Volitional regulation of brain responses to food stimuli in overweight and obese subjects: a real-time fMRI feedback study

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Abstract

Obese subjects who achieve weight loss show increased functional connectivity between dorsolateral prefrontal cortex (dlPFC) and ventromedial prefrontal cortex (vmPFC), key areas of executive control and reward processing. We investigated the potential of real-time functional magnetic resonance imaging (rt-fMRI) neurofeedback training to achieve healthier food choices by enhancing self-control of the interplay between these brain areas. We trained eight male individuals with overweight or obesity (age: 31.8 ± 4.4 years, BMI: 29.4 ± 1.4 kg/m^2) to up-regulate functional connectivity between the dlPFC and the vmPFC by means of a four-day rt-fMRI neurofeedback protocol including, on each day, three training runs comprised of six up-regulation and six passive viewing trials. During the up-regulation runs of the four training days, participants successfully learned to increase functional connectivity between dlPFC and vmPFC. In addition, a trend towards less high-calorie food choices emerged from before to after training, which however was not associated with changes in covertly assessed snack intake. Findings of this proof-of-concept study indicate that overweight and obese participants can increase functional connectivity between brain areas that orchestrate the top-down control of the desire for high-calorie foods. Neurofeedback training might therefore be a useful tool in achieving and maintaining weight loss.

Introduction

Obesity is strongly associated with increased intake of high-calorie and energy-dense palatable food [1]. Accordingly, obese in comparison to lean individuals display altered activity of brain areas involved in reward processing, eating motivation, and cognitive control, which may contribute to the persistence of elevated body weight [2, 3]. Recent experiments have shown that individuals can learn to voluntarily control their brain activity with the help of real-time functional magnetic resonance imaging (rt-fMRI) providing online feedback of neuronal activity [4]. Since rt-fMRI paradigms have been found to trigger intended behavioural effects [5] and factors critical for food intake control like self-regulation and impulse control are suitable targets of neurofeedback [3, 6, 7], respective interventions might be a promising avenue to the modulation of eating behaviour [8, 9]. Of particular interest in this regard is the interplay between the dorsolateral and the ventromedial prefrontal cortices (dlPFC and vmPFC). While the vmPFC is assumed to encode the valence of a stimulus [10], the dlPFC rather mediates self-control over consummatory behaviours [11]. Accordingly, healthy food choice is positively related to functional connectivity between dlPFC and vmPFC, and dlPFC activity is increased when participants exercise self-control [12]. In line with these results, individuals who show greater diet-induced weight loss than others exhibit stronger dlPFC-vmPFC functional connectivity [13]. In the present proof-of-principle study we investigated whether rt-fMRI neurofeedback training enables overweight and obese subjects to increase dlPFC-vmPFC functional connectivity during visual stimulation with unhealthy, high-calorie food stimuli and, if so, how such changes relate to food choices and eating behaviour.

Methods

Participants. Eight healthy male participants with overweight or obesity participated in the study (age: 31.8 ± 4.4 years, BMI: 29.4 ± 1.4 kg/m^2). Exclusion criteria included weight loss

exceeding 5 kg within 3 months before participation, eating disorders, neurological or psychiatric diseases, use of medication, and contraindications for MRI. Prior to participation subjects were informed about the procedure and gave written informed consent. The study protocol was approved by the local Ethics Committee and in accordance with the Declaration of Helsinki.

Experimental Procedure. Within four weeks, subjects participated in six sessions separated by at least two days, a pre-training session in the first week, four neurofeedback training sessions in the second and third week, and one post-training session in the fourth week. Sessions took place in the late morning after at least two hours of post-breakfast fasting. In the pre-training session, individual regions of interest (ROI) for neurofeedback training (dlPFC and vmPFC) were determined [12] (Supplementary Figure S1). In the training sessions, participants learned to self-control dlPFC-vmPFC functional connectivity (Figure 1). These sessions each comprised three runs consisting of six trials, with each trial including 30 s of up-regulation and 30 s of passive viewing separated by 12 s of rest. During up-regulation and viewing, subjects were presented pictures of high-calorie food items selected according to ratings given in the pre-training session. During up-regulation, participants had to up-regulate dlPFC-vmPFC functional connectivity visualized by a thermometer icon, while during passive viewing subjects merely looked at the respective picture. Psychometric ratings were obtained in all sessions; at pre- and post-training, food preferences were determined and snack intake was covertly assessed.

