.001*	p<0.001*	p=0.021*
Medication used:						
- Stimulants #	-	13	11	-	-	p=0.294
-Anti-depressants #	-	1	0			p=0.413
-Sodium oxybate #	-	3	1			p=0.531
-Stimulants plus sodium oxybate #	-	2	0			p=0.241
-No medication#	20	4	1			p=0.339

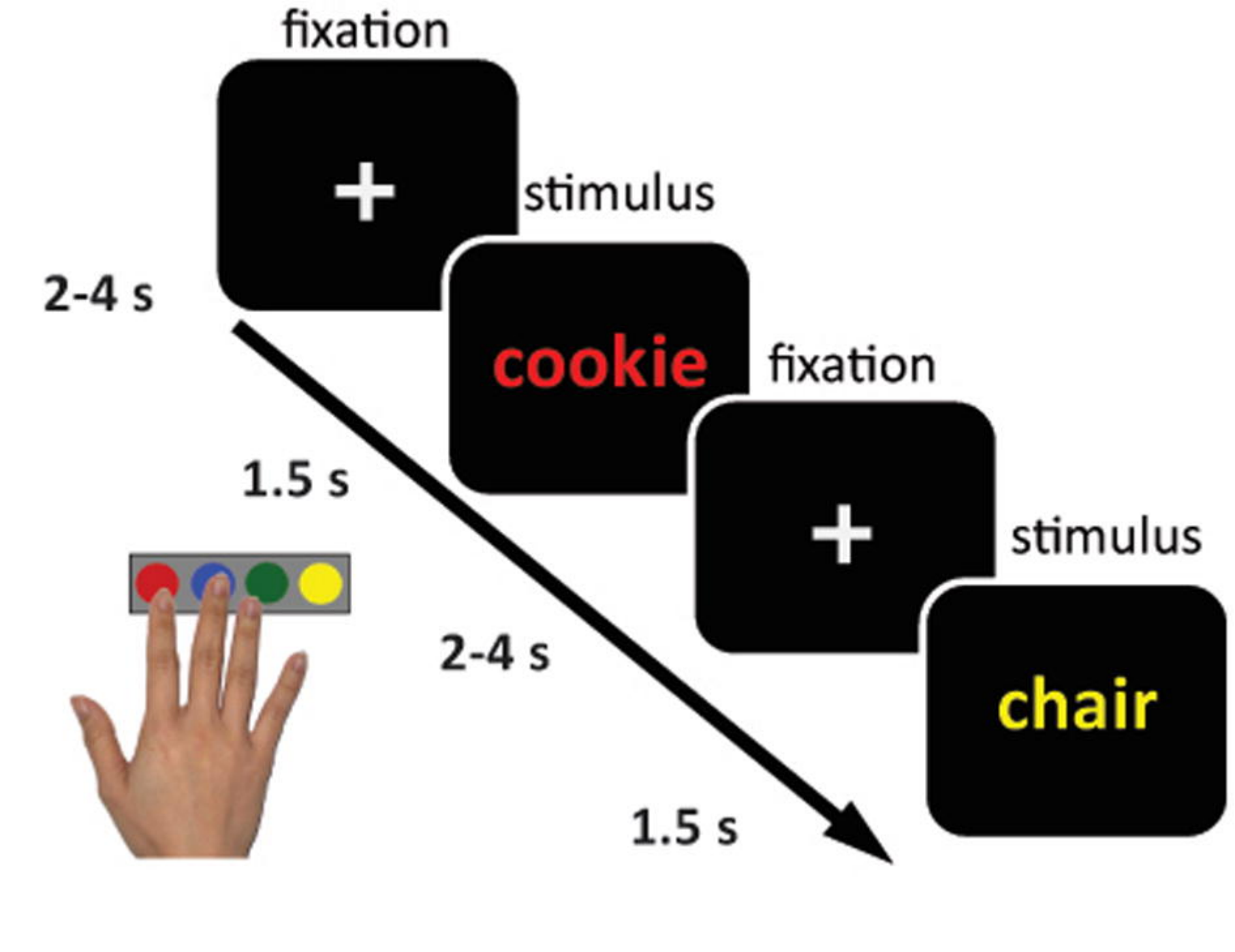
Note. Variables are reported as mean and (standard deviations). Disease duration is reported in mean years. Education levels were categorized as 1= Lower Vocational Education, 2= Intermediate Vocational, 3= Higher Vocational, 4= University; BMI= Body Mass Index; ESS= Epworth Sleepiness Scale; PSQI= Pittsburgh Sleep Quality Index; #= number of participants;

*=Significant at < 0.05; Group differences on age, gender, education level and medication use were tested with an Chi-square test. Other tests were F-tests. NT1: narcolepsy type 1 patients; IH: idiopathic hypersomnia patients.

Table 2. Behavioral results from the classic Stroop task and Food Stroop task

Classic Stroop Task	**Congruent RTs (ms)**	**Incongruent RTs (ms)**	**Stroop RT effect (ms) (incongruent – congruent)**	**Congruent accuracy (%)**	**Incongruent accuracy (%)**	**Stroop accuracy effect (%) (congruent - incongruent)**
Healthy controls (n=20)	1010.60 (425.15)	1162.90 (411.95)	152.30 (87.93)	96.88 (5.37)	91.75 (7.35)	5.12 (5.65)
NT1 (n=21)	933.37 (155.49)	1094.66 (175.52)	161.29 (72.65)	95.71 (5.07)	91.55 (7.00)	4.17 (6.39)
IH (n=13)	971.05 (315.46)	1127.95 (311.78)		98.08 (3.56)	94.23 (4.26)	
Food Stroop task	**Food RTs (ms)**	**Neutral RTs (ms)**	**Food Stroop RT effect (ms) (food – neutral)**	**Food accuracy (%)**	**Neutral accuracy (%)**	**Food Stroop accuracy effect (%) (neutral – food)**
Healthy controls (n=20)	1018.13 (365.89)	992.13 (357.83)	25.99 (70.88)	97.88 (2.37)	97.12 (4.00)	-0.75 (4.45)
NT1 (n=23)	854.41 (110.60)	967.37 (126.31)	-12.96 (65.09)	96.85 (3.30)	97.50 (2.72)	0.65 (4.54)
IH (n=15)	879.71 (399.25)	882.99 (415.35)	-3.28 (42.39)	97.36 (2.85)	98.27 (2.37)	0.33 (3.26)