Neuroimaging Assessments. Scans were performed with a 3-Tesla PRISMA Siemens scanner. The vmPFC ROI was defined by significant clusters in the vmPFC mask [12] that showed a parametric modulation with tastiness and healthiness ratings of food pictures. The dlPFC ROI was defined by comparing signals in Brodmann areas 9 and 46 during food choices [14]. Neuronal activation was thresholded at $P < 0.005$ (uncorrected) to detect activation on an individual level.

Functional connectivity was estimated online by partial correlations in time windows of eight data-points (12 s) with Turbo Brain Voyager (Version 3.2; Brain innovation, Maastricht, Netherlands). In subsequent analyses the online connectivity values were compared between runs and sessions by means of aligned rank transformation and a nonparametric analysis of variance on repeated measures (R-version of ARTool). Post-hoc Tukey-Kramer tests were applied for single-step multiple comparisons. Offline analyses were performed using CONNtoolbox (version v15, https://www.nitrc.org/projects/conn). Left and right dlPFC and vmPFC were used as seeds [13] and amygdala served as control region. Differential brain activity during up-regulation vs. viewing was analysed using SPM12 (http://www.fil.ion.ucl.ac.uk/spm/). A threshold of $P < 0.05$ Family-wise-error (FWE) was considered significant.

Behavioural Assessments. In each session, participants gave hunger- and mood-related ratings on 0-100 mm visual analogue scales (VAS). At pre- and post-training, tastiness and healthiness of food items were rated on 5 point-scales. In a choice task, participants had to indicate preferred food items, resulting in healthy, unhealthy high-calorie, and neutral choices. For the implicit assessment of snack intake, participants had to taste and rate three different kinds of snacks, and their intake was covertly measured. Statistical analyses of behavioural data were based on repeated-measures ANOVA (SPSS 22.0) and post-hoc, paired t-tests ($P < 0.05$, Bonferroni-corrected). Data are presented as means ± SEM. (See Supplementary Information for details on neuroimaging and behavioural set-ups).

Results

Functional Connectivity. Collapsed across all four training days, participants successfully increased dlPFC-vmPFC functional connectivity across the three consecutive runs ($F(2,14) = 5.69$, $P = 0.01$), yielding increased functional connectivity during up-regulation in run 3 compared to run 1 ($P < 0.05$; Figure 2). In contrast, there was no respective change during

passive viewing runs ($F(2,14) = 1.76$, $P = 0.22$). Across the four individual training days, there was no incremental increase in functional connectivity ($F(3,21) = 1.06$, $P = 0.31$). In dlPFC seed-based offline analyses, an increase in functional connectivity to the vmPFC was found across all days and runs during up-regulation compared to viewing (FWE-corrected $P < 0.05$; Figure 2).

Regional Activation. During up-regulation of functional connectivity, activity of bilateral insula/inferior frontal gyrus (IFG), left and right dlPFC and bilateral striatum was increased compared to viewing (FWE-corrected $P < 0.05$; Figure 2 and Supplementary Table S1). In contrast, viewing did not lead to any significant activation compared to up-regulation. Comparing the first to the fourth training day, increased activity of the right dlPFC (up-regulation vs. viewing) was observed (FWE-corrected $P < 0.05$), while dlPFC activity during viewing was not changed.

Behavioural Results. In the food choice task, a trend towards less high-calorie food choices emerged from pre- (51%) to post-training (40%; $P = 0.095$; $F(1,7) = 3.67$, $P = 0.097$ for Time). Hunger, fullness, satiety and appetite ratings remained unchanged (all $P > 0.1$) while fear ($F(1,7) = 7.89$, $P = 0.026$) and agitation ($F(1,7) = 7.47$, $P = 0.029$) ratings declined across training sessions. Ratings of tastiness and healthiness of foods presented in the scanner did not change (all $P > 0.71$). From before to after training, a trend towards increased snack intake emerged ($F(1,7) = 4.19$, $P = 0.08$). See Supplementary Table S2 for detailed behavioural results.