Note: Values are means and (Standard deviations); RTs are reported as non-transformed data, but statistics were done on the reciprocal transformed data; %=percentages; ms= milliseconds. NT1: narcolepsy type 1 patients; IH: idiopathic hypersomnia patients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+
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fixation
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+
stimulus
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chair
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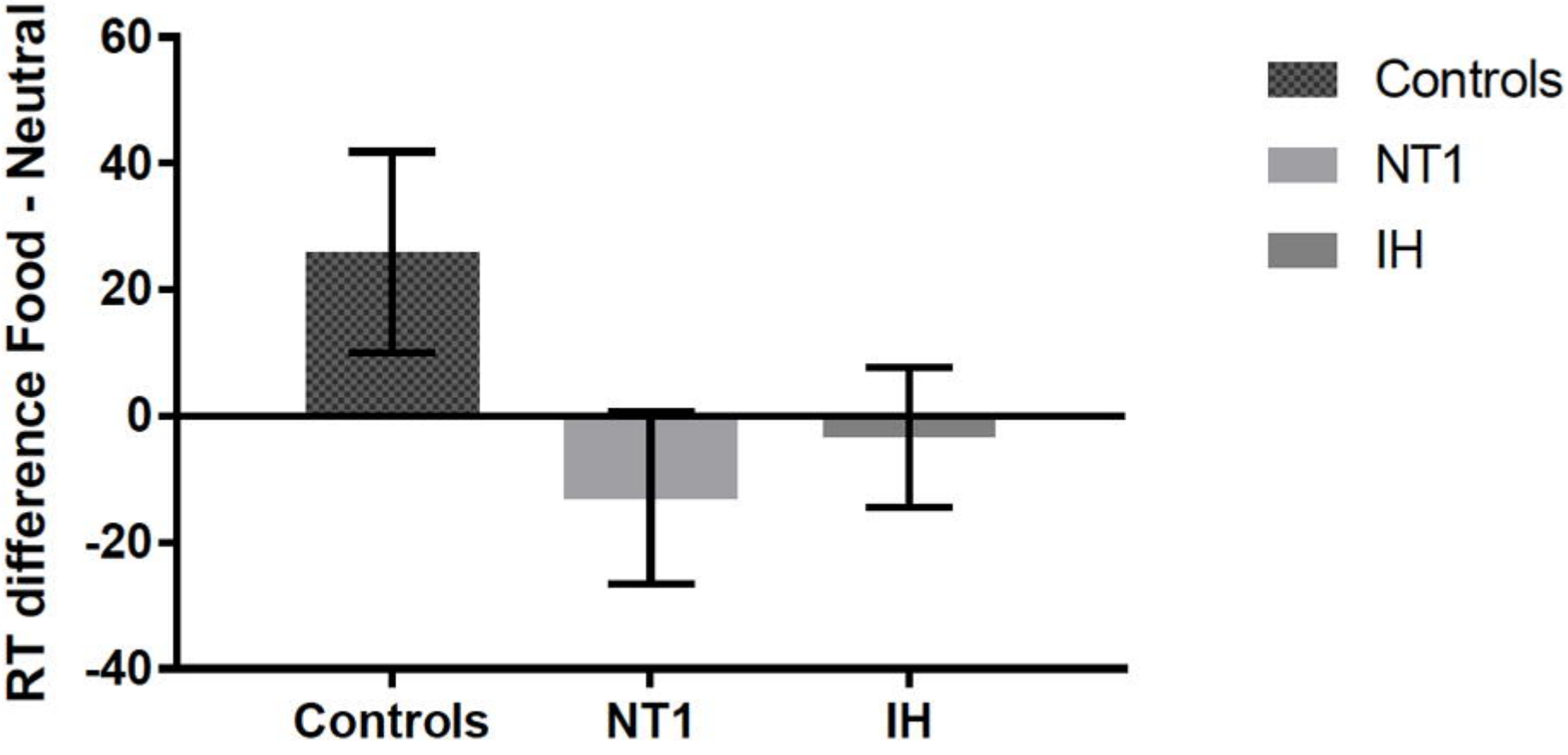