Discussion

We demonstrate that overweight and obese subjects can up-regulate functional connectivity between dlPFC and vmPFC during rt-fMRI neurofeedback training. This effect was associated with a trend towards less high-calorie food choices but did not affect actual food intake. Functional connectivity between dlPFC and vmPFC has been associated with reward-

related decisions both regarding food [12, 15] and monetary reward [16], suggesting that dlPFC activation mediates volitional control over reward value signals processed by the vmPFC [12, 13, 15]. Responsivity of the vmPFC changes in dependence of dlPFC input when participants focus on health aspects of a food [15], and the interplay between both areas may reflect food-related impulse control [13]. Our participants with overweight or obesity were able to up-regulate dlPFC-vmPFC functional connectivity, but there was no additional effect of the four consecutive training days. This pattern might indicate that the training effect does not persist between training sessions or that only a higher number of training sessions might induce incremental effects.

During up-regulation vs. passive viewing, we observed enhanced activation of dlPFC, IFG/insula and striatum, i.e., key areas of food intake regulation [2, 3], in particular on the first training day. Insular activity is a regular concomitant of brain self-regulation [17] while the striatum is involved in reward- and instrumental skill-learning [7]. Similar activation patterns where found in individuals using cognitive reappraisal strategies to down-regulate their desire for food [11]. Against this background, our results suggest improved top-down control of the desire for palatable foods, a conclusion supported by the tendency to choosing less high-calorie food items after neurofeedback training. The surprising opposite trend towards increased snack intake after training may have been due to effects of anticipation and habituation to the experimental set-up at post-training [18], which is also suggested by the decrease in rated agitation and fear across the sessions. In sum, our proof-of-principle exploration of the potential of rt-fMRI neurofeedback training to influence eating motivation demonstrates that participants with elevated body weight are able to up-regulate functional connectivity between brain regions of relevance for food intake control. Future studies relying on crossover comparisons with sham trainings may allow more definite conclusions about the (long-term) behavioural implications of food-focused rt-fMRI neurofeedback training.

Supplementary information is available at International Journal of Obesity*'s website.*

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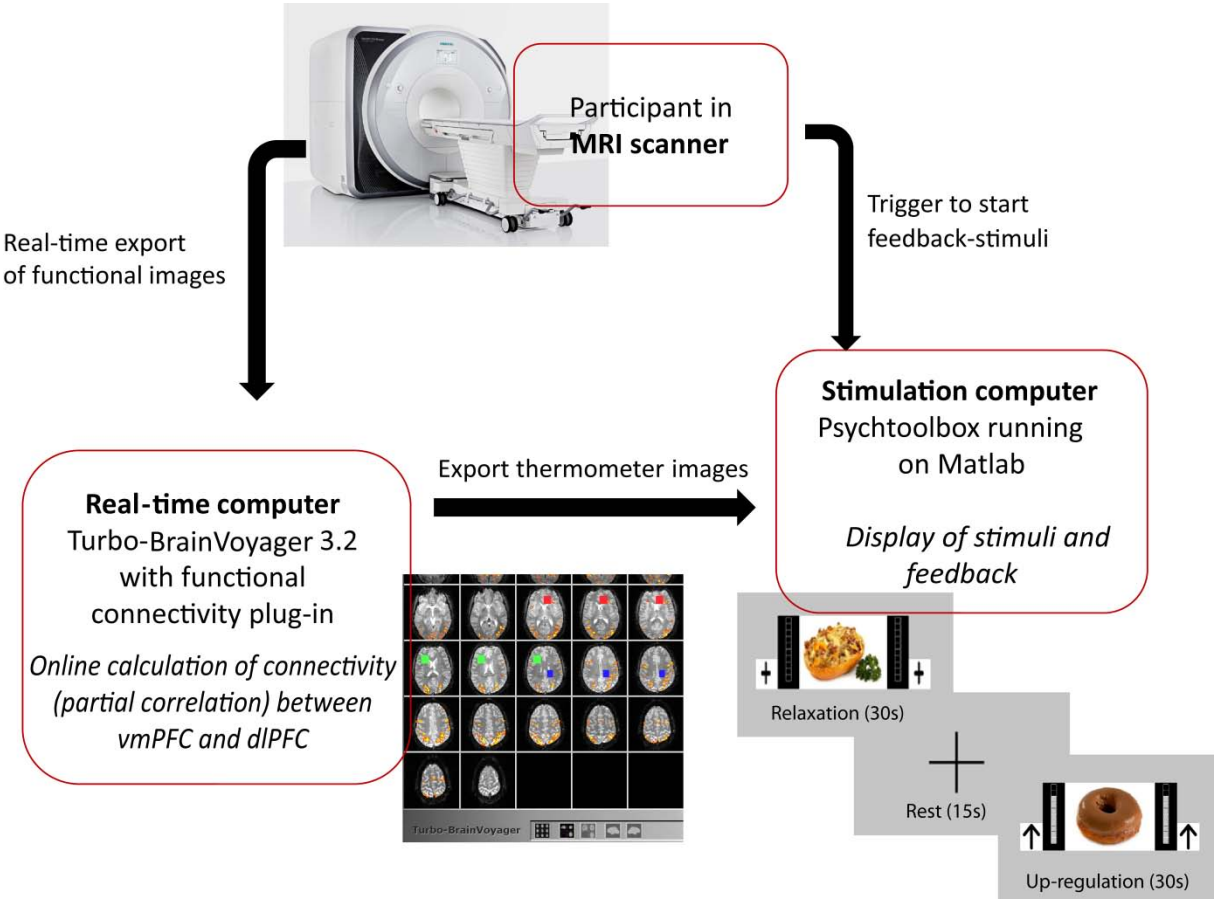
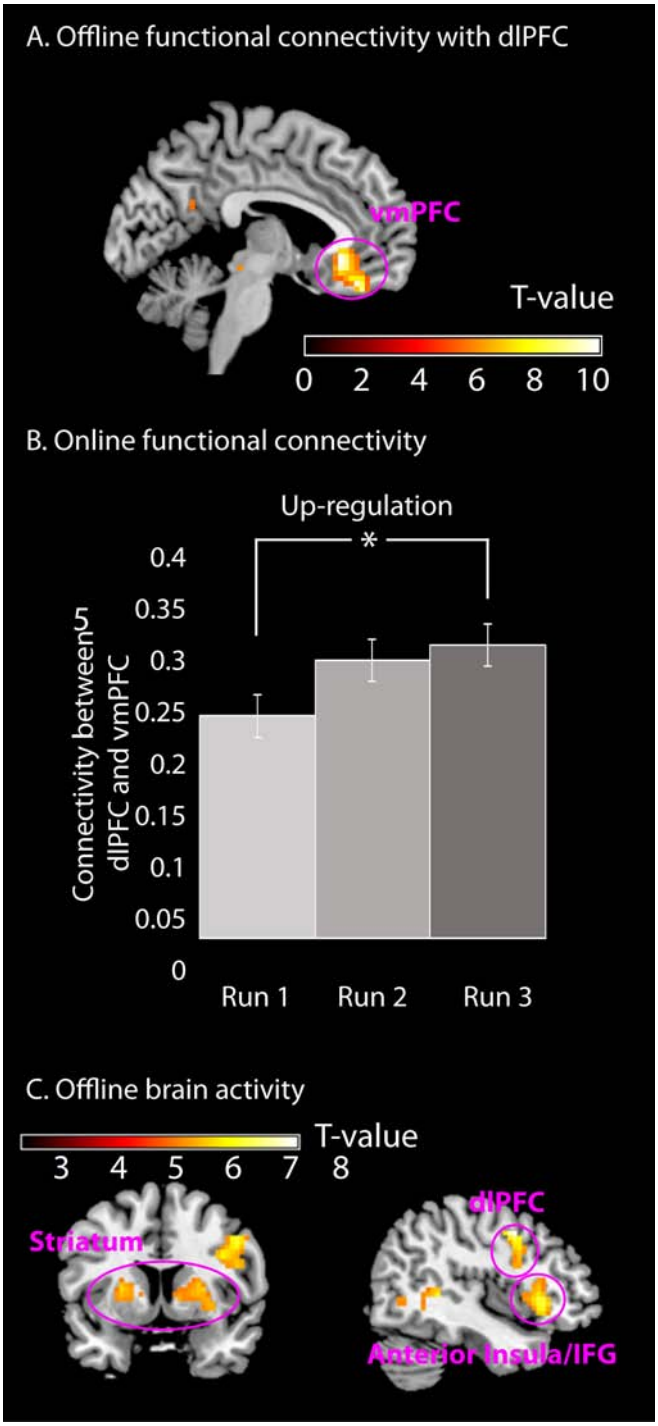
Figure 1. Setup of rt-fMRI neurofeedback training. BOLD signals were acquired via fMRI scans, processed in real-time and presented as visual feedback on the stimulation computer. Visual feedback was provided in the form of thermometer bars indicating increases in functional connectivity between the dorsolateral prefrontal cortex (dlPFC) and the ventromedial prefrontal cortex (vmPFC; partial correlation). Visual feedback was updated only during up-regulation phases (cued by arrows appearing next to the thermometer bars). During the up-regulation phases participants were instructed to increase the thermometer bars, whereas during passive viewing and rest phases, participants were instructed to relax and no feedback was provided.