RT difference Food - Neutral
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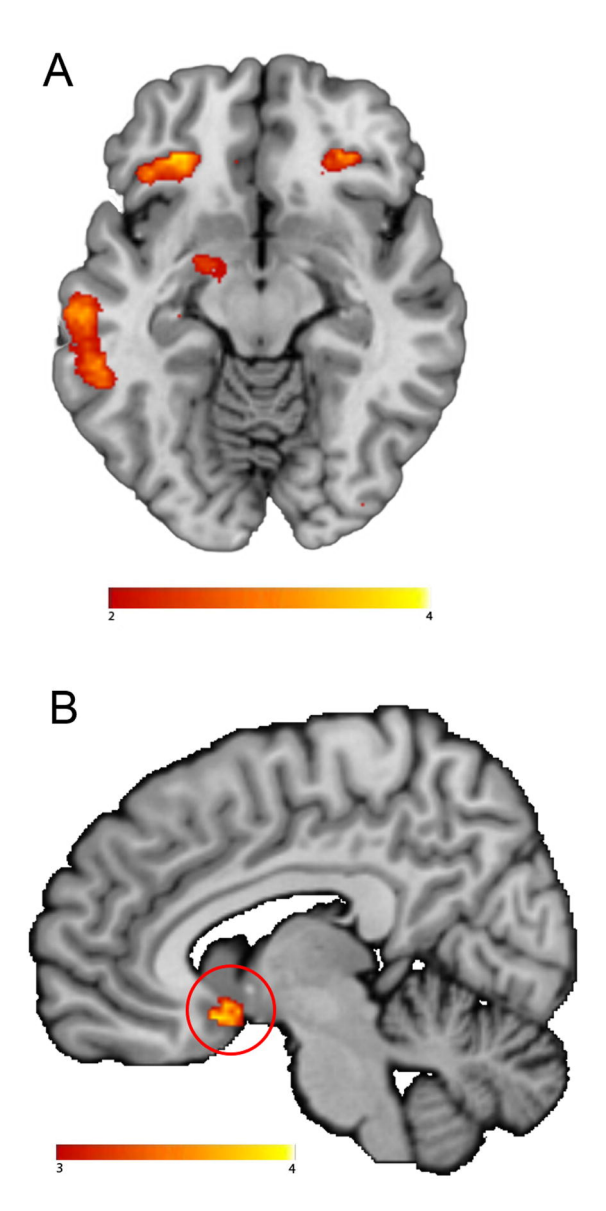
40
20
0
-20
-40
Controls
NT1
IH
Controls
NT1
IH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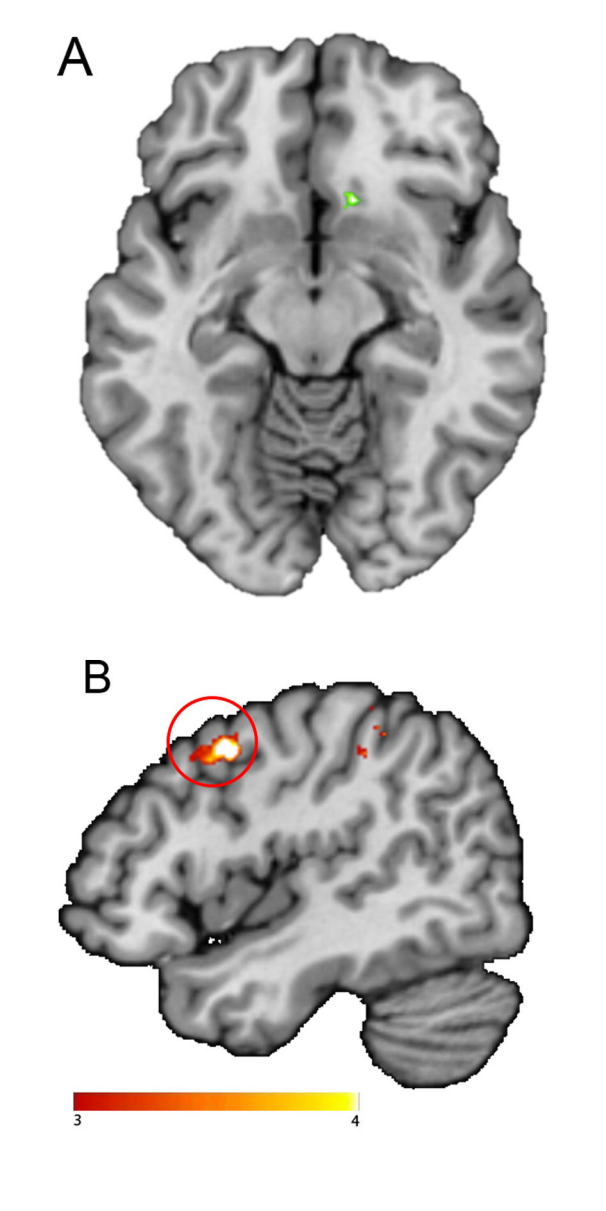
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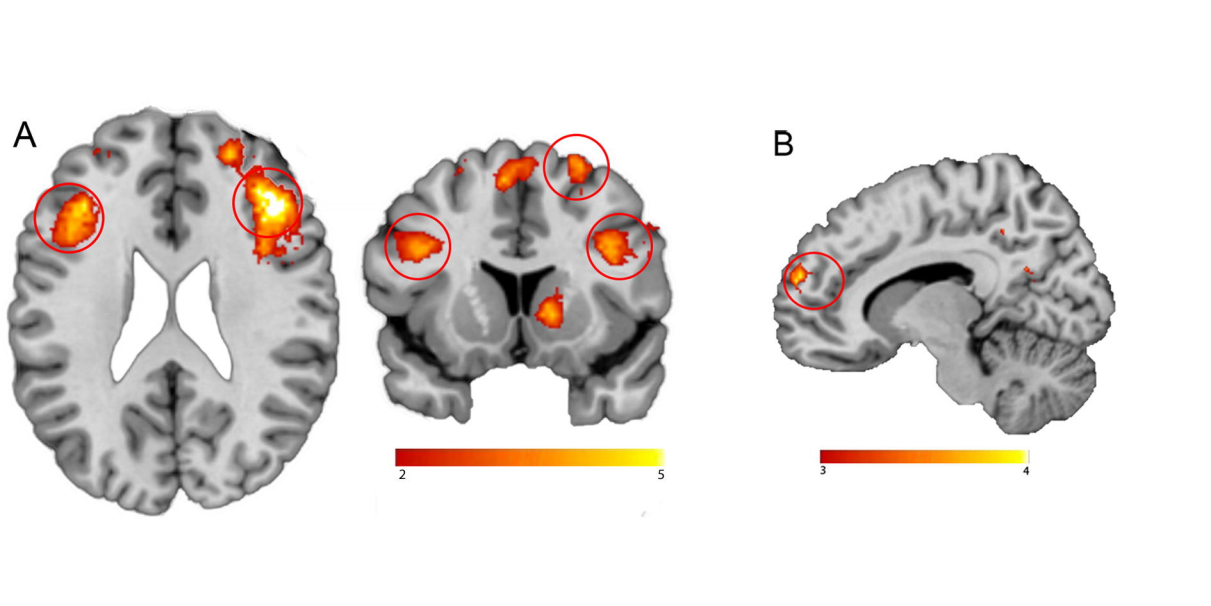
A
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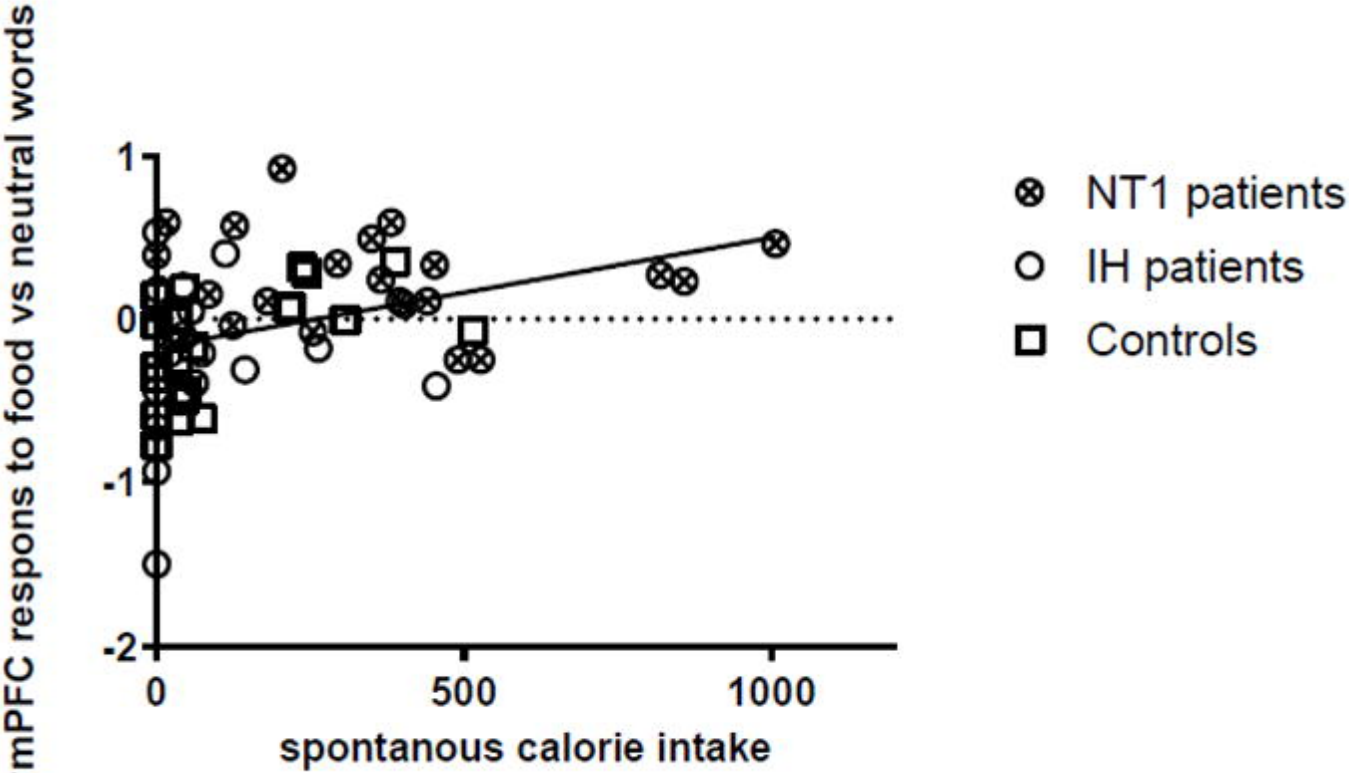
vmPFC respons to food vs neutral words
1
0
-1
-2
0
500
1000
spontanous calorie intake
NT1 patients
IH patients
Controls