Figure 2. Effects of rt-fMRI up-regulation training. (A) Offline analysis of functional connectivity. The dorsolateral prefrontal cortex (dlPFC) was selected as a seed in the whole brain seed-to-voxel analysis. The ventromedial prefrontal cortex (vmPFC) was the only region to show significant connectivity with the dlPFC across all days and runs when up-regulation vs. passive viewing were compared. T-value was thresholded at $P < 0.05$ (FWE-corrected). (B) Online connectivity analysis. Changes in dlPFC-vmPFC functional connectivity assessed online during up-regulation. During up-regulation runs 1-3, a significant increase in connectivity emerged. (C) Offline analysis of brain activity. Brain regions with increased responses during up-regulation as compared to passive viewing are indicated by activation maps of up-regulation vs. passive viewing collapsed across all days and all runs. Left panel, activation in bilateral striatum; right panel, activation in bilateral anterior insula/ inferior frontal gyrus (IFG) and dlPFC. T-value was thresholded at $P < 0.05$ (FWE-corrected).


Participant in
MRI scanner
Real-time export
of functional images
Trigger to start
feedback-stimuli
Stimulation computer
Psychtoolbox running
on Matlab
Display of stimuli and
feedback
Real-time computer
Turbo-BrainVoyager 3.2
with functional
connectivity plug-in
Online calculation of connectivity
(partial correlation) between
vmPFC and dlPFC
Export thermometer images
Turbo-BrainVoyager
Relaxation (30s)
Rest (15s)
Up-regulation (30s)


A. Offline functional connectivity with dlPFC
vmPFC
T-value
0 2 4 6 8 10
B. Online functional connectivity
Up-regulation
*
Connectivity between dlPFC and vmPFC
0.4
0.35
0.3
0.25
0.2
0.15
0.1
0.05
0
Run 1
Run 2
Run 3
C. Offline brain activity
T-value
3 4 5 6 7 8
Striatum
dlPFC
Anterior Insula/IFG

Supplementary Methods

Neuroimaging protocols, fMRI acquisition and analyses, and behavioural assessments

Regions of interest determination protocol. Scans for the determination of regions of interest (ROI) for neurofeedback training (dlPFC and vmPFC) were performed in the pre-training session. Participants first rated 90 food images [1] on tastiness (1 = not tasty at all, 2 = not tasty, 3 = neutral, 4 = tasty, 5 = very tasty) and healthiness (1 = very unhealthy, 2 = unhealthy, 3 = neutral, 4 = healthy, 5 = very healthy) in separate sessions on 5-point scales while they were scanned. One item that was rated as neutral both regarding tastiness and healthiness was selected as the reference image for the subsequent choice task. (If necessary, a tastiness rating of 4 was taken to represent relative neutrality). In that task, participants first saw their personalized reference image and were told that in each of the following trials they would have to indicate if they preferred to eat the food item presented in the trial or their reference food [1]. This procedure yielded healthy, neutral and unhealthy choices. Food images were displayed for 3 s on a computer screen (Presentation, Neurobehavioral Systems Inc, www.neurobs.com) and ratings during the scan were given via an fMRI-compatible button box (www.curdes.com).

Neurofeedback training sessions. On the first neurofeedback day, the idea of neurofeedback (self-regulation) was explained and suggestions to control the specific brain areas were given (reappraisal techniques [2]; see Supplementary File). Subsequently the participant was placed in the scanner and underwent three training runs of 9 min each (see Figure 1 in main document). Each run consisted of 6 trials of 30 s up-regulation of functional connectivity between dlPFC and vmPFC and 30 s of passive viewing, including 12 s of rest in-between and between trials. During up-regulation and viewing, an appetitive high-calorie food picture (rated high in tastiness and low in healthiness in the rating task of the pre-training session), two black thermometers on the right

and respectively left side of the food image (providing feedback on functional connectivity) and two additional symbols indicating the type of the trial (upward arrow during up-regulation, plus sign during passive viewing) were displayed. The thermometer bars included ten levels which turned from black to grey in an upward, incremental fashion whenever functional connectivity between the ROIs increased by 0.1. Only increases in functional connectivity were fed back to the participants, otherwise the thermometer bars were displayed as empty. Participants received feedback only during up-regulation trials. During passive viewing, participants were instructed to relax, and the same visual cues as during up-regulation were shown without updating the feedback thermometers. During rest, a cross appeared. Stimuli were displayed on a screen through a computer interface and run with the program Psych-toolbox on Matlab (version 17). Procedures were identical during all four neurofeedback days.

fMRI data acquisition. All scans were performed with a 3-Tesla PRISMA Siemens scanner equipped with a 20-channel head coil at the Max Planck Institute of Biological Cybernetics, High-Field MR Centre, Tübingen, Germany. T1-weighted anatomical scans were acquired with the following parameters: TR/TE = 2300/4.18 ms, flip angle = 9°, FOV = 256 × 175mm, 176 axial slices, and voxel size = 1×1×1 mm^3 (MPRAGE GRAPPA). Functional images at pre- and post-training were acquired with a single-shot echo-planar imaging (EPI) sequence with the following parameters: repetition time TR = 2500 ms, flip angle = 70°, echo time TE = 30 ms, matrix size = 64 × 64, and 40 slices (thickness = 3 mm), resulting in a voxel size of 3×3×3. Functional images in the neurofeedback training sessions (comprising 356 scans) were acquired with a single-shot EPI sequence with a short repetition time TR = 1500 ms, flip angle of 79°, echo time TE = 30 ms, matrix size = 64 × 64, and 20 slices (thickness = 4 mm), resulting in a voxel size of 3×3×4. To assure scanning the same slices (and hence ROIs) in the brain during the

different training days of each participant, we used the landmark-based automated positioning system (AutoAlign Head using AC-PC line). Positioning parameters were saved at the beginning of the pre-training and the neurofeedback training sessions.

fMRI data preprocessing and analyses. All functional imaging data were pre-processed and analyzed using SPM 12 (Wellcome Department of Cognitive Neurology, London, UK) run with MATLAB 2013 (The Mathworks Inc, Natick, MA) and the WFU Pickatlas-tool. Images were first motion-corrected and realigned. The high-resolution T1 image was then co-registered to the mean image of the EPI series for each participant. Segmentation was performed to compute spatial transformation parameters that were used to normalize the structural (1×1×1) and the functional (3×3×3.5) scans to a standard Montreal Neurological Institute (MNI) template. Normalized images were spatially smoothed with a 9 mm full-width half-maximum Gaussian kernel. Low frequency drifts were removed using a high-pass filter with 128 second cut off. After functional data pre-processing, a general linear model was adopted to perform first-level statistical analysis.

ROI analyses. For ROI determination the functional images obtained during tastiness and healthiness ratings and the choice task (see above) were pre-processed and analysed. For both tasks separate GLM analyses with two regressors representing mean activation and covariation with the individual ratings (parametric modulation) were performed. Significant clusters within the vmPFC mask (based on ref. [1]) that showed a positive covariation with the individual tastiness ratings were selected to define ROI 1. In the choice task two regressors were defined, i.e., healthy choice (selection of a low-calorie food) and unhealthy choice (high-calorie item), resulting in the contrast image healthy vs. unhealthy choice. ROI 2 was determined by comparing brain activity within a dlPFC mask (covering Brodmann areas 9 and 46) during healthy and

unhealthy choices [3]. A rectangular box (comprising 6 × 6 voxels) centred on the individual peak voxels covering three slices was selected to represent each of the two ROI. In all models, the six movement parameters from the corresponding sessions were added as covariates of no interest to correct for motion-related variance. Brain activation determining the ROI was considered significant when exceeding a threshold of $P < 0.005$ uncorrected on an individual level. In the post-training session participants underwent the same tasks as outlined above, this time without determining the ROI for neurofeedback training.

Analyses of neurofeedback training results. For the analysis of neurofeedback training data, a design matrix was constructed for all days and sessions using up-regulation and passive viewing as separate regressors. Conditions were modelled with a canonical hemodynamic response. For each participant contrast images were created for up-regulation versus viewing for each session on each day. Contrast images were then entered into a second-level full factorial design with the factors day × run to allow population-level inferences. A threshold of $P < 0.05$ Family-wise-error (FWE) was considered as significant brain activation.

Online analysis of functional connectivity. During the neurofeedback sessions, all functional images were analysed with Turbo Brain Voyager (TBV; Version 3.2; Brain innovation, Maastricht, Netherlands). The MR images were exported in real-time from the MRI console computer to a computer running TBV. To avoid T1 saturation effects the first 10 images were excluded. Real-time motion correction was achieved by aligning all functional images to the first recorded volume in the first session; images in all other sessions were aligned accordingly. Motion corrected functional images were then spatially smoothed by a kernel of 9 mm. Incoming images were used for calculating functional connectivity using partial correlations (plugin TBV, Version 3.2; Brain innovation, Maastricht, Netherlands) between the mean time courses within

individually selected ROI in the vmPFC, dlPFC, and white matter (parietal lobes) as a reference area. Partial correlations were used to regress out any global fluctuations or unwanted movement artefacts that may not have been corrected by pre-processing algorithms. Time windows of 12 s including 8 data points were used to calculate partial correlations. Feedback was updated at every repetition time. Connectivity values calculated online were compared between sessions and runs by means of aligned rank transformations and post-hoc Tukey-Kramer tests.

Offline analysis of functional connectivity. Offline connectivity analysis was performed using CONN toolbox (version v15 http://www.nitrc.org/projects/conn) implemented in SPM12. Functional connectivity was determined by evaluating the temporal correlation between seed regions as well as between each seed and all remaining voxels in the brain. Seeds were left and right dlPFC and vmPFC [4]. The amygdala was included as a control region. Spheres of 6 mm radius centred at the most significant voxel were imported for connectivity analyses. Before computing connectivity, confounds from BOLD signals from white matter, cerebrospinal fluid, estimated subject motion parameters, and all main task effects were removed by linear regression analysis. A threshold of $P < 0.05$ Family-wise-error (FWE) was considered significant.

Snack intake. For the covert investigation of snack intake, three plates were placed on a table containing snacks which were different in taste but roughly comparable in calorie content and macronutrient composition [5, 6]. They were labelled snack A, B, and C, respectively. The three types were, “TUC Cracker Classic” (salty taste; Griesson-de Beukelaer, Polch, Germany, 488 kcal/100 g), “Rice Waffles” (bland taste; Continental Bakeries B.V., Dordrecht, The Netherlands, 389 kcal/100 g), and “Double Chocolate Cookies” (sweet taste; EDEKA, Hamburg, Germany, 503 kcal/100 g), all broken down into bite-sized pieces. Of each variety a considerable amount could be eaten without the plates appearing empty, to ensure that participants would not restrict

snack intake based on whether the experimenter could see how much had been consumed. In addition, a glass of water was provided. The participant was instructed to taste and rate each type of cookie on a visual analogue scale assessing palatability, sweetness and saltiness, anchored at 0 (not at all) and 10 cm (very palatable/sweet/salty). The importance of giving accurate ratings was emphasized and participants were informed that during and after completion of the rating task they could eat as many snacks as they liked because any remaining snacks would be discarded, and were left alone for 10 min. Snack intake was covertly measured by weighing before and after the test without awareness of the participant.

Statistical analysis. Behavioural data were analysed using SPSS 22.0 (IBM Corp.). Ratings and snack intake were analysed by repeated-measure ANOVAs with the within-subject factor "time point". Healthiness and tastiness ratings of food pictures were analysed by 2 × 2 repeated-measure ANOVA with the factors "time point" (pre- vs. post-training) and "calorie" (high vs. low). In addition, the percentages of healthy and unhealthy food items chosen during the choice task before and after the training sessions were analysed by repeated-measures ANOVA. Post-hoc, paired t-tests were used to specify comparisons ($P < 0.05$, Bonferroni-corrected for multiple comparisons).

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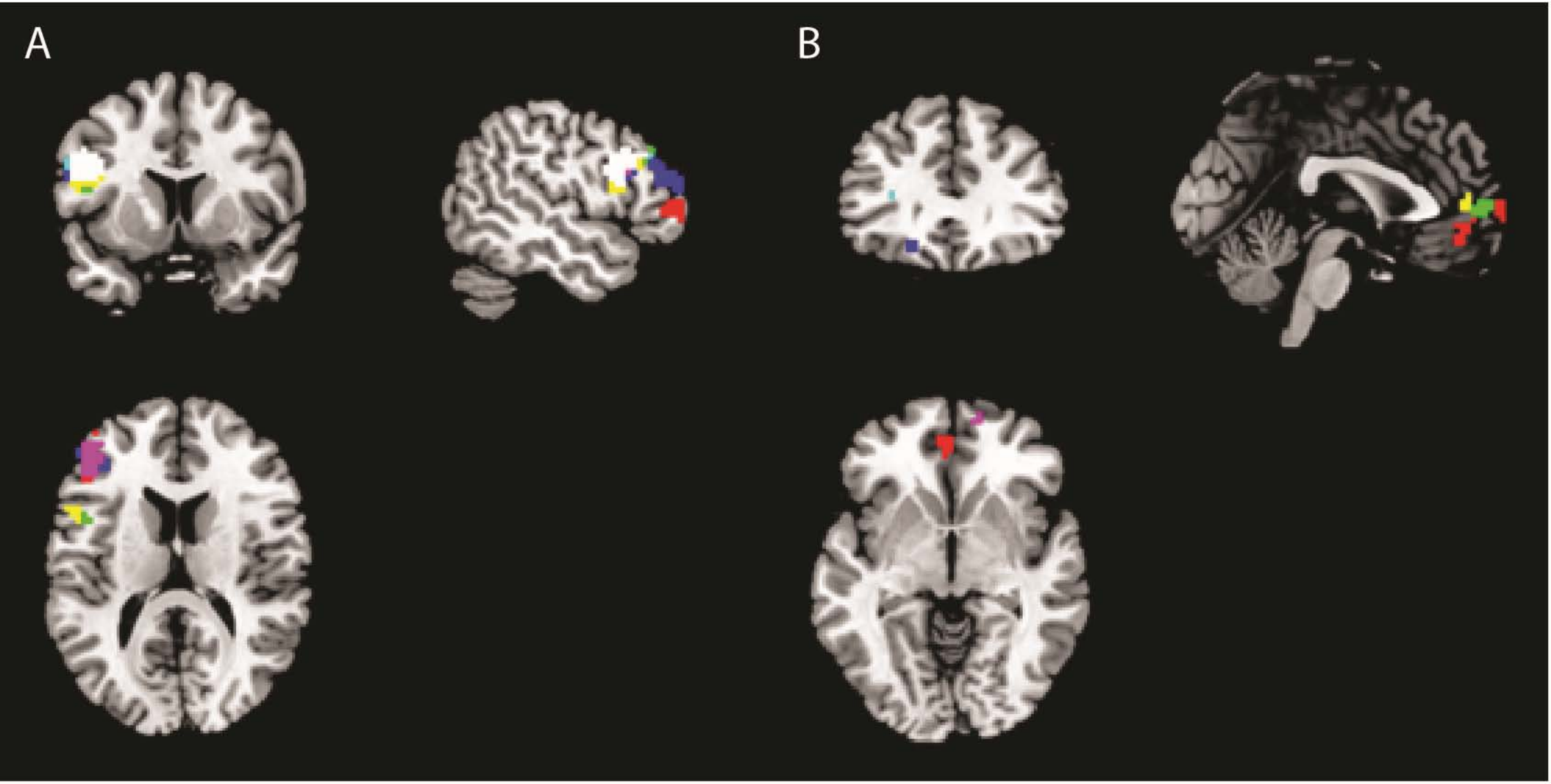

Supplementary Figure S1. Localization activation. A: Individual dlPFC activation calculated during the food-choice task by comparing low- vs. high-calorie choices (n = 6). B: Individual ROI selection according to the modulation of vmPFC activation during tastiness and healthiness ratings of high and low-calorie food pictures (n = 6). For both areas, ROI could be individually localized in six out of eight participants. For the four cases in total where this was not possible, coordinates from previous studies were used to identify vmPFC and dlPFC ROI (using inverse transformations from MNI to individual space). Each colour corresponds to one participant.